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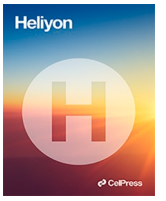

Research article

Relationship between exposure to multiple heavy metals and depressive symptoms in the US: The impact of alcohol consumption

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ABSTRACT

Background/aim: Although some heavy metals and alcohol consumption are known to have adverse effects on neurobehavioral symptoms, studies on the relationship between exposure to multiple metals and interaction between these factors are limited. In this study, we aimed to explore how multiple exposure to heavy metals with drinking habit in affecting depression using the National Health and Nutrition Examination Survey (NHANES) data.

Methods: Data from the U.S. NHANES between 2007 and 2014 were used to examine the cross-sectional relationships between heavy metal exposure and depression in adult over 20 years. After applying the exclusion criteria, 6021 subjects were included in the final analysis. We used four urinary metals, including mercury (Hg), cadmium (Cd), lead (Pb), and arsenic (As), as exposure variables. The Patient Health Questionnaire (PHQ-9) was used to assess the depression symptoms of the participants. Multivariate linear regression (MLR) and quantile g-computation models were applied to investigate the effects of individual and multiple heavy metal exposures on depression, respectively. We also performed stratified analysis according to the alcohol habit of the participants.

Results: The MLR models revealed that urinary Cd was positively associated with a continuous depression score ($\beta = 0.39$, 95 % confidence interval (CI): 0.24–0.53). Meanwhile, other urinary metals showed an insignificant positive relationship with depression. In quantile g-computation model, statistically significant positive relationship was observed between urinary heavy metal mixture and depression score (difference in PHQ-9 score increase = 0.32, 95 % CI: 0.14–0.50). When the model was stratified by drinking habit, a stronger relationship was observed in the heavy drinker group.

Conclusions: Comparing the results from different models, both individual urinary Cd and all the heavy metal mixtures were positively associated with depression. This association was stronger among those with heavy drinking habits. Future cohort studies are needed to confirm these associations and to clarify the causal relationship.

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1. Introduction

Depression is a common illness throughout the world, and it has been reported that approximately 280 million people suffer from depression worldwide [1]. Depression may cause serious health conditions and even lead to suicide. There are many socio-environmental, psychological or physical factors that are related to depression, such as alcohol consumption, physical activities or coincident chronic diseases [2–4]. Interestingly, heavy metals have also been reported as a risk factor for mental illness and depressive symptoms in recent studies [5–7].

Exposure to heavy metals has increased because of anthropogenic activities and modern industrialization [8]. It occurs as a result of water, soil or air contamination, as well as other environmental factors such as food or personal care products [9–11]. Although some heavy metals are necessary for life and called essential elements, which play a role in biochemical and physiological functions in the human body, many heavy metals are known to have various harmful effects in the human body. Particularly, mercury (Hg), cadmium (Cd), lead (Pb), and arsenic (As) are the most common heavy metals that cause human poisoning [12,13] including central nervous system damage and neurotoxicity [14,15].

Some studies have investigated the relationship between these single heavy metals and mental health, and Cd is mostly known to have an adverse effect. For example, Nguyen et al. reported that the doubling of serum Cd was associated with a 21 % increase in depression in South Korea [5], and Ayuso-Álvarez, A. et al. found that higher concentrations of Pb, Cd, and As in topsoil were associated with an increased probability of having a mental disorder, which is measured by General Health Questionnaire [7]. Meanwhile, previous studies have suggested that alcohol consumption is another risk factor for depression and may influence the effects of heavy metals in the human body, potentially exacerbating the neurotoxic effects and further increasing the risk of mental health issues [2, 16]. Another study also suggested that alcoholism may affect the metabolism and toxicity of heavy metals, as ethanol could enhance the absorption of these metals in the body [17].

Although the numerous studies have investigated the effects of exposure to single heavy metals, few studies have investigated the effect of poisonous heavy metal mixtures on depressive symptoms. Considering that people are not only exposed to individual metals but are simultaneously exposed to multiple metals, it is important to consider the effect of exposure to multiple metals on human health. Furthermore, understanding how these effects vary based on drinking habits is also necessary.

Therefore, in this study, we used cross-sectional data from the National Health and Nutrition Examination Survey (NHANES) and evaluated the effect of overall impact of four heavy metals (Hg, Cd, Pb and As) on depressive symptoms using a recently developed statistical method called quantile g-computation [18], and examined the differences in associations according to alcohol drinking behavior.

2. Methods

2.1. Study population

In this study, we used the dataset from the publicly available NHANES database, which comprises a national representative health survey conducted by the U.S. National Center for Health Statistics. This survey is designed to evaluate the health and nutritional status of adult and children in the United States, and it includes interviews and physical examinations [19]. NHANES examines approximately 5000 individuals from across the US each year, and a computer process randomly selects some, all, or none of the household members. Health interviews were conducted in the homes of respondents and health measurements were also performed in specially designed and equipped mobile centers. Demographic, socioeconomic, nutritional and health-related questions were asked during the interview, and laboratory tests were conducted by highly trained medical personnel.

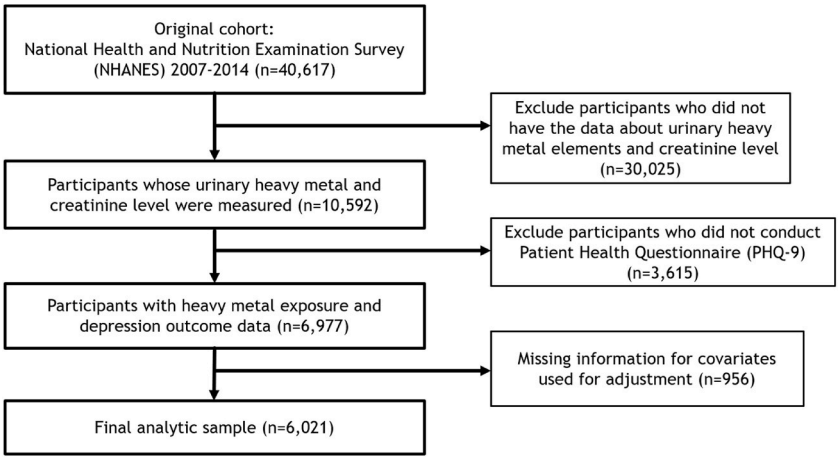

Fig. 1. Flow chart for selecting the study participants.

Since the covariates, moderate and vigorous recreational activities from physical activity data had consistent definitions from the 2007–2008 cycle onwards, and the current job's occupation group code had consistent definitions until the 2013–2014 cycle, we used data from four consecutive cycles (2007–2008, 2009–2010, 2011–2012, 2013–2014) in this study. We also included alcohol consumption habit as a covariate in the model and since only participants over the age of 20 were asked questions regarding their alcohol consumption habits, participants over the age of 20 were included in this study.

Fig. 1 shows the flowchart for selecting the study participants from the original cohort. There were 40,617 participants between 2007 and 2014, and we excluded participants without data on their urinary heavy metal and creatinine levels. Subsequently, we excluded the participants who did not complete the Patient Health Questionnaire (PHQ-9), which is our depression outcome. After excluding the participants without information on other covariates, 6021 participants were included in the analyses.

2.2. Assessment of heavy metal exposure

We used four heavy metals, including Hg, Cd, Pb, and total As from urine, as the main exposure variables because they are the most common heavy metals that cause human poisoning and are widely dispersed in the environment [12,20]. We did not include other metals, such as manganese or cobalt, which are essential elements in organism to specifically assess the mixture effect of harmful heavy metals in our main model [21].

Inductively coupled plasma-mass spectrometry (ICP-MS) [22] and inductively coupled plasma dynamic reaction cell mass spectroscopy (ICP-DRC-MS) were used to measure Pb and Cd, whereas ICP-DRC-MS was used to measure Hg and As. Meanwhile, urinary excretion is the major pathway for eliminating As from the mammalian body; thus, ICP-DRC-MS can achieve rapid and accurate quantification of the total urinary As concentration [23,24]. Reported results for all assays met the quality control and quality assurance performance criteria of the Division of Laboratory Science for accuracy and precision [25]. More details regarding the detection limit or methodology for each heavy metal measurement can be found in the NHANES website [23]. The concentrations of metals in the urine were expressed in μg/L.

2.3. Assessment of depression symptom (PHQ-9)

Participants performed the Patient Health Questionnaire (PHQ-9) at the Mobile Examination Center, where trained interviewers asked the questions using the Computer-Assisted Personal Interview (CAPI) system to assess the depression symptoms [26,27]. This self-report screening instrument comprised nine items on the frequency of depressive symptoms over the past two weeks before the exam (Supplementary Table 1). These nine items were created using the major depressive disorder diagnostic criteria in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). The items correspond to symptoms of anhedonia, low mood, sleep problems, low energy or fatigue, changes in appetite, feelings of worthlessness or guilt, concentration difficulties, psychomotor alterations, and thoughts of self-harm or death [28]. Scores ranging from 0 to 3 were given to each response category ("Not at all", "Several days", "More than half the days", and "Nearly every day"), and a total score was calculated between the range 0–27. A total score higher than 10 has been well validated and is commonly used to define moderate depressive symptoms in clinical studies [29,30]. Other cut-off points can also be used to define depressive symptoms. In this study, we used two depression outcomes: the continuous sum score of PHQ-9 and the binary depression response using the moderate depression cut-off score (PHQ-9 score $\geq$ 10).

2.4. Covariates and statistical analyses

To identify the confounding factors and covariates, we used a directed acyclic graph (DAG) to select a set of plausible covariates that will be included in our final statistical model (Supplementary Fig. 1). The final covariates were age, sex, body mass index (BMI), alcohol consumption (Non-heavy drinker, heavy drinker), citizenship (Citizen, non-citizen), marital status (Married, widowed, divorced, separated, never married, living with partner), poverty–income ratio (PIR) (<1, ≥ 1), physical activity (No moderate/vigorous activity, moderate activity, vigorous activity), occupation (White-collar, Science/art/education and entertainment, health-related, Sales/finance/business related, office/administrative support, food and household related, agriculture, protective service and armed forces, blue-collar, unemployed), and urinary creatinine level. We added urinary creatinine level in the final model because the creatinine concentration corrects for variations in urine diluteness at the time of measurement [31]. We also classified the participants' current jobs into ten occupation groups following previous studies [32,33].

To define the alcohol consumption group, we used two questions related to their alcohol consumption habit, including "In the past 12 months, how often did you drink any type of alcoholic beverage?" and "In the past 12 months, on those days that you drank alcoholic beverages, on the average, how many drinks did you have?". Considering the guidelines of the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and previous references [34,35], we classified heavy drinkers as men and women who consumed more than four (men) and three (women) drinks on any day, respectively.

For the statistical analysis, baseline characteristics of the participants and the distribution of urinary heavy metal exposure were reported. Additionally, the characteristics of the depression (PHQ-9 score ≥ 10) and non-depression groups (PHQ-9 score <10) were compared using χ^2 test for categorical variables and t-test for continuous variables. Moreover, the correlations between the concentrations of the four heavy metals were computed using Pearson's correlation coefficients. Multivariate linear regression (MLR) and logistic regression were used to identify the effect of a single heavy metal on the PHQ-9 score. We also set the heavy metal exposure levels below the 25th percentile as reference categories and categorized into quartiles with three cut-off points (25th, 50th, and 75th

percentiles) to compare the results based on the lowest quartile of heavy metal exposure. We tested the interaction effects between alcohol consumption and heavy metals in each MLR model and $p < 0.10$ was considered statistically suggestive for interaction terms [36,37]. Afterward, the model was stratified by alcohol consumption group. We also performed restricted cubic spline regression with four knots to examine the nonlinearity in the associations between urinary heavy metals and the binary PHQ-9 outcome.

To estimate the association between the four heavy metal mixtures and depression, we used quantile g-computation method, which is a novel statistical model that estimates the overall effect of exposures on the outcome when all the exposures increase by one quartile. In this method, the exposure variables are not constrained to have the same effect direction to the outcome [18]. In this model, all the exposures of interest are first converted into quartiles. A linear/logistic regression model is then used to fit the outcome onto the set of quantized exposures and covariates. Finally, by adding the regression coefficients for the exposures within the mixture, the overall mixture effect is defined. This model also calculates the weights for each exposure from the regression coefficients, which explains the proportion of negative or positive partial effects. We estimated the OR (95 % CI) of the binary response of PHQ-9 and the β (95 % CI) of the PHQ-9 score for a one-quartile increase in all the metals. Each of the four metals were natural log-transformed in regression and quantile g-computation analysis due to the skewed distribution. NHANES survey weight was not considered in our statistical analysis because of the difficulty to handling weight in the quantile g-computation model. R package 'qgcomp' version 2.8.6 was used to perform the quantile g-computation, and all statistical analyses were conducted with R (version 4.0.5).

3. Results

3.1. Characteristics of the participants and heavy metal exposure

Table 1 represents the baseline characteristics of the final study participants. From 6021 participants, the mean age of the participants was 49.0, and 12.39 % of the participants were considered heavy drinkers. We compared the characteristics of the depression

Table 1
Baseline characteristics of the selected study participants from NHANES, 2007 to 2014 (n = 6021).

	N (%) or mean ± SD[a]			
	Total	Depression (n = 558)	Non-depression (n = 5463)	P-value[b]
Age	49.02 ± 17.64	48.07 ± 15.94	49.12 ± 17.81	0.15
Sex				
Male	3019 (50.14)	193 (35.59)	2826 (51.73)	<0.001
Female	3002 (49.86)	365 (65.41)	2637 (48.27)	
BMI	29.05 ± 6.92	30.78 ± 8.71	28.87 ± 6.69	<0.001
Alcohol consumption				
Non-heavy drinker	5275 (87.61)	476 (85.30)	4799 (87.85)	0.10
Heavy drinker	746 (12.39)	82 (14.70)	664 (12.15)	
Citizenship				
Citizen	5244 (87.09)	497 (89.07)	4747 (86.89)	0.16
Non-citizen	777 (12.90)	61 (10.93)	716 (13.11)	
Marital status				
Married	3074 (51.05)	189 (33.87)	2885 (52.81)	<0.001
Widowed	465 (7.72)	54 (9.68)	411 (7.52)	
Divorced	670 (11.12)	98 (17.56)	572 (10.47)	
Separated	193 (3.21)	34 (6.09)	159 (2.91)	
Never married	1138 (18.90)	121 (21.68)	1017 (18.62)	
Living with partner	481 (7.99)	62 (11.11)	419 (7.67)	
Poverty income ratio (PIR)				
<1	1305 (21.67)	221 (39.61)	1084 (19.84)	<0.001
≥ 1	4716 (78.33)	337 (60.39)	4379 (80.16)	
Physical activity				
No moderate/vigorous activity	3125 (51.90)	397 (71.15)	2728 (49.94)	<0.001
Moderate activity	1646 (27.34)	110 (19.71)	1536 (28.12)	
Vigorous activity	1250 (20.76)	51 (9.14)	1199 (21.95)	
Occupation				
White-collar	294 (4.88)	11 (1.97)	283 (5.18)	<0.001
Science, art, education and entertainment	465 (7.72)	18 (3.23)	447 (8.18)	
Health-related	400 (6.64)	25 (4.48)	375 (6.86)	
Sales, finance, business-related	383 (6.36)	21 (3.76)	362 (6.63)	
Office, administrative support	377 (6.26)	21 (3.76)	356 (6.52)	
Food and household related	176 (2.92)	22 (3.94)	154 (2.82)	
Agriculture	29 (0.48)	0 (0)	29 (0.53)	
Protective service and armed forces	84 (1.40)	5 (0.90)	79 (1.45)	
Blue-collar	1002 (16.6)	47 (8.42)	955 (17.5)	
Unemployed	2811 (46.7)	388 (69.5)	2423 (44.4)	

[a] Unweighted mean ± SD and percentages.
[b] Comparison between depression (PHQ-9 score ≥ 10) and non-depression (PHQ-9 score <10) groups.

and non-depression groups, and the results showed that the proportion of females was significantly higher in the depression group than in the non-depression group. Furthermore, the proportions of the "no moderate/vigorous activity" group and participants with poverty income ratio (PIR) < 1 were significantly higher in the depression group. This result indicates that some socio-demographic variables including sex, poverty or exercise status should be considered as a covariate in the depression analysis.

Table 2 and Supplementary Fig. 2 show the distribution and Pearson correlation of the four urinary heavy metal levels. Since the distribution of heavy metal levels is skewed and values are all positive, we calculated the geometric mean. The mean of Cd (0.29 μg/L) and Pb (0.48 μg/L) were higher in the heavy drinker group. In addition, the strongest correlation was observed between Cd and Pb (r = 0.58).

3.2. Effect of exposure to a single heavy metal

In the single-metal regression models (Fig. 2), the results showed that Cd was positively associated with PHQ-9 score ($\beta = 0.39$, 95 % CI: 0.24–0.53) and binary PHQ-9 response (OR = 1.24, 95 % CI: 1.10–1.41). When an interaction term was included between alcohol consumption habit and heavy metal concentration in each model, Cd and Hg showed significant interaction effects suggesting that an effect modification by alcohol consumption habit exists. In the stratified analysis by alcohol consumption habit, Cd showed a significant association with two PHQ-9 scores in both alcohol consumption groups. In addition, Hg was positively associated with PHQ-9 score only in the heavy drinker group ($\beta = 0.43$, 95 % CI: 0.06–0.80).

In the linear regression model to identify the association between urinary heavy metal categorized in quartiles and depression score in the heavy drinker group (Supplementary Table 2), the result showed that the PHQ-9 score significantly increased at the second ($\beta = 1.10$, 95 % CI: 0.15–2.04), third ($\beta = 1.32$, 95 % CI: 0.30–2.34) and fourth ($\beta = 1.52$, 95 % CI: 0.43–2.61) quartile of Pb exposure compared to the lowest quartile. This association showed an increasing pattern according to the quartile groups. Cadmium also showed an increasing pattern according to the quartile groups and the result was marginally significant at the fourth quartile exposure compared to that in the lowest quartile.

We also examined the non-linear association between each heavy metal and binary PHQ-9 response by using restricted cubic splines (Supplementary Figs. 3, 4, 5). The linear shape of the curves for Cd, Pb, and As was more distinct in heavy drinkers compared to non-heavy drinkers, and a positive relationship was observed for these three metals in non-heavy drinkers.

3.3. Quantile g-computation results for heavy metal mixtures and depression

In Table 3, after adjusting for the covariates, the increasing concentrations of all the heavy metals by one quartile was associated with a 0.32 increase in PHQ-9 score (mean change in PHQ-9 per quartile increase = 0.32; 95 % CI: 0.14–0.50). In the stratified model by drinking habit, although a positive relationship of heavy metal mixtures was observed in both groups, the relationship was stronger in the heavy drinker group (mean change in PHQ-9 per quartile increase = 0.70; 95 % CI: 0.14–1.26). In the binary PHQ-9 model, a one quartile increase in all heavy metals was associated with higher odds of moderate depression (OR = 1.20, 95 % CI: 1.03–1.40). In the stratified analysis, only the heavy drinker group showed a significant relationship with moderate depression (OR = 1.80, 95 % CI: 1.15–2.83). In the sensitivity analysis, we performed the quantile g-computation in an unadjusted model and a model adjusted for different covariates, and the results showed a similar pattern and significance (Supplementary Table 3).

From the PHQ-9 score model (Fig. 3), Cd was assigned the largest positive weight in the total group whereas As was negatively weighted. This is because As shows negative coefficient in the model compared to other metals. In the non-heavy drinker group, Cd was assigned the largest positive weight and Hg was also assigned a very small positive weight. In the heavy drinker group, Cd, Hg, and Pb were assigned positive weights greater than 0.23. From the binary PHQ-9 score model, Cd and Pb were assigned positive weights in all the groups (Supplementary Fig. 6).

Table 2
Distribution of urinary heavy metal exposure stratified by alcohol consumption habits.

Group	**Heavy metal (μg/L)**	GM(GSD)	Percentile		
			25th percentile	50th percentile	75th percentile
Total	Cadmium	0.22 (2.77)	0.12	0.23	0.45
	Lead	0.44 (2.48)	0.25	0.45	0.80
	Mercury	0.36 (2.88)	0.16	0.35	0.75
	Arsenic	8.39 (3.11)	3.86	7.75	16.4
Non-heavy drinker	Cadmium	0.22 (2.85)	0.11	0.22	0.44
	Lead	0.44 (2.34)	0.25	0.45	0.79
	Mercury	0.36 (2.77)	0.16	0.36	0.76
	Arsenic	8.44 (2.93)	3.83	7.80	16.6
Heavy drinker	Cadmium	0.29 (2.75)	0.15	0.31	0.59
	Lead	0.48 (2.49)	0.30	0.51	0.82
	Mercury	0.35 (2.89)	0.17	0.33	0.70
	Arsenic	7.99 (3.13)	3.95	7.40	14.7

GM: geometric mean; GSD: geometric standard deviation

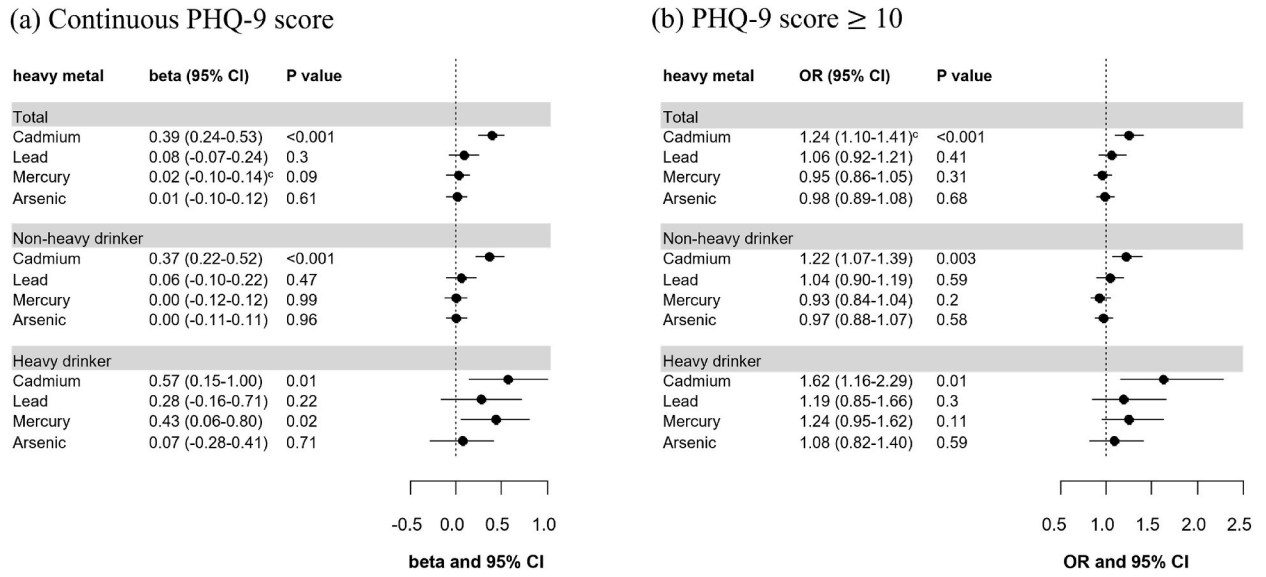

Fig. 2. Linear and logistic regression estimates of the association between individual metals and PHQ-9 score[ab].
[a] In the total group, the model was adjusted for age, sex, BMI, alcohol consumption, citizenship, marital status, poverty, physical activity, occupation and urinary creatinine level.
[b] In the stratified analysis by alcohol consumption habit, the model was adjusted for age, sex, bmi, citizenship, marital status, poverty, physical activity, occupation and urinary creatinine level.
[c] alcohol consumption interaction is statistically significant at p-value <0.1 after including the interaction term.

Table 3
Quantile g-computation estimates for the change in PHQ-9 score for a one quartile increase in all metals.

Group	PHQ-9 score	**PHQ-9 score ≥ 10**
	β (95 % CI)	OR (95 % CI)
Total[a]	0.32 (0.14–0.50)	1.20 (1.03–1.40)
Non-heavy drinker[b]	0.24 (0.05–0.43)	1.10 (0.93–1.30)
Heavy drinker[b]	0.70 (0.14–1.26)	1.80 (1.15–2.83)

[a] The model was adjusted for age, sex, BMI, alcohol consumption, citizenship, marital status, poverty, physical activity, occupation and urinary creatinine level.
[b] The model was adjusted for age, sex, BMI, citizenship, marital status, poverty, physical activity, occupation and urinary creatinine level.

4. Discussion

In this national cross-sectional study, we considered two main statistical models to evaluate the effect of heavy metal exposure on depression in adults. In the regression model, Cd level was significantly and positively related to both PHQ-9 score and binary PHQ-9 response. The most consistent association was between Cd exposure and depression, showing a significant positive association in the total population and within all the alcohol consumption groups. This result is consistent with those in past studies, which showed that Cd exposure may be related to depression or other mental health problems, such as memory loss [38,39]. For example, a study conducted in Korea identified that increased blood Cd level was significantly associated with depression in the elderly population, which was measured by the Korean version of the Geriatric Depression Scale-Short Form [38]. Another study on the behavior of rats also reported that Cd exposure may lead to behavioral pathologies, including affective and cognitive disorders [39].

When an interaction term was included between alcohol consumption habit and heavy metal concentration in the model, the results showed that heavy metal exposure affected depression in a different manner according to the alcohol consumption status. In the stratified analysis, the results showed that the magnitude of association between all the metals and depression increased in heavy drinkers compared to the people who are not heavy drinkers, showing that heavy drinkers could be more susceptible to metal toxicity compared to non-heavy drinkers. In heavy drinker group, both Cd and Hg were significantly and positively associated with PHQ-9 score.

Linear or logistic regression results are usually straightforward to interpret. However, in terms of environmental exposure, it is necessary to consider mixed environmental exposures to assess complex interactions between the exposures because, in reality, humans are simultaneously exposed to multiple pollutants [40]. Therefore, in this study, we performed quantile g-computation to consider the mixed exposure effect of heavy metals. The model showed a significant effect of heavy metal mixture on depression in the

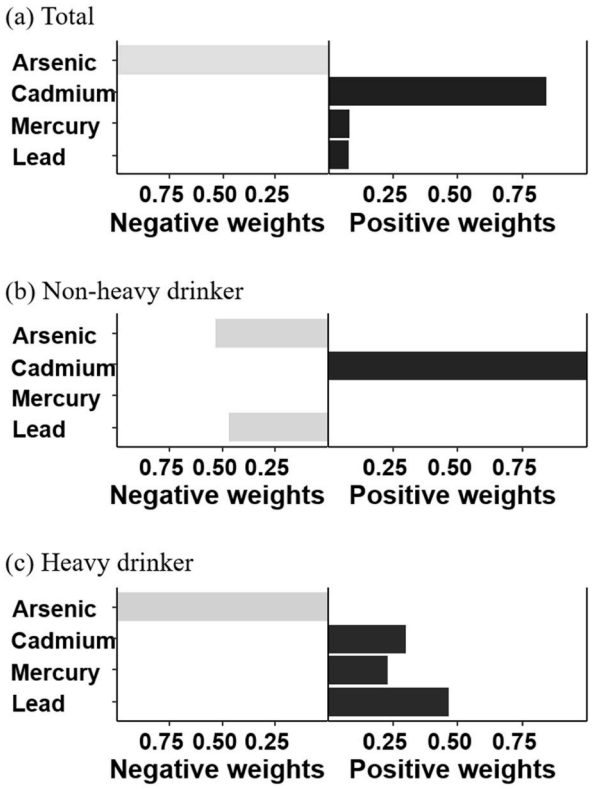

Fig. 3. Weights representing the proportion of the positive or negative partial effects for each metal in the quantile g-computation model.[a].
[a] Weight in quantile g-computation model that uses a continuous PHQ-9 score as an outcome.

total group, and the results of the quantile g-computation revealed an increased effect of heavy metal mixture on depression in the heavy drinker group. The weight plot of the quantile g-computation results also identified a partial effect for each metal in the model, and the results showed that Cd mainly dominated the positive partial effect in non-heavy drinkers, whereas multiple metals (Cd, Hg and Pb) shared a positive partial effect in heavy drinkers. Additionally, Pb showed a positive weight in the heavy drinker group, compared to a negative weight in the non-heavy drinker group, suggesting increased toxicity of Pb and Hg among heavy drinkers. In our model, As did not show any significant results with the depression. As is mostly known for its short-term poisoning effects, including vomiting or abdominal pain, and the first symptoms of chronic exposure to inorganic As are related to skin disorders or bladder and lung cancer [41].

Although the exact mechanism of heavy metal exposure and depression is still unclear, several toxicological studies have revealed some potential mechanisms by which exposure to heavy metals may have a lasting impact on the brain or similar effects [42,43]. Additionally, previous studies suggested that Cd changes the levels of dopamine, norepinephrine, and serotonin, or has a potential toxic effect on thyroid function which could be related to depressive symptoms [44–46]. In quartile analysis, Pb had a significant association with depression in the heavy drinker group. Although there are controversial results between the Pb exposure and depression in previous studies [47,48], possibly due to the differences in sample size or statistical model, some studies on Pb exposure have reported that Pb can interfere the catecholaminergic systems causing anxiety disorders and reducing serotoninergic activity in the frontal cortex and brainstem of rats [43,49].

Our results also suggested that heavy drinkers are susceptible to heavy metal effects. One rat study reported that ethanol increased the accumulation of Cd in their bodies and identified Cd-induced changes in the metabolism of bioelements such as zinc or copper [50]. In our results, considering that Cd and Pb levels were higher in heavy drinkers than in non-heavy drinkers, alcohol can be a factor that increases the retention of these metals and prolongs their effects in the human body. Additionally, previous studies have suggested that patients with alcohol use disorder are prone to reduced kidney function and increased metabolic syndrome, possibly related to the increased heavy metals in the body and their heightened toxicity [51].

One of the strengths of this study is that we used the NHANES database, which is constructed from a large, well-characterized sample from the general population of the United States. These characteristics enhanced the robustness of the analysis results. Moreover, compared to other studies focusing on the one or two cycles of NHANES to assess the effect of heavy metals or evaluate the depressions status, we combined four cycles of NHANES across eight years and maintained a sizable number of participants in the final statistical model. Additionally, since PHQ-9 depression measurement was continuously conducted across several cycles of NHANES and it has been widely validated in the general population [52], the adoption of PHQ-9 provided our study a reliable depression metric. We also selected the covariates using DAG to obtain minimal adjustment sets and minimize the bias introduced by over-adjustment

when estimating the associations [53]. Finally, in terms of statistical model, we used newly introduced quantile-g-computation, which maintains precision despite strong correlations between exposures and may be less affected from outlier because of its quantization characteristic [18].

However, there are also limitations to this study. First, this analysis was conducted based on its cross-sectional nature; hence, we could not determine whether heavy metal exposure preceded manifestation of depression without a prospective dataset. However, urine sample analysis is known to estimate chronic exposure to heavy metal and urine is a good representation of the chronic body burden of Cd because it has a high half-life of approximately 30 years in the human body [54]. Secondly, although we assessed the depression outcome based on well validated PHQ-9 measurement, it is a self-report instrument and participants were not diagnosed with depression by a psychiatrist. Leveraging electronic health records to identify depression could provide detailed clinical outcomes for more in-depth analysis. Moreover, the PHQ-9 asks participants about their depression symptoms over the past two weeks and does not measure their longer duration of depression. This self-reported questionnaire may lead to recall bias and could cause an underestimation or overestimation of depression. Future studies that investigate this relationship could consider the diagnostic aspect of depression and evaluate the association between heavy metal exposure and long-term depression.

In conclusion, our results showed that exposure to individual and mixtures of heavy metals may have an adverse effect on depression, and a heavy drinking habit could aggravate this association. Further evaluation should be conducted in other prospective cohort studies to validate the present results and better understand the impact of multiple exposures of heavy metals on depression in adults, children, and adolescents. Our results have public health implications, suggesting that continuous efforts are needed to mitigate the effects of poisonous heavy metals and to prevent heavy drinking habits in the population for the sake of mental health.

CRediT authorship contribution statement

Jiyoung Shin: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Yuan Luo:** Writing – review & editing, Supervision, Project administration, Methodology, Data curation, Conceptualization.

Data availability statement

As NHANES is a public database, the data is accessible to the general public at all times (http://www.cdc.gov/nchs/nhanes.htm).

Ethics approval and consent to participate

NCHS Research Ethics Review Board (ERB) reviewed and approved the NHANES study. All participants provided informed consent prior to participating in the 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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e40221.

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