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Associations of serum zinc, copper, and selenium with sleep disorders in the American adults: Data from NHANES 2011–2016

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ABSTRACT

Background: Even though various studies have been conducted to investigate the relationship between trace metals and sleep, few epidemiological studies have evaluated the relationship between trace metals and sleep disorders in American adults.
Objective: This study intended to evaluate the associations of serum zinc (Zn), copper (Cu), selenium (Se), Zn/Cu, Zn/Se, and Cu/Se ratios with sleep disorders in American adults.
Methods: We conducted a cross-sectional analysis of 3660 adults aged ≥18 years old who participated in the National Health and Nutrition Examination Survey (NHANES) 2011–2016. Binary logistic regression was employed to calculate the odds ratio (OR) and 95 % confidence interval (CI) of either serum trace metals or serum trace metals ratios with risks among sleep disorder phenotypes. The restricted cubic spline (RCS) model was additionally utilized to check the dose-response relationships between serum trace metals, serum trace metals ratios, and sleep disorders.
Results: Logistic regression demonstrated that higher serum Zn (OR: 0.70, 95 % CI: 0.51–0.97, $p = 0.035$), Zn/Cu (OR: 0.62, 95 % CI: 0.45–0.87, $p = 0.007$), and Zn/Se (OR: 0.68, 95 % CI: 0.49–0.95, $p = 0.025$) were related to a decreased likelihood of self-reported sleep disorders, and dose-response relationships were detected by the RCS models, after adjustment for sociodemographic, behavioral, and health characteristics. No associations between serum Cu, Se, Cu/Se, and sleep disorders were observed. The findings in the sensitivity analyses were consistent with these results.
Conclusion: Our study revealed that serum Zn, Zn/Cu, and Zn/Se were inversely associated with the risk of self-reported sleep disorders in US adults.

1. Introduction

Healthy/normal sleep patterns, often evaluated by healthy sleep scores, are characterized as early chronotype, sleep 7–8 h per day, reported never or rare insomnia symptoms, no self-reported snoring, and no frequent daytime sleepiness (Fan et al., 2020; Li et al., 2021). Sleep disorders, including insomnia, sleep apnea, narcolepsy, and restless leg syndrome, are one of the most common clinical problems which disturb sleep patterns (Karna and Gupta, 2022). Besides the direct negative influence on enthusiasm and mental state, sleep disorders have been reported to be associated with various adverse health outcomes, such as obesity, hypertension, type 2 diabetes, cardiovascular disease, and increased mortality (Huyett et al., 2021; Kase et al., 2021; Medic et al., 2017). Moreover, the prevalence of sleep disorders has been rising in the past decades and peaked at a high level, for instance, a recent study revealed that the prevalence of sleep disorders in American adults was 27.1 % (Kase et al., 2021). Since the high prevalence and correlation with various adverse health outcomes, exploring the risk factors of sleep disorders is of vital significance.

Essential trace metals refer to trace metals that performed critical

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functions in human bodies, such as anti-inflammation, regulation of cellular signaling (Skrajnowska and Bobrowska-Korczak, 2019), oxygen metabolism, antioxidant defense, and neurotransmitter synthesis (Gromadzka et al., 2020; Rayman, 2012), and the lack led to structural and physiological dysfunction while it would return to normal if receiving appropriate supplementation. Zinc (Zn), copper (Cu), and selenium (Se) were important trace metals in human health, which have been linked to the risk of cardiovascular diseases (Choi et al., 2018; Gać et al., 2021), cancers (Skrajnowska and Bobrowska-Korczak, 2019; Yarmolinsky et al., 2018; Lin and Yang, 2021), thyroid functions (Arthur et al., 1993; Beserra et al., 2021), depression (Wang et al., 2018; Słupski et al., 2020), etc. The associations between these three essential trace metals and sleep have recently been investigated as well. For instance, higher serum Zn or higher dietary Se intake can help American adults obtain an optimal (Jia et al., 2022) or longer sleep duration (Grandner et al., 2013), respectively. Previous studies also explored the relationship

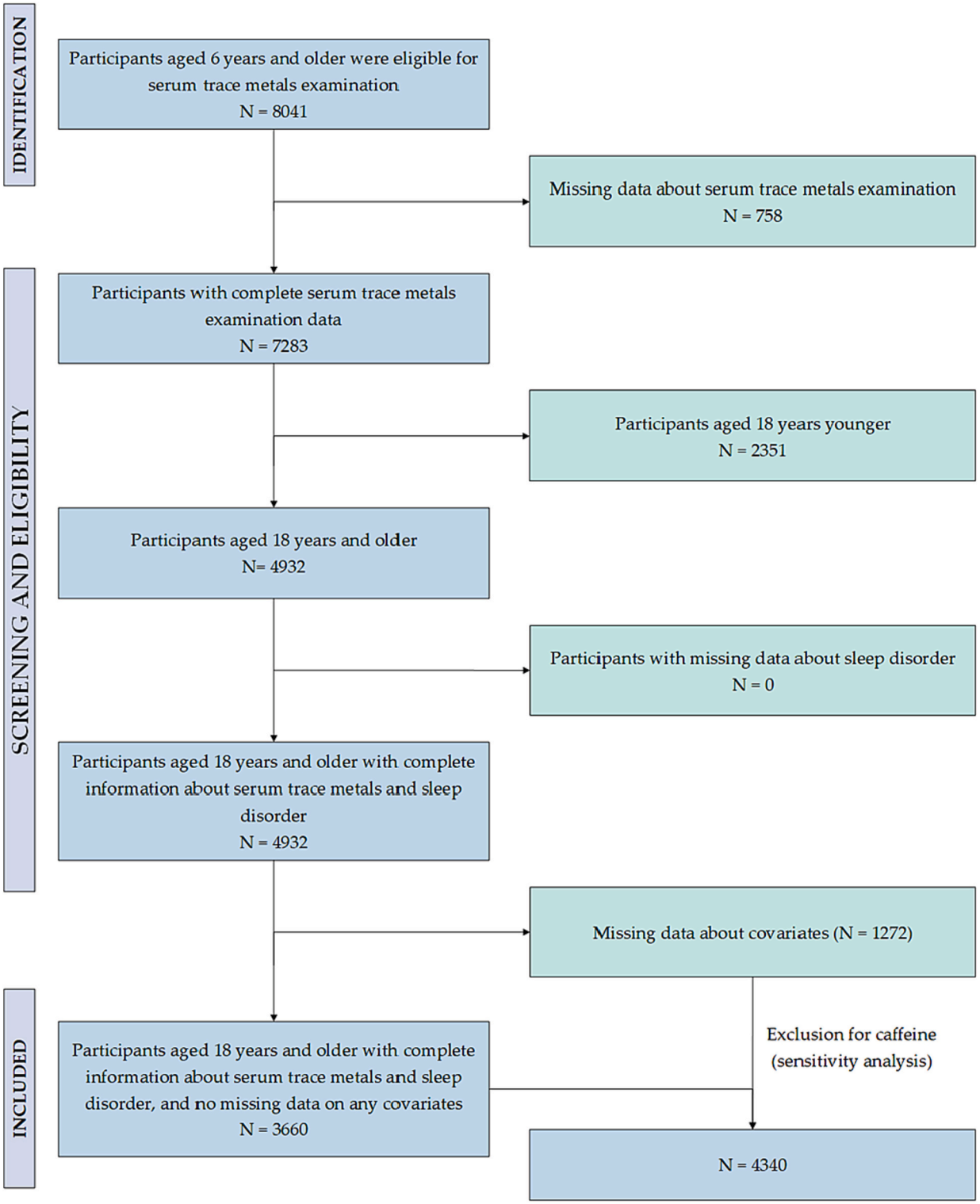

Fig. 1. Flowchart of the population included in our final analysis.

between serum Cu and sleep duration but reported a null association (Jia et al., 2022; Song et al., 2012).

Nevertheless, plenty of studies have made substantial contributions to our understanding of the associations between trace metals and sleep, but most of them focus on a single element and sleep duration but not various elements and sleep disorders. Although a few studies have investigated the relationship between trace metals and sleep disturbance or sleep quality (Jafari et al., 2020; Hajianfar et al., 2021; Asker et al., 2015; Akyuz et al., 2013), the findings are inconsistent. Additionally, the relationship between sleep disorders and the ratios among essential trace metals, which have been acknowledged to be significant indicators of function performance (Mirończuk et al., 2021; Ozturk et al., 2013), are rarely studied.

Certain studies have explored the potential mechanism of metals on sleep patterns in the past decades. For instance, Yoan Cherasse hypothesized that rapidly increasing serum zinc activates a signaling pathway that is responsible for the promotion of sleep, but it would be unrealistic that dietary zinc could be responsible for regulating sleep in physiological conditions (Cherasse and Urade, 2017). Copper was thought to play an antagonistic role in the activity of NMDA receptors (Vlachová et al., 1996), and NMDA receptor antagonists could increase nonrapid eye movement sleep (Campbell et al., 2002). As for selenium, it is an essential micronutrient that plays an important role in initiating and enhancing immunity as well as in immunoregulation, which may be associated with sleep disorders (Huang et al., 2012). In light of the above studies, this study aimed to explore whether the correlations between serum trace metals, serum trace metals ratios, and self-reported sleep disorders existed in a large and nationally-representative study of American general adults.

2. Materials and methods

2.1. Data source and participants

The data used in this study was obtained from the National Health and Nutrition Examination Survey (NHANES), which was a stratified, multistage probability sample representative of the civilian non-institutionalized U.S. population (Fain, 2017). Relevant information about NHANES can be accessed at https://www.cdc.gov/nchs/nhanes/index.htm.

The protocols for NHANES were approved by the National Center for Health Statistics of the Centers for Disease Control and Prevention Institutional Review Board, and informed consent was obtained from all participants, available online at https://cdc.gov/nchs/nhanes/irba98.htm.

Fig. 1 illustrated the procedures of the study design, sampling, and exclusion. American adults (aged ≥18 years old) who engaged in the 2011–2012, 2013–2014, and 2015–2016 cycles of NHANES were included in this study, as the interesting trace metals were only examined in these three survey waves.

A total of 8041 participants eligible for serum trace metals examination were initially included. After exclusion of participants aged <18 years old and missing data on any of the measures and covariates, a total of 3660 individuals were finally enrolled in our study, with an average age of 47.58 years old, a sex ratio of about 1:1, and the majority race of Non-Hispanic White. These included sample could represent a weighted population of 163 million non-institutionalized US adults.

2.2. Measures

2.2.1. Serum trace metals

Serum Zn, Cu, and Se were detected at the Environmental Health Sciences Laboratory of the CDC National Center for Environmental Health using the inductively coupled plasma dynamic reaction cell mass spectrometry following extensive quality control procedures. The lower limit of detection (LLOD) for serum Zn, Cu, and Se were 2.9 μg/dL, 2.5 μg/dL, and 4.5 μg/L, respectively, and all the data was above the LLOD for all three tests.

In the binary logistic models, serum trace metals and serum trace metals ratios were categorized into three groups (<Q_1, Q_1-Q_3, and >Q_3), according to the tertiles of the detected values. The cut-off values were presented in Table 1.

2.2.2. Sleep disorder

Sleep disorders were assessed with Sleep Disorder Questionnaire and participants were asked whether they have ever told a doctor or other health professional that they have trouble sleeping (Kase et al., 2021; Beydoun et al., 2016). And then participants were categorized according to the answers (yes or no), while the answers of "Do not know" and "Refused" were considered missing.

2.3. Covariates

Covariates of interest consisted of sociodemographic, behavioral, and health characteristics deemed a priori as potential confounders.

Sociodemographic variables consisted of age groups (18–39 years, 40–59 years, and ≥60 years), sex (female and male), race (Non-Hispanic White, Mexican American, Non-Hispanic Black, and Other/multiracial) (Vilar-Gomez et al., 2022), education level (less than high school graduate, high school graduate or GED, some college or above) (Scholes and Bann, 2018), family income level (0 – 130 % FPL, 130 % – 350 % FPL, and >350 % FPL, FPL refer to the ratio of family income to poverty) (Philbrook et al., 2020).

Behavioral characteristics comprised smoking (never, former, and current) (Purani et al., 2019), drinking (no or yes) (Koob and Colrain, 2020), physical activity (inactive or active) (Hartescu et al., 2015), and caffeine intake (<38.0 mg/day (<Q_1), 38.0–240.0 mg/day (Q_1 – Q_3), and >240.0 mg/day (>Q_3)). Individual physical activity was the total amount concerning work and recreational moderate to vigorous activity, and the value of 600 metabolic equivalents of task (MET) min/week, which have been consistently associated with substantial health benefits (Piercy et al., 2018), was treated as the cut-off point for physical activity inactive or active. The cut-off points of caffeine intake categories were defined by tertiles of the mean amounts of two 24-h dietary recalls.

Health factors included body mass index (underweight/normal, overweight, and obese) (Liu et al., 2017), hypertension (no or yes) (Moon et al., 2021), diabetes (no or yes) (Li et al., 2016), and depression (no or yes) (Fang et al., 2019).

2.4. Statistical analysis

Analyses were conducted according to the Centers for Disease Control and Prevention (CDC) guidelines for the analysis of NHANES data. Serum Zn, Cu, and Se were measured in a one-third subsample of participants aged 6 years and older, and accordingly, one-third laboratory environmental subsample A weights (WTSA2YR), stratum (SDMVSTRA), and primary sampling units (SDMVPSU) were taken into account for the complex survey design.

We summarized the baseline characteristics of participants by survey cycles (2011–2012, 2013–2014, and 2015–2016) and sleep disorder phenotypes (with or without sleep disorder). Variables were summarized as the frequency with their weighted percentages. The difference in percentages of baseline characteristics among survey cycles or sleep disorder phenotypes were tested using the Rao & Scott adjusted χ^2 test.

Stepped binary logistic regression was employed to calculate the odds ratio (OR) and 95 % confidence interval (CI) of either serum trace metals or serum trace metals ratios with risks among sleep disorder phenotypes. Sociodemographic characteristics were adopted in model I, behavioral characteristics were further added in model II, and model III was additionally adjusted for health factors.

Moreover, we examined possible dose-response relationships between serum trace metals, serum trace metals ratios, and sleep disorders,

Table 1
Characteristics of participants across NHANES 2011–2016 cycles.

Characteristics	Cut-off value	Overall N = 3660	2011–2012 N = 962	2013–2014 N = 1128	2015–2016 N = 984	*p*-value
Sleep disorder						0.610
No		2693(71.1 %)	836(72.4 %)	994(70.8 %)	863(70.1 %)	
Yes		967(28.9 %)	284(27.6 %)	360(29.2 %)	323(29.9 %)	
Zn (%)						0.229
$<Q_1$	71.7 μg/dL	954(25.4 %)	252(21.3 %)	364(26.7 %)	338(28 %)	
Q_1 - Q_3		1812(49.9 %)	590(53.3 %)	662(49.6 %)	560(46.9 %)	
$>Q_3$	90.8 μg/dL	894(24.7 %)	278(25.4 %)	328(23.7 %)	288(25.1 %)	
Cu (%)						0.791
$<Q_1$	98.6 μg/dL	891(25.1 %)	289(26.2 %)	321(24.7 %)	281(24.5 %)	
Q_1 - Q_3		1784(49.9 %)	536(50.5 %)	661(48.6 %)	587(50.8 %)	
$>Q_3$	132.0 μg/dL	985(25 %)	295(23.3 %)	372(26.7 %)	318(24.7 %)	
Se (%)						0.066
$<Q_1$	118.7 μg/L	950(25.3 %)	342(28.9 %)	308(24 %)	300(23.2 %)	
Q_1 - Q_3		1850(49.8 %)	531(44.1 %)	674(49.8 %)	645(55.3 %)	
$>Q_3$	140.7 μg/L	860(25 %)	247(27 %)	372(26.3 %)	241(21.5 %)	
Zn/Cu (%)						0.287
$<Q_1$	0.59	1064(27 %)	303(24.2 %)	398(27.7 %)	363(29.1 %)	
Q_1 - Q_3		1799(49.4 %)	556(50.6 %)	667(49.7 %)	576(47.9 %)	
$>Q_3$	0.86	797(23.6 %)	261(25.2 %)	289(22.6 %)	247(23 %)	
Zn/Se (%)						0.507
$<Q_1$	5.51	943(25 %)	236(22.2 %)	395(26.9 %)	312(25.7 %)	
Q_1 - Q_3		1791(50.2 %)	576(50.7 %)	634(50 %)	581(49.8 %)	
$>Q_3$	7.08	925(24.8 %)	308(27 %)	324(23.1 %)	293(24.5 %)	
Cu/Se (%)						0.663
$<Q_1$	7.44	868(25 %)	272(26.6 %)	320(23.4 %)	276(25.3 %)	
Q_1 - Q_3		1817(50 %)	537(47.8 %)	680(51.2 %)	600(50.7 %)	
$>Q_3$	10.55	975(25 %)	311(25.6 %)	354(25.4 %)	310(24 %)	

Zn, zinc; Cu, copper; Se, Selenium.

using the restricted cubic spline model (RCS) with three knots located at the 5th, 50th, and 95th percentiles of the distribution (Jia et al., 2022; Dong et al., 2020; Sun et al., 2019a; Sun et al., 2019b).

Among the 4932 eligible participants, about 26 % of missing values of covariates results in a total sample size of 3660 participants. To evaluate the potential selection bias, we checked the missing values of covariates and found the participants without caffeine intake accounted for the most (N = 680). The multivariable logistic models illustrated that caffeine intake was unlikely to be associated with the risk of sleep disorders (Supplementary Table S1). As a result, we excluded the caffeine intake to perform sensitivity analyses to evaluate the robustness of our findings, with the sample size being 4340.

Statistical analyses were performed using the R software (version 4.1.0, R Foundation for Statistical Computing) and Stata/IC 16.0 (StataCorp, Texas, USA). All statistical tests were two-sided, and significance was considered at $p < 0.05$.

3. Results

3.1. Main analyses

The baseline characteristics of participants across survey waves were presented in Table 1. The overall prevalence of self-reported sleep disorder was 28.9 % and showed a slightly climbing trend from 27.6 % in 2011–2012 to 29.9 % in 2015–2016, but without statistical significance ($p = 0.610$). The distributions of serum trace metals and serum trace metals ratios across three cycles did not significantly alter.

Characteristics of participants with and without self-reported sleep disorders were presented in Table 2. From the perspective of univariate analysis, education level, family income, physical activity, caffeine intake, serum Zn, serum Cu, serum Se, and serum Zn/Se were not related to the prevalence of sleep disorders. Advanced age, female gender, non-Hispanic white race, smoking, drinking, obesity, hypertension, diabetes, depression, lower Zn/Cu, and higher Cu/Se were likely to be risk factors for sleep disorders in American adults.

The results of binary logistic regression models of serum trace metals and serum trace metals ratios on self-reported sleep disorders were described in Table 3. After fully adjusted for sociodemographic, behavioral, and health covariates, serum Cu and serum Se were not related to the risk of sleep disorders in American adults. However, compared to individuals in the lowest tertiles of serum Zn ($<Q_1$), adults with the highest tertiles of serum Zn ($>Q_3$) had a 30.0 % (OR: 0.70, 95 % CI: 0.51–0.97, $p = 0.035$) lower risk to report sleep disorders.

Concerning serum trace metals ratios, compared with adults with the lowest tertiles ($<Q_1$) of Zn/Cu ratio and the lowest tertiles ($<Q_1$) of Zn/Se ratio, participants with the highest tertiles ($>Q_3$) of Zn/Cu ratio (OR: 0.62, 95 % CI: 0.45–0.87, $p = 0.007$) and Zn/Se ratio (OR: 0.68, 95 % CI: 0.49–0.95, $p = 0.025$) were less likely to report sleep disorders. Nevertheless, serum Cu/Se was not related to the risk of sleep disorders.

Subsequently, the RCS analyses were applied to explore the dose-response relationship between serum trace metals, serum trace metals ratios, and the risk of sleep disorders, and the results were presented in Fig. 2. The RCS model demonstrated that higher serum Zn, Zn/Cu, and Zn/Se levels were related to decreased risk of sleep disorders, the *p*-value for non-linearity were 0.017, 0.069, and 0.039, respectively. The dose-response relationships between serum Cu, Se, Cu/Se, and sleep disorders were in line with the logistic model, in which no significant results were presented.

3.2. Sensitivity analyses

The distributions of sleep disorders, serum trace metals, and serum trace metals ratios among the research cycles were presented in Supplementary Table S2, which did not present an obvious difference with distributions in the main analyses. Characteristics of participants with and without self-reported sleep disorders were presented in Supplementary Table S3. The univariate analyses showed that active physical activity status and lower serum Cu level were associated with a lower risk of sleep disorder, which was different from the results in Table 2, and the others were similar to the main analyses results.

Supplementary Table S4 and Supplementary Fig. S1 demonstrated the logistic model results and the dose-response relationships by the RCS

Table 2
Characteristics of participants with/without the sleep disorder.

Characteristics	Overall N = 3660	Without sleep disorder N = 2693	With sleep disorder N = 967	p-value
Age (%)				<0.001
18–39 years	1350 (35.3 %)	1095(39.6 %)	255(24.8 %)	
40–59 years	1164 (37.2 %)	807(34.6 %)	357(43.4 %)	
≥60 years	1146 (27.5 %)	791(25.8 %)	355(31.8 %)	
Sex (%)				
Female	1850(52 %)	1311(50 %)	539(56.9 %)	0.007
Male	1810(48 %)	1382(50 %)	428(43.1 %)	
Race (%)				<0.001
Non-Hispanic White	1532 (69.4 %)	1018(65.6 %)	514(78.8 %)	
Mexican American	468(7.6 %)	371(8.8 %)	97(4.8 %)	
Non-Hispanic Black	761(10 %)	582(10.7 %)	179(8.5 %)	
Other or multiracial	899(12.9 %)	722(14.9 %)	177(7.9 %)	
Education (%)				0.444
Less than high school graduate	751(13.6 %)	562(14.1 %)	189(12.1 %)	
High school graduate or GED	822(21.4 %)	598(21.5 %)	224(21.3 %)	
Some college or above	2087(65 %)	1533(64.3 %)	554(66.6 %)	
Income (%)				0.494
0– 130 % FPL	1160(21 %)	817(20.8 %)	343(21.5 %)	
130 % ~ 350 % FPL	1357 (36.1 %)	1025(36.8 %)	332(34.3 %)	
>350 % FPL	1143 (42.9 %)	851(42.4 %)	292(44.1 %)	
Smoke (%)				<0.001
Never	2112 (56.7 %)	1649(60.4 %)	463(47.6 %)	
Former	878(25.5 %)	617(23.9 %)	261(29.5 %)	
Current	670(17.8 %)	427(15.7 %)	243(22.9 %)	
Drink (%)				<0.001
No	1018 (21.3 %)	795(23.4 %)	223(16.2 %)	
Yes	2642 (78.7 %)	1898(76.6 %)	744(83.8 %)	
Physical activity (%)				0.187
Inactive	1128 (25.6 %)	822(24.8 %)	306(27.5 %)	
Active	2532 (74.4 %)	1871(75.2 %)	661(72.5 %)	
Caffeine (%)				0.103
$<Q_1$	1111 (25.2 %)	850(26.3 %)	261(22.4 %)	
Q_1 - Q_3	1878 (49.9 %)	1386(50 %)	492(49.7 %)	
$>Q_3$	671(24.9 %)	457(23.6 %)	214(28 %)	
Body mass index (%)				0.014
Underweight/ Normal	1010 (27.1 %)	781(27.6 %)	229(25.8 %)	
Overweight	1179 (33.6 %)	896(35.2 %)	283(29.7 %)	
Obese	1471 (39.3 %)	1016(37.2 %)	455(44.5 %)	
Hypertension (%)				<0.001
No	2360 (67.6 %)	1858(71.4 %)	502(58.2 %)	
Yes	1300 (32.4 %)	835(28.6 %)	465(41.8 %)	
Diabetes (%)				<0.001
No	3079 (86.6 %)	2337(88.9 %)	742(81 %)	
Yes	581(13.4 %)	356(11.1 %)	225(19 %)	
Depression (%)				<0.001
No	3345 (92.7 %)	2579(96.2 %)	766(84 %)	
Yes	315(7.3 %)	114(3.8 %)	201(16 %)	
Zn (%)				0.104
$<Q_1$	954(25.4 %)	698(24.4 %)	256(27.8 %)	
Q_1 - Q_3	1812 (49.9 %)	1307(49.6 %)	505(50.6 %)	
$>Q_3$	894(24.7 %)	688(26 %)	206(21.6 %)	
Cu (%)				0.081
$<Q_1$	891(25.1 %)	701(26.3 %)	190(22.2 %)	
Q_1 - Q_3	1784 (49.9 %)	1298(49.5 %)	486(50.8 %)	
$>Q_3$	985(25 %)	694(24.1 %)	291(27 %)	
Se (%)				0.397
$<Q_1$	950(25.3 %)	712(25.4 %)	238(25 %)	
Q_1 - Q_3	1850 (49.8 %)	1373(50.3 %)	477(48.5 %)	
$>Q_3$	860(25 %)	608(24.3 %)	252(26.6 %)	
Zn/Cu (%)				0.001
$<Q_1$	1064(27 %)	751(25.7 %)	313(30.2 %)	
Q_1 - Q_3	1799 (49.4 %)	1309(48 %)	490(52.9 %)	
$>Q_3$	797(23.6 %)	633(26.3 %)	164(16.9 %)	
Zn/Se (%)				0.143
$<Q_1$	943(25 %)	678(24.1 %)	265(27.3 %)	
Q_1 - Q_3	1791 (50.2 %)	1302(49.7 %)	489(51.4 %)	
$>Q_3$	925(24.8 %)	712(26.3 %)	213(21.3 %)	
Cu/Se (%)				0.022
$<Q_1$	868(25 %)	670(26.4 %)	198(21.6 %)	
Q_1 - Q_3	1817(50 %)	1330(49.5 %)	487(51.2 %)	
$>Q_3$	975(25 %)	693(24.1 %)	282(27.2 %)	

FPL, family income to poverty; Zn, zinc; Cu, copper; Se, Selenium.

models, and the results were consistent with the findings from the main analyses. After adjustment for sociodemographic, behavioral, and health characteristics, higher serum Zn (OR: 0.70, 95 % CI: 0.51–0.95, $p = 0.024$, p for non-linearity = 0.075), Zn/Cu (OR: 0.64, 95 % CI: 0.49–0.84, $p = 0.002$, p for non-linearity = 0.034), and Zn/Se (OR: 0.67, 95 % CI: 0.47–0.94, $p = 0.021$, p for non-linearity = 0.035) were associated with lower risks of sleep disorders. Serum Cu, Se, and Cu/Se were not associated with the risk of sleep disorders both in logistic and RCS models.

4. Discussion

With sampling weights, strata, and units considered in the analyses, we were able to assess the association of serum trace metals and serum trace metals ratios with sleep disorders in a representative sample of American general adults. Our study revealed that higher serum Zn, Zn/Cu, and Zn/Se were associated with a lower risk of self-reported sleep

Table 3
Associations of serum trace metals and serum trace metals ratios with sleep disorder in American adults.

Characteristics	Model I		Model II		Model III	
	OR (95 % CI)	p-value	OR (95 % CI)	p-value	OR (95 % CI)	p-value
Zn						
<Q_1	ref	–	ref	–	ref	–
Q_1 - Q_3	0.86(0.64–1.14)	0.283	0.83(0.62–1.11)	0.201	0.82(0.61–1.11)	0.196
>Q_3	0.73(0.53–0.99)	0.046	0.71(0.52–0.98)	0.039	0.70(0.51–0.97)	0.035
Cu						
<Q_1	ref	–	ref	–	ref	–
Q_1 - Q_3	1.05(0.83–1.33)	0.676	0.97(0.78–1.21)	0.778	0.92(0.71–1.18)	0.509
>Q_3	1.12(0.82–1.53)	0.460	1.02(0.76–1.38)	0.877	0.94(0.68–1.30)	0.710
Se						
<Q_1	ref	–	ref	–	ref	–
Q_1 - Q_3	0.98(0.80–1.20)	0.844	1.02(0.83–1.24)	0.853	1.04(0.84–1.29)	0.702
>Q_3	1.10(0.85–1.42)	0.481	1.15(0.89–1.47)	0.278	1.13(0.87–1.48)	0.349
Zinc/Cu						
<Q_1	ref	–	ref	–	ref	–
Q_1 - Q_3	0.90(0.68–1.17)	0.411	0.91(0.69–1.20)	0.507	0.96(0.73–1.27)	0.769
>Q_3	0.56(0.41–0.77)	<0.001	0.60(0.45–0.82)	0.002	0.62(0.45–0.87)	0.007
Zinc/Se						
<Q_1	ref	–	ref	–	ref	–
Q_1 - Q_3	0.89(0.67–1.19)	0.438	0.87(0.65–1.16)	0.326	0.91(0.66–1.23)	0.519
>Q_3	0.71(0.51–0.98)	0.040	0.66(0.47–0.92)	0.016	0.68(0.49–0.95)	0.025
Cu/Se						
<Q_1	ref	–	ref	–	ref	–
Q_1 - Q_3	1.15(0.90–1.47)	0.251	1.09(0.85–1.38)	0.495	1.11(0.85–1.45)	0.428
>Q_3	1.25(0.96–1.63)	0.095	1.13(0.87–1.47)	0.335	1.11(0.81–1.51)	0.502

Zn, zinc; Cu, copper; Se, Selenium; OR, odds ratio; 95 % CI, 95 % confidence interval; Model I: Adjusted for sociodemographic characteristics. Model II: Adjusted for sociodemographic and behavioral characteristics. Model III: Adjusted for sociodemographic, behavioral, and health characteristics.

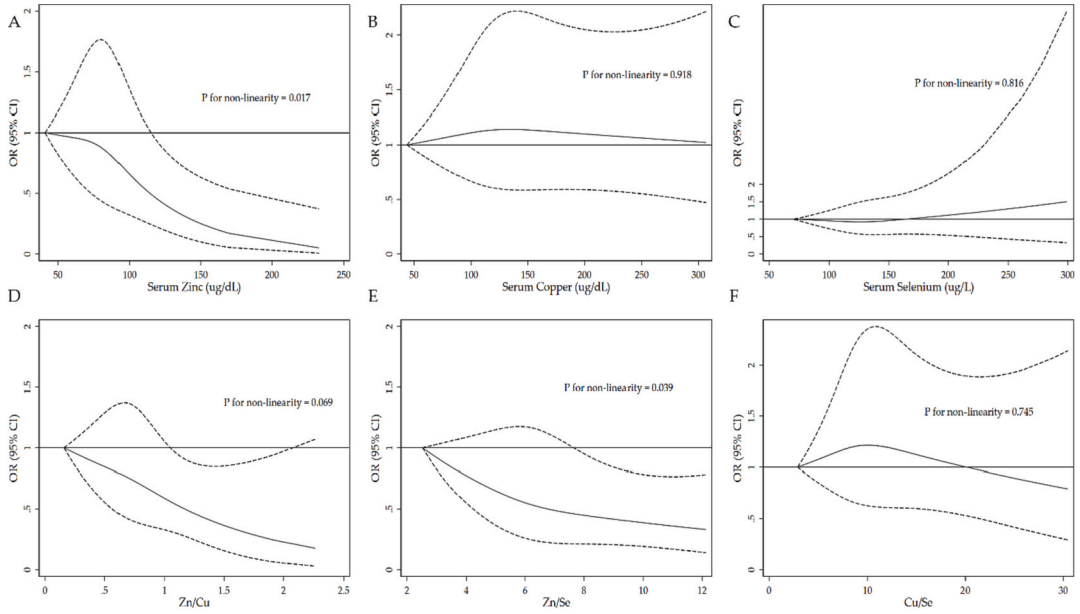

Fig. 2. Restricted cubic spline model of the odds ratios of sleep disorder with serum Zn (A), Cu (B), Se (C), Zn/Cu ratio (D), Zn/Se (E), and Cu/Se (F). All were adjusted for sociodemographic characteristics, behavioral characteristics, and health characteristics.

disorders in American general adults.

Our findings about serum Zn and sleep disorders were in line with most previous epidemiological studies. For instance, a clinical study claimed that the administration of nightly zinc complemented with melatonin and magnesium could improve sleep quality in long-term care facility residents with primary insomnia (Rondanelli et al., 2011). China Jintan child cohort study found sufficient blood zinc concentration was associated with good sleep quality (Ji and Liu, 2015). Besides, moderate-severe insomnia symptoms were related to a higher prevalence of inadequate intake of Zn in Japanese women (Matsuura et al., 2020). Additionally, apnea/ hypopnea index (AHI), an indicator of obstructive sleep apnea (OSA) severity, was shown to be negatively associated with concentrations of plasma Zn in a cross-sectional study in Taiwan (Chen et al., 2013). Nevertheless, some studies also offered different opinions. A study of Iranian female students found dietary Zn intake was positively correlated with the prevalence of sleep disorders (Hajianfar et al., 2021). Another study discovered serum and brain levels of zinc are elevated in restless legs syndrome (Chen et al., 2021). The disparities in measurement methods of Zn, sex, age of subjects, sample size, as well as sleep disorder symptoms, may partly explain the inconsistent conclusions.

Regarding Cu and sleep, most current studies concentrated on sleep

duration and OSA, but the results were relatively inconsistent. As for sleep duration, our findings were similar to Jia et al., who obtained a null association between serum Cu and sleep duration in either females or the whole US adults (Jia et al., 2022). Meanwhile, Song et al. did not get any significant difference in sleep durations across tertiles of serum Cu levels in Korean adult women (Song et al., 2012). In addition, the mean concentrations of serum Cu in healthy Jinan residents were relatively constant across sleep hour groups (Zhang et al., 2009). However, another study came to a different conclusion that serum Cu levels were highest in the group with a sleep duration of 10 h or more among Eastern Finnish older men (Jia et al., 2022). With regard to OSA, Chen, P C et al. and Volná, Jana et al. found that plasma Cu concentration was positively linked to AHI (Chen et al., 2013; Volná et al., 2011), and Asker et al. discovered serum Cu levels increased in OSA patients (Asker et al., 2015), however, Akyuz et al. found no difference of serum Cu levels between OSA patients and healthy controls (Akyuz et al., 2013). The general limitation of these four studies was a small sample size, further studies are necessary to evaluate the exact association of serum Cu and OSA in a large population.

Concerning the relationship between Se and sleep disorders, our findings were not consistent with previous studies. Higher total Se intake was less likely to be associated with difficulty falling asleep (Grandner et al., 2014), and short sleep duration (Grandner et al., 2013) in American adults. Chen et al. also found that AHI values were also negatively associated with concentrations of erythrocyte Se (Chen et al., 2013). Additionally, findings from Turkey provided evidence that Se could exert a treatment effect on OSA due to its antioxidant mechanism (Saruhan et al., 2021). In our study, the means ± SD (standard deviation) of serum Se concentrations in American adults with and without sleep disorders were 130.69 ± 19.15 μg/L and 130.35 ± 18.59 μg/L (*p-value* = 0.720), respectively, after adjustment for sociodemographic, behavioral and health factors, it was still uncorrelated to the prevalence of sleep disorders.

Although serum Cu and Se levels were not correlated to sleep disorders in our study, the Zn/Cu and Zn/Se may provide some novel insights. In this investigation, compared to adults with sleep disorders, individuals without sleep disorders had a higher Zn/Cu level, and the means ± SD of Zn/Cu in American adults with and without sleep disorders were 0.70 ± 0.19 and 0.74 ± 0.22 (*p-value* < 0.001). The negative associations between Zn/Cu level and the risk of sleep disorders were discovered by the logistic and RCS models. Some possible mechanisms may provide an explanation. The Zn/Cu has been used as a predictive measure of several clinical complications, including cancers (Leone et al., 2006), cardiovascular disease (Reunanen et al., 1996), and major depressive disorder (Liu et al., 2020), which were related to an increased risk of sleep disorders. In addition, the negative associations of Zn/Cu with interleukin 6 (IL-6) and C-reactive protein (CRP) were discovered (Malavolta et al., 2010), and these two systemic inflammation markers were considered the risk factors for sleep disorders (Irwin et al., 2016). Currently, epidemiological studies about Zn/Se and sleep were limited, making it hard to compare our results with those of other studies. In our study, we found a significant difference in Zn/Se between American adults with and without sleep disorders in univariate analysis (*p-value* = 0.014), their means ± SD were 6.25 ± 1.22 and 6.41 ± 1.24, respectively. Even though this difference was not that huge, multivariate logistic regression indicated that compared with adults with the lowest tertiles ($<Q_1$) of Zn/Se, people with the highest tertiles ($> Q_3$) were less likely to report sleep disorders, and the RCS revealed that Zn/Se was related to a lower risk of sleep disorder when Zn/Se >8, which further illustrated the consistency of our findings. The inverse associations of serum Zn, and Zn/Cu, Zn/Se with sleep disorders enlightened us that increasing Zn intake may be an excellent approach to prevent sleep disorders due to its benefits from these three aspects.

The major strength of this study was the use of a large nationally representative sample of adults in the US, which enhanced the reliability and precision of our findings. Additionally, we adopted the trace metals in serum as measures, which can overcome the bias of dietary recall investigations and the confounding from individual metabolic factors. However, several limitations must be pointed out to intercept our findings. First of all, self-reported sleep disorders may induce bias as no objective sleep measures were collected. Moreover, limited to the questionnaires in NHANES 2011–2016, we were unable to explore the relationships between serum trace metals and specific sleep disorder symptoms, such as insomnia, OSA, and restless legs syndrome. Furthermore, the causal relationships between serum Zn, serum Zn/Cu, serum Zn/Se, and sleep disorders could not be inferred because of the cross-sectional design.

In conclusion, our study indicated that higher serum Zn, Zn/Cu, and Zn/Se were inversely associated with the risk of self-reported sleep disorders in US adults.

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CRediT authorship contribution statement

Ming-Gang Deng: Data curation, Formal analysis, and Writing - original draft; **Fang Liu:** Writing- Reviewing and Editing; **Yuehui Liang:** Writing- Reviewing and Editing; Yanling Chen: Writing- Reviewing and Editing; **Jia-Qi Nie:** Writing- Reviewing and Editing; **Chen Chai:** Writing- Reviewing and Editing; **Kai Wang:** Conceptualization, Writing - original draft, Writing - review & editing, and Validation.

Conflicts of Interest

The authors declare no conflict of interest.

Data availability statement

The NHANES dataset is publicly available online, accessible at cdc.gov/nchs/nhanes/index.htm (accessed on 16 May 2022).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2022.11.088.

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