Joint effect of whole blood metals exposure with dyslipidemia in representative U.S adults in NHANES 2011-2020

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Abstract

With little knowledge on the joint effects of metal exposure on dyslipidemia, we aimed to investigate the relationship between exposure to metal and dyslipidemia among U.S adults based on the National Health and Nutrition Examination Survey(NHANES). Based on the five NHANES waves(2011-2020), we selected five metals in blood as exposure, namely, Cadmium(Cd), Lead(Pb), Total Mercury(Hg), Manganese(Mn) and Selenium(Se), which were detected by inductively coupled plasma mass spectrometry. Survey-multivariable logistic regression, Generalized Weighted Quantile Sum(WQS) and Bayesian kernel machine regression(BKMR) were performed to determine whether dyslipidemia was associated with single metals or mixed metals. Our study included 12,526 participants aged from 20 to 80, representing 577.1 million non-institutionalized U.S. adults. We found a positive association between several metals including Pb [Adjusted odds ratio(AOR)=1.332, 95%CI:1.165, 1.522], Total Hg(AOR=1.264, 95%CI:1.120, 1.427), Mn(AOR=1.181, 95%CI:1.046, 1.334) and Se(AOR=1.771, 95%CI:1.576, 1.992) and dyslipidemia. According to the WQS approach, metal mixtures were positively associated with dyslipidemia(AOR:1.310, 95%CI: 1.216, 1.411) after a full-model adjustment. As is shown in the BKMR model, mixed metals tended to be positively associated with dyslipidemia ratios in a significant manner. Females, non-Hispanic white populations, people aged over 60 and those who did a little physical activity had a greater risk for dyslipidemia. Our findings suggest metals including Cd, Pb, Hg, Mn and Se and their combinations may adversely affect dyslipidemia among U.S adults. Due to the cross-sectional nature of the study, it is possible that reverse causation may exist.

Highlights

- Limited evidence on influence of several metals exposure on the risk of dyslipidemia.
- A large, representative, multiracial sample that represented 577 million U.S adults.
- Weighted quantile sum regression and Bayesian kernel machine regression were adopted.
- Single(Pb, Hg, Mn, Se) and mixed metal exposures were associated with dyslipidemia.

Introduction

Defined as abnormal metabolism of lipid levels in a person's blood, dyslipidemia is presented by indicators of triglycerides(TGs), total cholesterol(TC), low density lipoprotein cholesterol(LDL-C) as well as high-density lipoprotein cholesterol(HDL-C). As a major risk factor for cardiometabolic diseases, dyslipidemia is also a prerequisite to them("2012 update of the Canadian Cardiovascular Society guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult," 2013; Kopin & Lowenstein, 2017; Tobert & Newman, 2016). Dyslipidemia affects approximately 40–50% of Americans based on the NHANES 1999–2010, and the figure reached up to 56.8% in 2018(Saydah et al., 2014), posing a tremendous risk disability and even death worldwide, particularly in the United States(Peters, Muntner, & Woodward, 2019; Shin, Bautista, Walsh, Malecki, & Nieto, 2015).

The causes of dyslipidemia involve both genetic and environmental factors, for example, metals(Simha, 2020; Yang et al., 2017). Metals, which fill the environment and are difficult to degrade, can be easily absorbed by people through dermal contact, assimilation of food chain or respiratory tract from water, air, and soil, accumulating in the human body over time(Fu & Xi, 2020). In daily life, people are often exposed to metals coming from industrial waste gases, wastewater, contaminated soil, drinking water, or food(Kang, Shin, & Kim, 2021b). For example, consuming raw meat and smoking(whether active or passive smoking) are two common examples of taking in metals into the human body, which, put more directly, is metal pollution, a very serious prevalent environmental threat. Previous epidemiologic studies documented the positive association between single metal and dyslipidemia such as cadmium and lead, the most prevalent poisonous metals that severely threaten human body. In an animal experiment, exposure to Pb can induce oxidative stress in rats, which alters lipid metabolism and results in lipid disorders(Tyrrell, Hafida, Stemmer, Adhami, & Leff, 2017). Moreover, the presence of strontium and cadmium in mice can inhibit their antioxidant activity and contribute to hyperlipidemia(Flora, Mittal, & Mehta, 2008; Fournier et al., 2012).

After reviewing earlier relevant evidence regarding metals and dyslipidemia, we found several limitations. First, only a few studies investigated the relationship between metals exposure and risk of dyslipidemia, and their findings were conflicting. A cross-sectional study in the US involving 43,196 participants showed that blood lead levels were positively correlated with hyperlipidemia concentrations(Zhang et al., 2022), while a study conducted in China failed to find a link between single cadmium or lead and the risk of dyslipidemia(Tingyu Luo et al., 2022). Second, although the relationship between metal and cardiovascular disease(CVD) has been well-documented in multiple epidemiologic studies(Messner, Knoflach, Seubert, Ritsch, & Bernhard, 2009; Yu et al., 2009), the association of metals with dyslipidemia is less investigated. Moreover, a wide range of environmental factors continually affect humans simultaneously since no exposure occurs in isolation in the real world. Nevertheless, studies on the effects of different categories of environmental chemicals in combination are scarce, which has partially contributed to selective reporting and further research is required. Thus, far less studies have explored the link between multiple metals and dyslipidemia, possibly due to the fact that conventional statistical methods are limited and thus, previous studies focused on relationship between exposure to one pollutant and certain health outcome. Finally, compared with the metals in urine collection, metals in circulating blood as a proximate indicator with high stability and repeatability can better reflect the short-term metal exposure level in an organism(Bushnik, Levallois, D'Amour, Anderson, & McAlister, 2014). Therefore, considering the above limitations, the purposes of this study were three-fold. Using the nationally representative sample of the civilian noninstitutionalized U.S population based on the National Health and Nutrition Examination Survey(NHANES) from 2011 to 2020 years: (1) To determine the current trend prevalence of dyslipidemia for

U.S adults from 2011 to 2020; (2) To examine the association between single blood metals concentration [Cadmium(Cd), Lead(Pb), Total Mercury(Hg), Manganese(Mn) and Selenium(Se)] and dyslipidemia among U.S adults to obtain possible proof that could help illustrate the inconsistent association between lipid biomarkers and metals exposure identified in prior studies; (3)To investigate the association between the joint effects of Cd, Pb, Total Hg, Mn and Se existing in the plasma of average people and dyslipidemia to help prevent and prevent dyslipidemia.

Methods

Study population

NHANES is a representative nationwide cross-sectional study conducted continuously by the Centers for Disease Control and Prevention(CDC) of the non-institutionalized civilian populations in the U.S. Stratified, multistage probability sampling was employed to obtain a representative sample through individual interviews including demographic information, socio-economic data, health and nutritional status, physical examinations including laboratory evaluation data(Statistics, Oct 18, 2016). Data were obtained from 5 successive waves of NHANES(2011–2012, 2013–2014, 2015–2016, 2017–2018, 2019–2020). Detailed information and data on NHANES can be found at http://www.cdc.gov/nchs/nhanes/about_nhanes.htm.

Initially, 111,066 individuals were included in the study, and we further excluded individuals younger than 20 years of age, those who could not be identified as dyslipidemia, and those who lacked data on five metals(n = 19,906), following by excluding individuals who lack the information of covariates(n = 79,044). Finally, a total of 12,526 subjects were included in this study. The details of the inclusion and exclusion process were shown in **Fig.S1**. The NHANES project was approved by the NCHS Research Ethics Review Committee. All participants in the project signed informed consent forms.

Laboratory Analyses

Determination of blood metals

The blood samples were all stored at -80 degrees Celsius before they were analyzed.

In preparation for the experiment, all laboratory tubes were thoroughly cleaned with 2% HNO3 before blood samples were pre-thawed at 4°C. Cd, Pb, Total Hg, Mn, and Se and their concentrations in whole blood were determined with inductively coupled plasma mass spectrometry(ICP-MS,Perkin Elmer NexION 350X, Shelton, CT, USA). A square root of 2 was used to replace all blood metal concentrations below the limit of detection(LOD) (Prevention, May 21, 2022). A normal distribution was approximated by log2-transforming all metal concentrations in the blood. The website dedicated to NHANES contains detailed laboratory methods and data on quality assurance(An example of 2019–2020 NHANES laboratory procedure manual for metals in blood can be found at https://wwwn.cdc.gov/Nchs/Nhanes/2017-2018/P_PBCD.htm#LBDBCDSI).

Definition Of Dyslipidemia

Prior studies have described in details how serum lipid profiles were measured(Perak, Ning, Kit, Ferranti, & Lloyd-Jones, 2019; Welsh & Jean, 2010). Dyslipidemia can be diagnosed if any of the following conditions occur. Participants who received any lipid-lowering medication currently reported, Serum total cholesterol(TC) ≥ 200 mg/dl, or/and triglycerides(TG) TG ≥ 150 mg/dl, or/and low-density lipoprotein cholesterol(LDL-C) ≥ 130 mg/dl, or/and high-density lipoprotein cholesterol(HDL) < 40 mg/d(male), or/and HDL < 50 mg/d(female) according to the National Lipid Association and National Cholesterol Education Program(Jacobson et al., 2014; "Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report," 2002).

Definition Of Covariates

Series of variables were selected as potential confounding factors, as presented below: Age(20–39 years, 40–59 years, and 60 years and above), gender(male, female), Body Mass Index(BMI), measured in kg/m2, was calculated as weight in kilograms divided by height in meters squared. Race/ethnicity was classified as non-Hispanic white, non-Hispanic black, Mexican American, and other races(multiracial and other Hispanic). The poverty-to-income ratio(PIR) was used to classify household income in relation to the federal poverty line, and families living below the federal poverty line with a PIR value less than 1.0. The highest education attainment was categorized into below 9th grade, 9-11th grade(including 12th grade without diploma), high school grad(GED or equivalent), college graduate or above, and some college or AA degree. Marital status was classified as widowed/divorced/separated, never married, and married/living with partner. Serum cotinine(continuous). Diabetes mellitus(DM) was defined as fasting blood glucose(FBG) ≥ 126 mg/dL, or a self-reported diabetes diagnosis. Hypertension was defined as an average systolic blood pressure > 140 mmHg and/or diastolic blood pressure of 90 mmHg, diagnosed by a physician, or taking hypertension medications. Smoking status was categorized as never smoking, smoking previously, or currently smoking. Alcohol consumption was divided into never, former, or current alcohol consumption. Physical activity(PA) was measured by weekly metabolic equivalent(MET) minutes through questionnaires, and classified into four quartiles(Q1, Q2, Q3, and Q4). Total energy intake, expressed in kcal, was also classified as four quartiles(Q1, Q2, Q3, and Q4).

Statistical Analyses

As NHANES was a complex multi-stage sampling design study, appropriate sample weights, strata, and clustering variables were used in the main analyses. Continuous variables were expressed as weighted mean ± standard error(SE), and categorical variables were expressed as counts(weighted percentages, %). The baseline characteristics of study participants were assessed using weighted Chi-square test and T-test based on dyslipidemia status. Survey-multivariable logistic regression(SMLR) was used to calculate adjusted odds ratios(AORs) and 95% confidence intervals(CI) for five metals(Cd, Pb, Total Hg, Mn, Se) associated with the risk of dyslipidemia. The crude Model was adjusted for no variables. Model 1 adjusted age, gender, and race/ethnicity. On the basis of Model 1, Model 2 was further adjusted for BMI, PIR, education attainment, marital status, smoking status, alcohol consumption, serum cotinine(continuous), DM, hypertension and PA(quartile). In addition, the trend test across increasing exposure groups was calculated in multivariable models. After adjusting the relevant covariates, Weighted Quantile Sum(WQS) Regression was constructed to assess the relationship between combined exposure to five metals and the risk of dyslipidemia. By using the WQS regression, it is possible to identify key components contributing to the dyslipidemia effect(Czarnota, Gennings, & Wheeler, 2015). Weights were assigned to exposure to metals, with a higher weight indicating greater contribution. By randomizing the original group into 40% training and 60% validation groups, bootstrap approaches were used to estimate weight values for each metal. As there may not exist a linear or additive relationship between mixed exposure and dyslipidemia, Bayesian kernel machine regression(BKMR) technology, a model not based on parameters and integrating with Bayesian and statistical learning techniques, was adopted to find out the association between the effect of five metals in combination with dyslipidemia, as well as their dose-response relationship(Bobb, Claus Henn, Valeri, & Coull, 2018). All statistical analyses were performed using the R language. $P < 0.05$ was considered statistically significant.

We performed stratified analyses by age, gender, race/ethnicity, PIR, education, marital status, smoking status, alcohol consumption, and PA(quartiles) based on both of the SMLR and WQS approaches. In interaction analyses, interaction terms were introduced into the same regression model as covariate. We had further conducted a battery of sensitivity analyses to assess the robustness of our results. First, we adjusted the total energy consumption variables for each individual. Second, we screened individuals exposed to extreme PIR values, extreme BMI values, or extreme PA MET values. Third, we adopted two different grouping methods, dividing the five metals into two groups according to the median concentration, and dividing into another three groups based on the tertile concentration(< 1st tertiles, 1st–2nd tertiles, or ≥ 3rd tertiles).

Results

Demographic characteristics

A total of 12,526 NHANES adult participants with valid lipid outcomes were included in five survey waves(2011–2020), representing 577,050,945 non-institutional residents of the United States(Fig. 1). The weighted mean age of participants in the final analysis was 45.84(0.40) years, of whom 52.5%(n = 6,581) were male and 47.5%(n = 5,945) were female participants. Among these responders, most were non-Hispanic white(39.8%, n = 4,980), followed by non-Hispanic black(22.5%, n = 2,813), Mexican American accounted for 12.0%(n = 1,503), and other race(including Multi-Racial, other Hispanic) accounted for 25.8%(n = 3,230). Furthermore, the age-adjusted prevalence of dyslipidemia was greater among female, older, Mexican American and those with a low level of PA, with the highest prevalence among female(67.2%), adults aged above 60(84.9%) and those who have insufficient PA(73.1%)(Fig. 1). There were 8,345 cases with dyslipidemia(66.6%) and 4,181 cases without(33.4%). Based on the weighted detailed characteristics of NHANES adults, we found significant differences between the dyslipidemia and the non-dyslipidemia participants in age, BMI, race/ethnicity, PIR, education, marital status, DM, hypertension, smoking status, alcohol consumption, moderate to vigorous PA, and total energy intake. The detailed weighted distributions of adult participants' characteristics classified by dyslipidemia were shown in Table 1, **Table S1**, **S2** presented the demographic characteristics and health variables of participants classified by five survey waves and blood concentrations of five metals, respectively. According to the results of spearman correlation analysis there was a mild correlation among five metals(Fig. 2).

Table 1
Survey-weighted detailed demographic characteristics of U.S adults with dyslipidemia status, NHANES 2011–2020

Demographic/Health variables	Age-adjusted dyslipidemia prevalence[(weighted, %(SE)]	Estimate U.S population(*n*)	Overall[*n*(%)]	Non-dyslipidemia[*n*(%)]	Dyslipidemia[*n*(%)]	*P*-value[b]
Total participants	66.5(0.75)	577,050,945	12,526(100.0)	4,181(33.4)	8,345(66.6)	-
Age(years)	-	-	45.84 ± 0.40	38.22 ± 0.43	49.69 ± 0.41	**< 0.001**
20–39	49.0(1.09)	231,788,482	4,749(37.9)	2,369(61.0)	2,380(29.6)	**< 0.001**
40–59	73.8(1.41)	211,533,651	4,276(34.1)	1,220(28.6)	3,056(40.8)	
60-	84.9(0.97)	133,728,812	3,501(28.0)	592(10.5)	2,909(29.6)	
Sex						
Male	65.8(1.06)	300,215,771	6,581(52.5)	2,255(54.0)	4,326(51.0)	0.080
Female	67.2(1.04)	276,835,174	5,945(47.5)	1,926(46.0)	4,019(49.0)	
BMI(kg/m^2)	-	-	29.01 ± 0.12	26.84 ± 0.15	30.11 ± 0.14	**< 0.001**
Race/Ethnicity						
Non-Hispanic White	66.1(0.96)	389,969,238	4,980(39.8)	1,539(65.0)	3,441(68.9)	**< 0.001**
Non-Hispanic Black	58.9(1.07)	56,110,383	2,813(22.5)	1,155(12.4)	1,658(8.4)	
Mexican American	70.1(1.62)	46,353,247	1,503(12.0)	464(8.0)	1,039(8.0)	
Other Race(including Multi-Racial, other Hispanic)	69.5(1.33)	84,618,077	3,230(25.8)	1,023(14.5)	2,207(14.7)	
PIR	-	-	3.15 ± 0.04	3.02 ± 0.05	3.21 ± 0.05	**< 0.001**
Below poverty(< 1.0)	65.2(1.75)	75,273,967	2,323(18.6)	832(15.3)	1,491(11.9)	**< 0.001**
Above poverty(≥ 1.0)	66.6(0.76)	501,776,978	10,203(81.5)	3,349(84.7)	6,854(88.1)	
Education attainment						
Less Than 9th Grade	69.1(2.53)	14,615,146	691(5.5)	160(2.1)	531(2.8)	**< 0.05**
9-11th Grade(including 12th grade with no diploma)	70.2(1.68)	38,516,142	1,223(9.8)	379(6.0)	844(7.0)	
High School Grad/GED or Equivalent	68.8(1.26)	134,414,709	2,769(22.1)	864(21.6)	1,905(24.2)	
College Graduate or above	62.8(1.17)	198,769,092	3,621(28.9)	1,314(37.7)	2,307(32.8)	
Some College or AA degree	67.7(1.17)	190,735,857	4,222(33.7)	1,464(32.7)	2,758(33.2)	
Marital status						
Widowed/Divorced/Separated	68.4(1.96)	94,066,956	2,397(19.1)	626(12.9)	1,771(18.0)	**< 0.001**
Never Married	64.0(1.70)	124,929,261	2,715(21.7)	1,334(32.3)	1,381(16.3)	
Married/Living with partner	68.7(0.86)	358,054,728	7,414(59.2)	2,221(54.8)	5,193(65.7)	
Diabetes mellitus						
Yes	81.3(1.48)	107,050,453	2,945(23.5)	508(8.3)	2,437(23.7)	**< 0.001**
No	64.1(0.82)	470,000,492	9,581(76.5)	3,673(91.7)	5,908(76.3)	
Hypertension						
Yes	74.9(1.29)	194,169,938	4,689(37.4)	981(20.7)	3,708(40.2)	**< 0.001**
No	63.9(0.85)	382,881,007	7,837(62.6)	3,200(79.3)	4,637(59.8)	
Smoking status						
Never	65.6(0.85)	331,887,034	7,228(57.7)	2,593(61.2)	4,635(55.7)	**< 0.001**

Demographic/Health variables	Age-adjusted dyslipidemia prevalence[(weighted, %(SE)]	Estimate U.S population(*n*)	Overall[*n*(%)]	Non-dyslipidemia[*n*(%)]	Dyslipidemia[*n*(%)]	*P*-value[b]
Former	66.3(1.50)	141,851,401	2,879(23.0)	749(20.8)	2,130(26.5)	
Current	68.6(1.23)	103,312,510	2,419(19.3)	839(18.0)	1,580(17.8)	
Alcohol consumption						
Never	67.3(1.55)	47,822,321	1,406(11.2)	407(7.8)	999(8.6)	**< 0.001**
Former	74.6(2.09)	36,737,338	877(7.0)	194(4.2)	683(7.5)	
Current	66.1(0.82)	492,491,286	10,243(81.8)	3,580(88.0)	6,663(84.0)	
Moderate to vigorous PA(MET minutes/week)	-	-	5197.83 ± 119.14	6005.94 ± 154.04	4789.12 ± 130.08	**< 0.001**
Quartile1(< 880)	73.1(1.27)	130,971,121	3,133(25.0)	792(16.0)	2,341(26.1)	**< 0.001**
Quartile2(880–2400)	66.6(1.40)	154,535,441	3,201(25.6)	1,018(25.7)	2,183(27.3)	
Quartile3(2400–6520)	63.0(1.24)	147,305,818	3,064(24.5)	1,164(29.2)	1,900(23.7)	
Quartile4(> 6520)	64.7(1.26)	144,238,565	3,128(25.0)	1,207(29.1)	1,921(22.9)	
Total energy intake(kcal)	-	-	2121.11 ± 12.08	2178.92 ± 17.50	2093.04 ± 14.98	**< 0.001**
Quartile1(< 1516.875)	66.8(1.18)	117,238,247	2,692(25.0)	785(21.6)	1,907(23.5)	**< 0.05**
Quartile2(1516.875–1965.5)	68.4(1.55)	131,194,320	2,695(25.0)	819(23.8)	1,876(26.5)	
Quartile3(1965.5–2544)	65.6(1.20)	133,897,373	2,690(25.0)	923(27.2)	1,767(25.6)	
Quartile4(> 2544)	65.7(1.29)	130,034,901	2,691(25.0)	991(27.4)	1,700(24.4)	
Serum cotinine(ng/mL)[a]	-	-	52.129(47.381, 56.877)	55.855(48.595, 63.114)	50.245(45.666, 54.824)	0.088
Cd(μg/L)[a]	-	-	0.437(0.420, 0.453)	0.410(0.384, 0.437)	0.450(0.429, 0.470)	**< 0.05**
Pb(μg/dL)[a]	-	-	1.190(1.138, 1.242)	1.035(0.991, 1.079)	1.268(1.200, 1.337)	**< 0.001**
Total Hg(μg/L)[a]	-	-	1.455(1.326, 1.585)	1.320(1.222, 1.418)	1.524(1.361, 1.687)	**< 0.05**
Mn(μg/L)[a]	-	-	9.615(9.521, 9.709)	9.567(9.384, 9.750)	9.640(9.531, 9.748)	0.507
Se(μg/L)[a]	-	-	194.560(193.328, 195.792)	190.932(189.690, 192.174)	196.394(194.947, 197.842)	**< 0.001**
Survey wave						
2011–2012 wave	68.9(1.48)	149,762,903	2,911(23.2)	932(24.1)	1,979(26.9)	0.390
2013–2014 wave	65.9(1.38)	76,339,890	1,689(13.5)	558(13.4)	1,131(13.2)	
2015–2016 wave	66.9(1.19)	76,959,808	1,503(12.0)	496(13.0)	1,007(13.5)	
2017–2018 wave	65.8(2.07)	137,111,996	2,440(19.5)	814(24.5)	1,626(23.4)	
2019–2020 wave	64.9(1.40)	136,876,348	3,983(31.8)	1,381(25.0)	2,602(23.1)	

Footnotes: Continuous variables are presented as mean ± SE or median(interquartile range), and categorical variables are presented as *n*(%).

[a] Presented as median(interquartile range).

[b] P-value based on survey t-test for binominal groups, and based on chi-square test in the qualitative variables. P-values in bold indicate statistical significance.

Abbreviations: AA, Associate's Degree; BMI, Body Mass Index; GED, General equivalent diploma; NHANES, National Health and Nutrition Examination Survey; PA, Physical activity; PIR, Poverty income ratio; SE, Standard error; Cd, Cadmium; Pb, Lead; Hg, Mercury; Mn, Manganese; Se, Selenium.

Relationship between metals and dyslipidemia(Based on the SMLR, WQS and BKMR)

Based on the SMLR, crude model showed that all the single metals significantly increased the risk of dyslipidemia[Cd, Crude odds ratio(COR) = 1.243, 95%CI:1.121, 1.379); Pb, (COR = 2.000, 95%CI:1.799, 2.225); Total Hg, (COR = 1.326, 95%CI:1.194, 1.472); Mn, (COR = 1.214, 95%CI:1.093, 1.348); Se, (COR = 1.793, 95%CI:1.612, 1.995);]. After full statistical adjustment, compared with the lowest quartile of metal exposure, only four single metals with the highest quartile were associated with dyslipidemia[Pb, (AOR = 1.332, 95%CI:1.165, 1.522); Total Hg, (AOR = 1.264, 95%CI:1.120, 1.472); Mn, (AOR = 1.181, 95%CI:1.064, 1.334); Se, (AOR = 1.771, 95%CI:1.576, 1.992);] except Cd(AOR = 1.057, 95%CI:0.909, 1.229). A linear trend test showed highly significant results for all types of metal exposures(Table 2).

Table 3 revealed the results of the association between total WQS index and dyslipidemia, along with an estimated chemical weight of each metal(Fig. 3). Similar results for the association between combined effect of total metals and dyslipidemia were obtained with no(COR = 1.639, 95%CI:1.526, 1.761, P-value < 0.001) or full(AOR = 1.310, 95%CI:1.216, 1.411, P-value < 0.001)covariate adjustment. As regard to the weights of metal pollutants, Se(58.7%) ranked the first, followed by Total Hg(14.6%), Pb(11.1%) and Cd(9.2%) while Mn(6.4%) ranked at the bottom(Fig. 3).

For the BKMR results, the results concerning the exposure-response of single metals exposure as well as their joint effect on dyslipidemia after adjustment for confounding factors were illustrated in Fig. 4. A linear correlation was observed between several single metals and dyslipidemia risk(Fig. 4A). The risk of dyslipidemia was shown to be positively correlated with exposure to all the metal chemical mixtures(Fig. 4B). Dyslipidemia risk ratio was significantly influenced by the joint effect of five metals above the 50th percentile. What is more, there is an apparent upward trend in dyslipidemia risk if metal chemicals were above this level(Fig. 4B).

Subgroup And Sensitivity Analyses

Subgroup analyses of five metals exposure and dyslipidemia were presented in **Table S3** to **S7**. Young adults(20–39 and 40–59 years old) who were exposed to several single metals(Cd, Total Hg and Mn) were more likely to develop dyslipidemia compared with elderly(above 60 years old). Gender difference was observed in participants with exposure to Cd and Mn. For race item, based on the results of Cd, Total Hg and Mn, Non-Hispanic White and other race groups seemed to have a higher risk of dyslipidemia than Non-Hispanic Black and Mexican American groups, but with Se exposure, the risk for developing dyslipidemia was detected in all races. Significant differences were also found in terms of other subgroups such as education attainment, household income, alcohol consumption and so on. For WQS subgroup analyses, we found that younger adults had a higher risk index of dyslipidemia than elderly, male were more prone to dyslipidemia than female, and adults with DM and hypertension were more likely to develop dyslipidemia. Other items such as smoking status, alcohol consumption and PA level were not significantly different regarding the association between metals and dyslipidemia(Table 3).

Results of the sensitivity analysis were generally in agreement with the results of the main study(Shown in **Table S8** to **S13**). After further adjustment for individual total energy confounders, and exclusion of the extreme BMI value and PA MET consumption, single metals exposure remained statistically significantly associated with the risk of dyslipidemia. Furthermore, dyslipidemia risks were higher in the groups with more exposure to metals, according to the cut-off value(median or tertiles) used for classifying participants into different groups.

Discussion

In this study, we utilized a representative and ethnically diverse dataset to test the association between metals and odds of dyslipidemia among general adults. It was found that either single Pb, Total Hg, Mn or Se was positively associated with dyslipidemia and, the combined metal effect was also associated with dyslipidemia ratio.

A high dyslipidemia prevalence(66.5%) in general U.S adults was detected by our study, which was basically in line with the prevalence of dyslipidemia(59.6%) in previous epidemiological studies(Okekunle, Asowata, Adedokun, & Akpa, 2021). Meanwhile, a high dyslipidemia prevalence was found among females(67.2%) and people aged over 60 years old(84.9%). Faced with a high morbidity, dyslipidemia precaution and control in the U.S. thus remain a formidable task that calls for effective countermeasures and intense efforts. Over the past few decades, evidence has reported that the risk of dyslipidemia may be increased by environmental toxicants, including Pb, Hg, and Se(Hx, Yu, Bx, & Yh, 2020; Joachim et al., 2008; Kang et al., 2021b). In our study, a similar finding was observed that four single metals, PB, Total Hg, Mn and Se, were significantly associated with an increased risk of dyslipidemia. Several possible mechanisms of such metals may account for this association. First, in spite of that we have fail to found a positive association between Cd and dyslipidemia, the validity study suggested that Cd was suspected to deplete glutathione and sulfhydryl groups from proteins to produce the reactive oxygen species, which can cause oxidative stress, and thus trigger dyslipidemia(Kuo, Moon, Thayer, & Navas-Acien, 2013). Furthermore, it was possible that Pb had a toxic effect on the liver and oxidized the cells' membranes(Liyun et al., 2018; Planchart, Green, Hoyo, & Mattingly, 2018), and brought about hepatotoxicity in rats, which indicates that Pb might directly affect liver function, namely, interfering with the synthesization of lipids(Abdel Moneim, 2016; Mabrouk, Bel Hadj Salah, Chaieb, & Ben Cheikh, 2016). One study with a limited sample size of the adolescents populations from developing countries investigated the joint effects of several metals mixtures on dyslipidemia(T. Luo et al., 2022). Surprisingly, the finding from this study that no positive correlations were observed between chromium(Cr), Ferrum(Fe), Zinc(Zn), Arsenic(As), Strontium(Sr), Cd, and Pb and dyslipidemia expect for Zn was inconsistent with the previous evidence. What’s more, the association between mixed metals on dyslipidemia found in this study also failed to reach statistical significance, which contradicted with the findings of numerous prior studies concerning combined metals and health-related outcomes such as CVD and hearing loss(Guo et al., 2022; Liang et al., 2022) and no previous study yielded similar result among adolescents population(Christensen, Werner, & Malecki, 2015).

Although some established potential risk factors for dyslipidemia(e.g., hypertension) are well known, studies examining metals and dyslipidemia still need to be conducted. Our finding showed a synergistic effect of all five metals(Cd, Pb, Total Hg, Mn and Se) on dyslipidemia when several metals were exposed simultaneously to individuals. The combined effect of other different metals including Cd, Sr and Pb were also confirmed as a risk factor for dyslipidemia in another study targeted at the elderly in China rather than general populations(Zhu et al., 2021). As these metals accumulate in the bones, they continuously interact with each other in the blood(Godt et al., 2006; Qu, Zhao, Ren, & Qu, 2012). This may be partly explained by the fact that the human body can be oxidized by both Cd and Pb, while Sr, along with Cd and other metals, may damage arterial endothelial cells(Baynes, 2007). However, it was strange that each of the above metal elements was not found to be significantly associated with dyslipidemia in this study. Compared with the above mentioned studies on the effect of metals on health outcomes, our study differs from them in study design, age of population, sample size and region, which may explain the discrepancy in our conclusions. On the other hand, however, it's worth noting that combined exposure to several metals, namely, vanadium(V), cobalt(Co) and aluminium(Al) within a certain concentration was associated with a decreased risk of dyslipidemia(Alissa, Bahijri, Lamb, & Ferns, 2004; Shahi, Haidari, & Shiri, 2011). As essential trace elements inside the human body, V and Co can prevent endogenous cholesterol from synthezing and speed up its decomposition to a certain extent. However, the underlying mechanism for this process remained poorly understood. It is obvious that exploration of the specific mechanism how combined metal exposure interfered with dyslipidemia requires additional researches.

Analyses of subgroups showed dyslipidemia risks increased in almost all the subgroups. Among males with dyslipidemia who were exposed to multiple metals, there were significant differences between the groups, which was in agreement with previous evidence(Kang, Shin, & Kim, 2021a). For other subgroup items, metals are more detrimental to the young than the elderly population, which were potentially attributable to the poor environmental conditions, unhealthy lifestyles, or bad eating habits(Skinner, Perrin, Moss, & Skelton, 2015; Ume et al., 2017). At the same time, young adults' lipid level lowered the risk of coronary heart disease resulted from aging in the future(Marie et al., 2015). Consequently, under direct blood metals effects, risks of dyslipidemia decreased with age. So far the underlying connection between metals concentrations in the blood and possible moderating biological processes in the progress of coronary vascular disease and time-varying effects, such as age, has not been completely illustrated by other research.

The major strength of the present study is that we identified a robust association between metals and dyslipidemia, which persisted after controlling for a wide range of relevant demographic confounders. More regression approaches and sensitivity analyses were performed for providing further validation of our findings. Additionally, with the well-characterized NHANES datasets, the large sample size and the nationally representative sample of U.S population, which contributes to the generalizability of our findings in public health and medical practice. Notwithstanding the above strengthens, there still exist some limitations. First, owing to the cross-sectional nature of NHANES study design, whether individual adults in our study all have been exposed to metals cannot be assured, it is therefore possible to underestimate the influence of blood metals levels on dyslipidemia stratified by age, gender or other demographic factors. Moreover, we could not identify direct causal relationship between metals and dyslipidemia. Second, restrictions by the NHANES on blood sample collecting for metals limited the number of participants that we were able to include. Thus, we can only based on the analysis for the joint effect of five blood metals for dyslipidemia. Subsequent studies with more metals on this issue should be performed.

Conclusions

Overall, based on the national estimates of 557.1 millions of five successive cycles of representative U.S population, we found a high dyslipidemia prevalence among U.S general adults, particularly in people aged 20–39 years old. Single metals including Pb Total Hg, Mn and Se were all associated with an increased risk of dyslipidemia, and moreover, mixed metals exposure was also related to the dyslipidemia ratio. Prospective studies may focus on the link between mixture exposures and dyslipidemia in the future so as to offer an insight into the complexity of biological mechanisms to understand how chemical mixtures affect dyslipidemia.

Abbreviations

AA, Associate's Degree; Al, Aluminium; AOR, Adjusted odds ratio; As, Arsenic; BKMR, Bayesian kernel machine regression; BMI, Body Mass Index; Cd, Cadmium; CDC, Centers for Disease Control and Prevention; CI, Confidence intervals; Co, Cobalt; COR, Crude odds ratio; Cr, Chromium; CVD, Cardiovascular disease; DM, Diabetes mellitus; FBG, Fasting blood glucose; Fe, Ferrum; GED, General equivalent diploma; HDL-C, High-density lipoprotein cholesterol; Hg, Mercury; ICP-MS, Inductively coupled plasma mass spectrometry; LDL-C, Low density lipoprotein cholesterol; LOD, Limit of detection; MET, Metabolic equivalent; Mn, Manganese; NCHS, National Center for Health Statistics; NHANES, National Health and Nutrition Examination Survey; PA, Physical activity; Pb, Lead; PIR, Poverty-to-income ratio; Q, Quartile; Se, Selenium; SE, Standard error; SMLR, Survey-multivariable logistic regression; Sr, Strontium; TC, Total cholesterol; TGs, Triglycerides; V, Vanadium; WQS, Weighted Quantile Sum; Zn, Zinc.

Declarations

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Ethics approval and consent to participate: The protocols of NHANES were approved by the institutional review board of the National Center for Health Statistics, CDC. Written informed consent was obtained from each participant before participation in this study.

Declaration of Competing Interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Consent to Publish: Not applicable.

Availability of data and materials: The datasets generated and analyzed during the current study are available in the NHANES databases repository, [https://www.cdc.gov/nchs/nhanes/participant.htm].

Credit authors statement

Jing-hong Liang: Conceptualization, Methodology, Data curation, and Writing - original draft & editing; **Ying-qi Pu**: Formal analysis, Data Curation, and Visualization; **Mei-ling Liu**: Formal analysis, Data Curation; **Li-xin Hu**: Software, Validation; **Wen-wen Bao**: Software, Validation; **Yu-shan Zhang**: Software, Validation; **Aerziguli Kakaer**: Methodology, Resources; **Yu Zhao**: Methodology, Resources; **Yi-can Chen**: Methodology, Resources; **Xue-ya Pu**: Methodology, Formal analysis; **Shao-yi Huang**: Methodology, Software; **Nan Jiang**: Validation, Resources; **Shan Huang**: Validation, Resources; **Guang-hui Dong**: Conceptualization, Writing - Review & Editing, and Supervision; **Ya-jun Chen**: Conceptualization, Writing - Review & Editing, Supervision, Funding acquisition, and Project administration.

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Tables

Tables 2 and 3 are available in the Supplementary Files section.

Figures

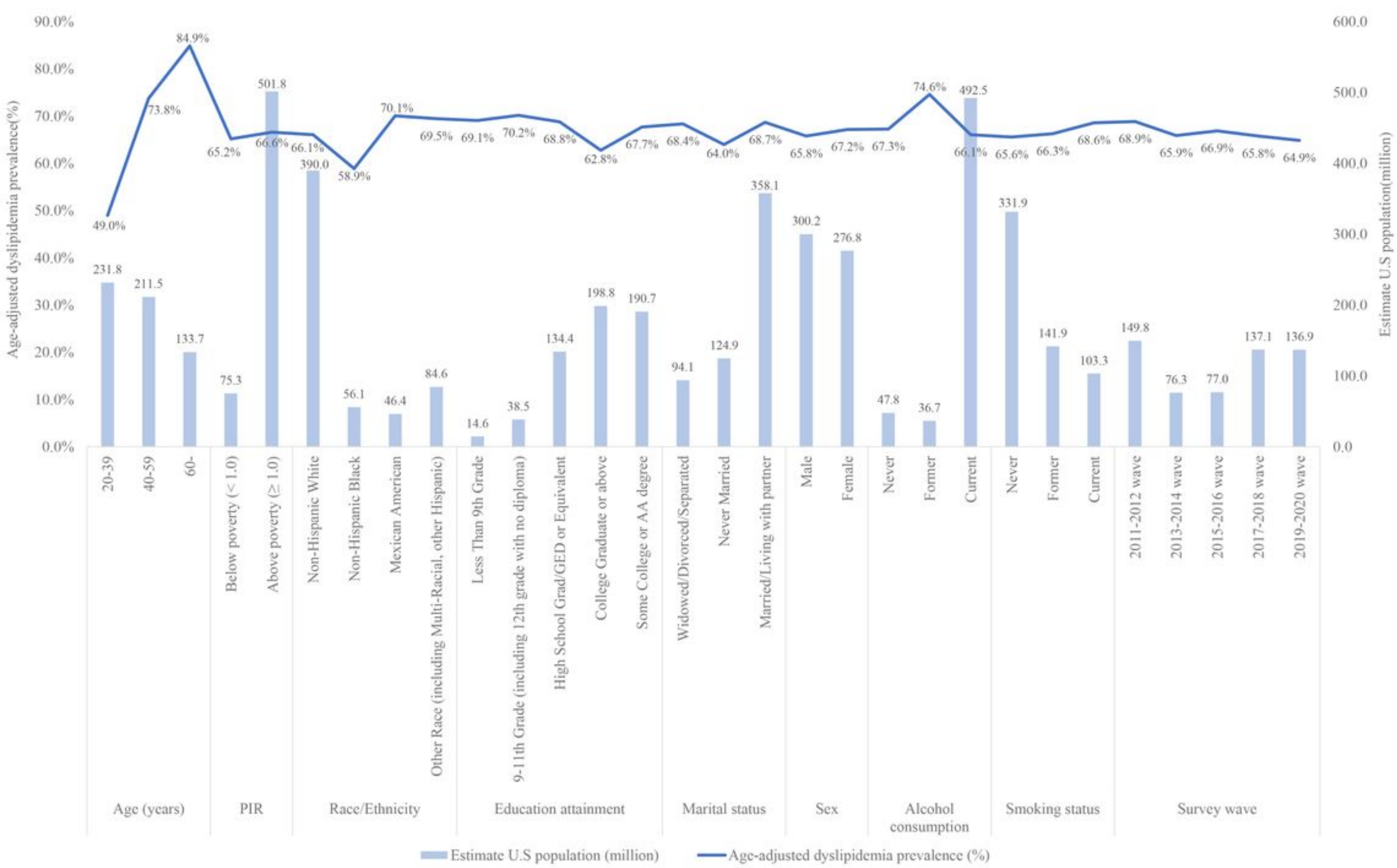

Figure 1

Age-adjusted dyslipidemia prevalence and estimate U.S population for the included 12,526 participants, NHANES 2011-2020

Abbreviations: AA, Associate's Degree; GED, General equivalent diploma; NHANES, National Health and Nutrition Examination Survey; PIR, Poverty income ratio.

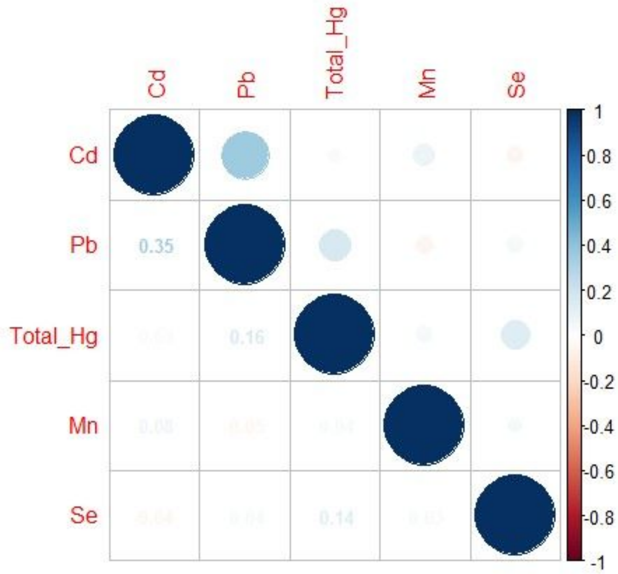

Figure 2

Spearman correlations between ln-transformed blood concentrations of five metals in the study participants(N = 12,526), NHANES 2011-2020

Abbreviations: NHANES, National Health and Nutrition Examination Survey; Cd, Cadmium; Pb, Lead; Hg, Mercury; Mn, Manganese; Se, Selenium.

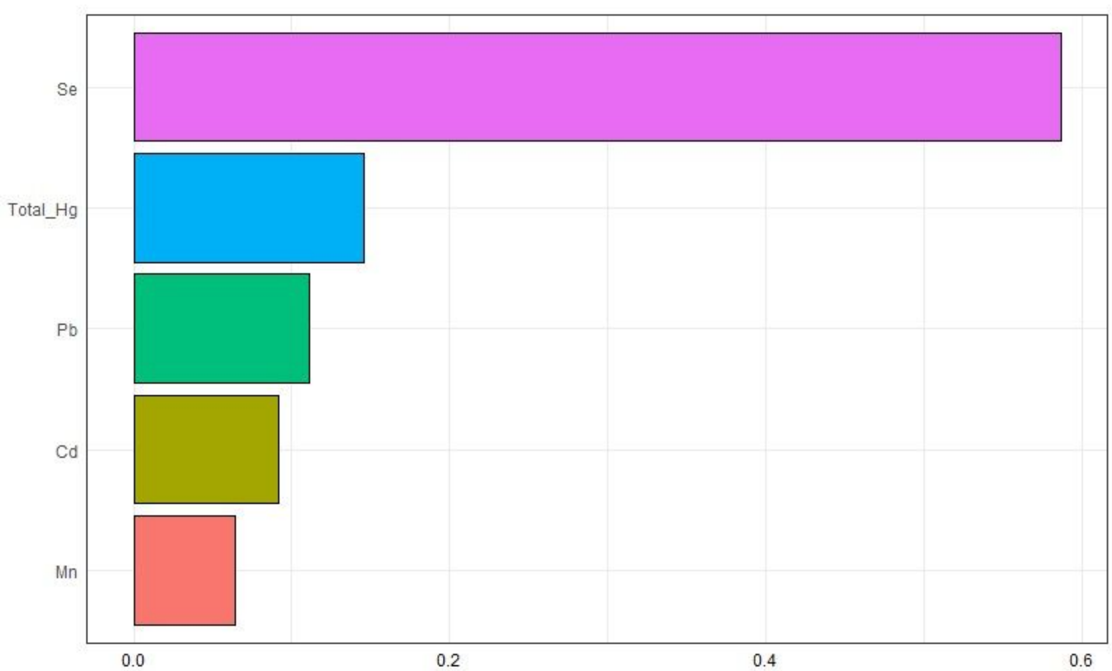

Figure 3

The WQS model regression index weights of ln-transformed blood concentrations of five metals for dyslipidemia outcome

The model was adjusted for age, sex, race/ethnicity, BMI, PIR, education attainment, marital status, serum cotinine(continuous, ng/mL), diabetes mellitus, hypertension, smoking status, alcohol consumption and PA(quartile).

Abbreviations: BMI, Body Mass Index; PA, Physical activity; PIR, Poverty income ratio; WQS, Weighted quantile sum; Cd, Cadmium; Pb, Lead; Hg, Mercury; Mn, Manganese; Se, Selenium.

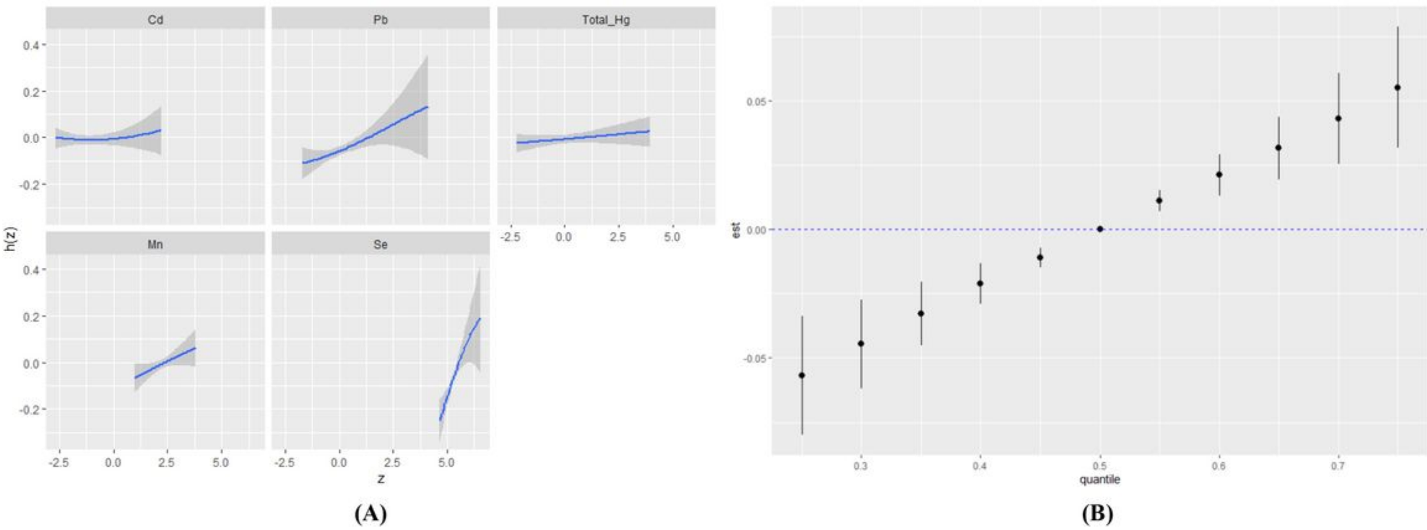

Figure 4

Exposure-response and joint effect of metals on dyslipidemia were estimated by BKMR models(N = 12,526), NHANES 2011-2020

The model was adjusted for age, sex, race/ethnicity, BMI, PIR, education attainment, marital status, serum cotinine(continuous, ng/mL), diabetes mellitus, hypertension, smoking status, alcohol consumption and PA(quartile). (A) Univariate exposure–response functions(95%CIs) between single metal and risk of dyslipidemia when other four metals fixed at the median(P_{50}). Y-axis represents the estimated difference in z-scores at a given level of metal compared to its median level when other four metals were at their medians. (B) Joint effect of the mixture on z-scores of five metals(Cd, Pb, total Hg, Mn, and Se) on dyslipidemia risk. Y-axis represents the estimated difference in z-scores when all the five metals were fixed at specific quantiles(ranging from 0.25 to 0.75), as compared to when metals were at the 50^{th} percentile. Dots indicate the estimate, and black vertical lines represent 95%CIs.

Abbreviations: BKMR, Bayesian Kernel Machine Regression; BMI, Body Mass Index; NHANES, National Health and Nutrition Examination Survey; PA, Physical activity; PIR, Poverty income ratio; Cd, Cadmium; Pb, Lead; Hg, Mercury; Mn, Manganese; Se, Selenium.

Supplementary Files

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