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Sex difference in the association between pyrethroids exposure and sleep problems among adolescents: NHANES 2007–2014

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Abstract

Background Pyrethroids have been widely used in the United States and worldwide. Few studies examined the effect of pyrethroids exposure on sleep problems among adolescents.

Objectives This study investigated the associations between pyrethroids exposure and sleep problems in male and female adolescents.

Methods The data were used from the National Health and Nutrition Examination Survey 2007–2014. In this study, 3-Phenoxybenzoic Acid (3-PBA) was used as a validated biomarker for pyrethroids exposure. The association between urinary 3-PBA and sleep problems was analyzed using logistic regression models.

Results A total of 805 adolescents aged 16–20 years old were included in this study. The proportion of sleep problems was higher in females than in males (10.18% vs.7.35%, $P=0.154$). A significant interaction was found between sex and 3-PBA (P interaction $=0.021$) in the risk of sleep problems. A positive association of 3-PBA exposure with sleep problems was observed in male adolescents after adjusting for all the other covariates (OR = 4.04, 95% CI 1.31, 12.42). No statistically significant association was observed in female adolescents.

Conclusions A positive association was observed between pyrethroids exposure and sleep problems in male adolescents, but not in female adolescents. More studies are required to confirm our findings.

Keywords 3-PBA, Sleep problems, Sex differences, Adolescents

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Introduction

Sleep disorders, categorized into insomnia, restless legs syndrome, and sleep apnea, are increasingly becoming severe problems in many countries [4, 13]. Sleep disorders problems are linked to a growing number of adverse health outcomes, including cardiovascular disease, obesity, and certain cancers among adult populations [9, 15, 19, 22, 28]. Besides, sleep disorders have also been related to a series of psychiatric problems, behavioral antecedents, and an increased risk of injury and motor vehicle accidents in adolescents [6, 26, 40]. Many factors can affect sleep quality such as proximity to noisy areas, alcohol consumption, smoking, and stress, etc. [12, 16, 38]. Recent studies have suggested a link between pesticide exposure and sleep problems. For example, Fuhrimann et al. found that the use of mancozeb and glyphosate could lead to an increased risk of sleep problems [14].

Pyrethroids are one of the most commonly used pesticides in the world. It is reported that more than 30% of pyrethroid pesticides are used worldwide and are commonly used in agricultural and domestic settings [5, 8]. In the general population, exposure to pyrethroids is mainly through ingestion of skin contact with contaminated house dust or ingestion of residues in food, or surface adhesion particles [29]. Zamora et al. found that longer sleep duration and later sleep timing were related to maternal prenatal chlorpyrifos exposure among adolescent offspring in a mother-adolescent pairs cohort, but found no significant associations between pyrethroids exposure(3-PBA) and sleep outcomes [42]. In another study, Zamora et al. also reported a significant association between urinary 3-PBA concentration and trouble sleeping among adults [41]. Moreover, males may tend to be easily affected by pyrethroids exposure [41, 42]. Consistently, previous studies also indicated that the toxicological effects of pyrethroid metabolites might have sex-related disparities in other health outcomes such as obesity and rheumatoid arthritis [17, 44].

Overall, few studies assessed the effect of pyrethroids pesticide exposure on sleep problems, and the associations were under-investigated in adolescents. In this study, we examined the cross-sectional associations between pyrethroids exposure and sleep problems and the potential sex differences in adolescents using a representative US (the United States) population.

Material and methods

Study population and design

The data comes from the National Health and Nutrition Examination Survey (NHANES) which aims to evaluate the health and nutritional status among US adults and children. The survey design, sampling procedures, and methods were detailed elsewhere [23]. We included the data from four cycles (2007–2014) in which urinary 3-PBA data were collected from participants. The National Center for Health Statistics Ethics Review Board has approved the protocol and written consent was provided for all participants. Pyrethroid exposure data were available in a random subsample of participants aged ≥ 16 years [23]. Overall, 17, 551 participants aged 16–20 years old among which 899 had completed data on 3-PBA and sleep problems. After excluding missing data on body mass index (BMI), physical activity, poverty income ratio (PIR), and urine creatine, 805 participants were included in the main analysis (Fig. 1).

Urinary pyrethroid exposure measurement

The random daytime spot urine of the participants at enrollment was stored at − 20° C within 4 h and analyzed by National Environmental Sanitation Center. The high-performance liquid chromatography combined with electrospray chemical ionization and tandem mass spectrometry methods were used to detect urinary concentrations of pyrethroid metabolites including 3-PBA, Trans-DCCA (trans-3-(2, 2-dichlorovinyl)-2, 2-dimethylcylopropane carboxylic acid), 4-F-3-PBA (4-fluoro-3-phenoxy-benzoic acid), and Cis-DBCA (cis-(2,2-dibromovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid) [1, 3]. In agreement with previous studies [37], 3-PBA was used as the primary marker for pyrethroids pesticide exposure, and other metabolites secondary markers were also tested.

Definition of sleep problems

Sleep problems included sleep disorders and trouble sleeping. Sleep problems were defined as having sleep disorders or trouble sleeping based on self-reported doctor diagnoses: "Have you ever been told by a doctor or other health professional that you have a sleep disorder?" and "Have you ever been told by a doctor or other health professional that you have a trouble sleeping?".

Covariates

Standardized questionnaires were used to collect sociodemographic characteristics including age, sex, race/ethnicity, PIR, BMI, and physical activity. Age was modelled as a continuous variable. PIR was divided into three groups according to the total family income ratio (< 1.3, 1.3–3.5, and > 3.5) [44]. Race/ethnicity was grouped as Hispanic (Mexican American and other Hispanic), non-Hispanic white, non-Hispanic black, and others. BMI was continuously sorted into four levels (BMI < 18.5, BMI ≥ 18.5 and BMI < 25, BMI ≥ 25 and BMI < 30, and BMI ≥ 30) which was calculated by dividing weight (kg) by height (m^2) [31]. The physical activity is based on the self-reported questions and classified into vigorous

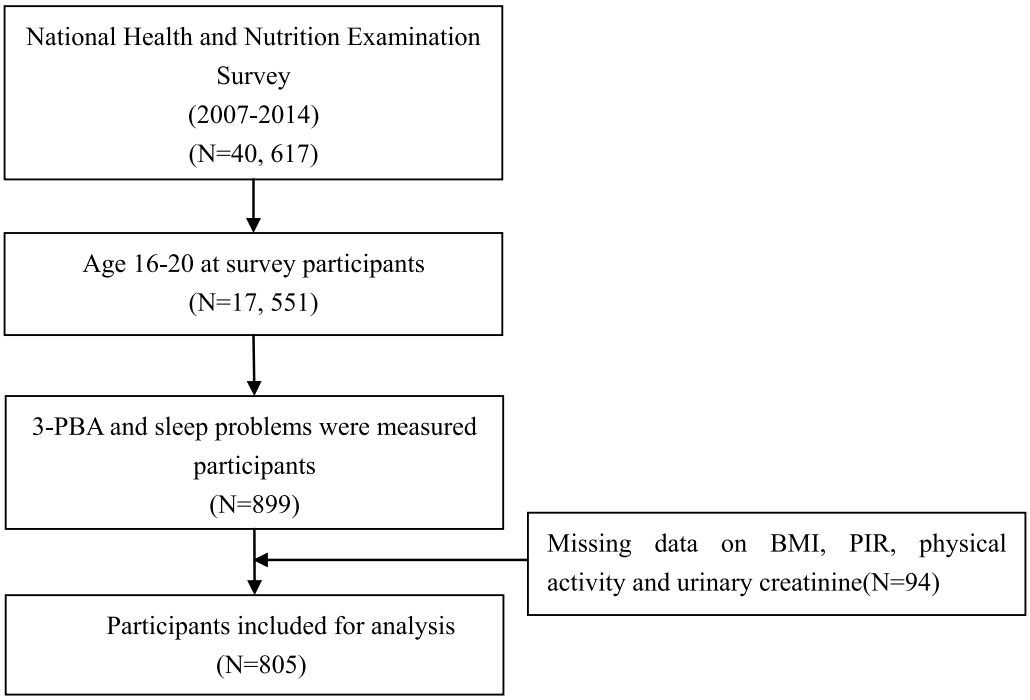

Fig. 1 A flowchart of inclusion and exclusion of study participants

activities(causing heavy sweating, or large increases in breathing or heart rate), moderate activities (causing light sweating or a slight to moderate increase in breathing or heart rate), and sedentary (neither vigorous recreation activities nor moderate recreation activities) [44]. The Roche/Hitachi modular P chemical analyzer was used to determine urinary creatinine. In this enzymatic process, creatinine is converted to creatine by the action of creatinase. Creatine is then formed into sarcosine and urea by the action of creatinase.

Statistical analysis

According to the NHANES guidelines, the weight of the smallest subpopulation that includes all the variables (WTSC2YR) was used to account for the complex survey design. The mean and standard deviation are used to describe continuous variables, whereas cases (n) and percentages (%) are used to present categorical variables. Urinary 3-PBA was log-transformed, and urinary creatinine was adjusted in all the analyses [2]. The association between 3-PBA exposure (categorized into Tertiles (T)) and sleep problems was analyzed using a multivariate logistic regression model. In addition, interaction effects were estimated by adding a 3-PBA × covariable term to the model. Due to the significant interaction between sex and 3-PBA, we investigated the relationship between 3-PBA and sleep problems in males and females separately. Model 1 adjusted for urinary creatinine; Age, race/ethnicity, and urinary creatinine were adjusted in Model 2; Model 3 was further adjusted for PIR, physical activity, and BMI.

Trans-DCCA, 4-F-3PBA, and Cis-DBCA were dichotomized as detected vs. undetected due to the low detection rates (11.52%, 7.52% and 0.75%, respectively). Furthermore, the associations of trouble sleeping, and sleep disorders with 3-PBA were also tested, respectively. In sensitivity analyses, we tested the associations by not excluding participants with missing data on the covariates, and a multiple imputation approach was adopted to impute the missing data. Further, we performed more sensitive analyses, including using the covariate-adjusted standardization method [24], using unsupervised summary scores of pyrethroid metabolites, did not incorporate the complex survey design, excluding participants with poor health status, and further controlling for dietary factors and cotinine. All of the above analyses were performed using Stata software version 14 (STATA Corp, TX, US). The difference was statistically significant if a P value < 0.05 on both sides.

Results

Basic characteristics of the study population

A total of 805 eligible participants were included in our analyses, among which 52.4% were males and the average age was 17.8 years old. Significant differences were found in the general characteristics between male and female

adolescents such as BMI and physical activity, as shown in Table 1. The proportion of sleep problems was higher in females than in males (10.18% vs 7.35%, $P=0.154$). The geometric means of uncorrected and creatinine uncorrected 3-PBA were 0.43 and 0.31 in males.

Associations between 3-PBA and sleep problems

A significant interaction was found between sex and 3-PBA on sleep problems (P for interaction = 0.021), suggesting a potential moderating effect in the association between 3-PBA and sleep problems (Fig. 2). Sex-stratified analyses showed a positive association of 3-PBA exposure with sleep problems in male adolescents (Tertile 3 vs. Tertile 1: OR = 3.20; 95%CI: 1.10–9.30; $P=0.030$). After controlling for age, sex, race, urinary creatinine, PIR, physical activity, and BMI, the results remained similar (Tertile 3 vs. Tertile 1: OR = 4.04; 95%CI: 1.31–12.42; $P=0.017$). Among female adolescents, no significant association was observed (Table 2).

Association between other metabolites and sleep problems

Similarly, a positive association was observed between the 4-F-3PBA exposure and sleep problems in male adolescents after adjusting for potential confounders (Tertile 3 vs. Tertile 1: OR = 4.40; 95% CI: 1.32, 14.58; $P=0.016$), but not in female adolescents (Tertile 3 vs. Tertile 1: OR = 1.25; 95% CI: 0.36, 4.35; $P=0.726$). There was no significant association for Trans-DCCA in male or female adolescents (Table 3). The relationship between urinary cis-DBCA and sleep problems was not tested in our study due to a low detection rate (0.75%).

Associations of 3-PBA with trouble sleeping and sleep disorders

The associations of 3-PBA with trouble sleeping and sleep disorders were further tested in Additional file 1: Tables S1 and S2. Consistently, after adjusting for the covariates, higher 3-PBA exposure was positively associated with a higher risk of trouble sleeping (Tertile 3 vs. Tertile 1: OR: 4.42; 95% CI: 1.32, 14.79; $P=0.018$) in male adolescents, but not in female adolescents (Tertile 3 vs. Tertile 1: OR: 0.78; 95% CI: 0.21, 2.88; $P=0.880$). No significant association was observed between 3-PBA and sleep disorders.

Sensitivity analysis

We imputed the missing data using multiple imputations and found similar associations between 3-PBA and sleep problems (Additional file 1: Table S3). Moreover, there was no significant difference in the general characteristics

Table 1 Basic characteristics of the study participants

	Males (n = 422)	Females (n = 383)	*P* value
3-PBA(ug/L) uncorrected*	0.43(0.38–0.49)	0.52(0.45–0.60)	< 0.001
3-PBA(ug/g) creatinine uncorrected *	0.31(0.27–0.35)	0.45(0.39–0.51)	< 0.001
Age (years) mean(SD)	17.78(1.40)	17.80(1.42)	0.754
Race/ethnicity (%)			0.113
Hispanic (%)	140(33.18)	147(38.38)	
Non-Hispanic White	137(32.46)	95(24.80)	
Non-Hispanic Black	105(24.88)	101(26.37)	
Other Race	40(9.48)	40(10.44)	
The Poverty Income Ratio (%)			0.169
< 1.3	177(41.94)	185(48.30)	
1.3–3.5	150(35.55)	126(32.90)	
> 3.5	95(22.51)	72(18.80)	
Physical activity (%)			< 0.001
Sedentary	90(21.33)	156(40.73)	
Moderate activity	44(10.43)	79(20.63)	
Vigorous activity	288(68.25)	148(38.64)	
Body mass index (kg/m^2, %)			0.011
< 18.5	22(5.21)	38(9.92)	
18.5–24.9	209(49.53)	207(54.05)	
25–29.9	104(24.64)	71(18.54)	
≥ 30	87(20.62)	67(17.49)	
Sleep problems (%)	31(7.35)	39(10.18)	0.154

* Geometric means (95%CI) were presented

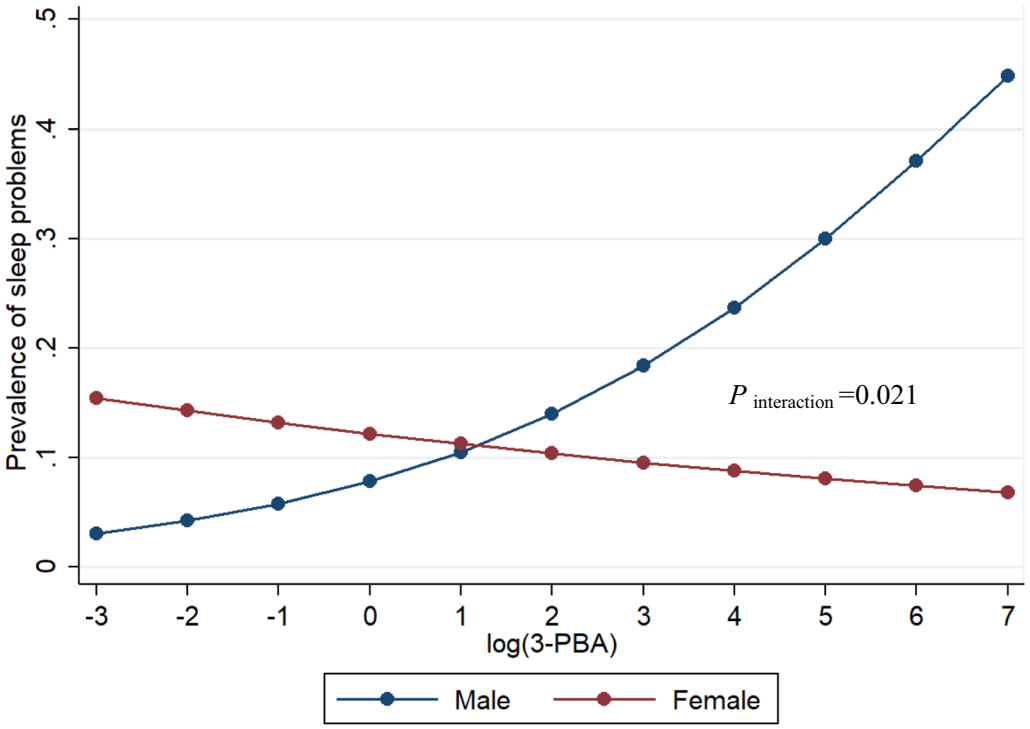

Fig. 2 Moderating effect of sex in the association between 3-PBA and sleep problems

Table 2 Associations between urinary 3-PBA level and sleep problems

Sleep problems	Volume-based 3-PBA levels, OR (95% CI)			*P* for trend
	Tertile 1 (0.07–0.29)	Tertile 2 (0.29–0.92)	Tertile 3 (0.93–286.53)	
Males				
Model 1	Reference	2.45(0.78,7.73)	3.20(1.10,9.30)	0.030
Model 2	Reference	2.53(0.81,7.85)	3.33(1.19,9.31)	0.023
Model 3	Reference	2.70(0.90,8.09)	4.04(1.31,12.42)	0.017
Females				
Model 1	Reference	1.85(0.72,4.78)	1.34(0.49,3.64)	0.579
Model 2	Reference	1.79(0.66,4.86)	1.19(0.42,3.38)	0.697
Model 3	Reference	1.52(0.54,4.32)	0.94(0.27,3.33)	0.894

3-PBA, 3-phenoxybenzoic acid; CI: confidence interval; OR: odds ratio

Model 1: Adjusted for urinary creatinine

Model 2: Adjusted for age, race/ethnicity, and urinary creatinine

Model 3: Adjusted for age, race/ethnicity, urinary creatinine, the poverty income ratio, physical activity, and body mass index

between those included and those excluded (Additional file 1: Table S4). Similar results were observed in other sensitivity analyses (Additional file 1: Tables S5–S9).

Discussion

Using NHANES data, a statistical interaction was found between sex and 3-PBA exposure level on sleep problems. In the further stratified analysis, we observed a significant association between urinary 3-PBA and sleep problems in male adolescents, but not in female adolescents.

In a cross-sectional survey of 4478 adults conducted in the United States, in line with our results, the authors reported that a higher log 3-PBA level was related to a higher risk of trouble sleeping (β = 1.14, 95% CI 1.02, 1.27) among male adults [41]. Our study extended the limited evidence of the association between pyrethroids

Table 3 Association of urinary Trans-DCCA (n = 807) and 4-F-3PBA with sleep problems (n = 824)

	Males OR (95%CI)	*P* value	Females OR (95%CI)	*P* value
Trans-DCCA				
Detection rate (%)	9.03		14.25	
Model 1	1.83 (0.57–5.94)	0.307	0.42 (0.14–1.31)	0.132
Model 2	1.85 (0.56–6.10)	0.307	0.36 (0.11–1.25)	0.107
Model 3	2.23 (0.75–6.62)	0.146	0.28 (0.06–1.21)	0.086
4-F-3PBA				
Detection rate (%)	6.48		8.67	
Model 1	3.91(1.17–13.10)	0.028	1.30 (0.38–4.43)	0.672
Model 2	3.82 (1.12–13.00)	0.032	1.53 (0.48–4.88)	0.469
Model 3	4.40 (1.32–14.58)	0.016	1.25 (0.36–4.35)	0.726

OR: odds ratio; CI: confidence interval

Metabolites were dichotomized as detected vs. undetected, and the undetected group was treated as a reference

Model 1: Adjusted for urinary creatinine

Model 2: Adjusted for age, race/ethnicity, and urinary creatinine

Model 3: Adjusted for age, race/ethnicity, urinary creatinine, the ratio of family income to poverty, physical activity, and body mass index.3-PBA: 3-Phenoxybenzoic Acid; NHANES: National Health and Nutrition Examination Survey; BMI: Body Mass Index; PIR: Poverty Income Ratio; Trans-DCCA: Trans-3-(2,2-Dichlorovinyl)-2,2-Dimethylcylopropane Carboxylic Acid; 4-F-3-PBA: 4-Fluoro-3-Phenoxy-Benzoic Acid; Cis-DBCA: Cis-(2,2-Dibromovinyl)-2,2-Dimethylcyclopropane-1-Carboxylic Acid; CI: Confidence Interval; OR: Odds Ratio

exposure and sleep problems in adolescents, especially in males.

The association between pesticides and sleep problems has been reported in human and animal studies. For example, Li et al. found adverse associations between pesticide exposure intensity and sleep problems among greenhouse vegetable farmers [20]. Other studies also showed that insomnia or disturbed sleep could result from the use of pesticides among the Southern Brazilian rural population [21]. Experimental studies have shown that there was an interaction between carbamates (one specific class of pesticides) and melatonin (sleep/wake hormone) [27]. Another pesticide chlorpyrifos was associated with a higher sleep apnea index in juvenile and adult rats [11].

The results showed that exposure to pyrethroids was significantly associated with a higher risk of sleep problems in males, but not in females. The effects of pyrethroids on health outcomes in males and females are mixed [41, 44]. One possible explanation is that the effects of pyrethroids on different health outcomes may have sex-specific pathways. It was reported that SOD and GPx activity decreased in female rats by the action of permethrin, while it increases in male rats [10]. Another animal study found sex differences in the toxicological effects of pyrethroid metabolites, which might be due to sex-related differences in metabolism and excretion kinetics [35]. In addition, 3-PBA has a function of anti-androgenic activity [33], and testosterone deficiency may have a deleterious effect on sleep quality that may be improved with testosterone replacement [39]. These results suggest that interventions targeting males tend to 3-PBA exposure need to be developed.

The underlying mechanisms are understudied. Pyrethroids could lead to hyperexcitation of the nervous system due to a prolonged sodium current to flow [43]. Hyperglycemia and elevated plasma levels of noradrenaline and adrenaline have also been shown in animal studies of pyrethroid toxicity [32]. Elevated plasma noradrenaline and adrenaline levels may be another possible reason for the sleep disorders. Studies also showed an association between exposure to 3-PBA and bad neurocognitive consequences [34]. Pyrethroids with the characteristics of endocrine-disrupting have been associated with obesity [18], which is linked to sleep quality [30]. In addition, exposure to pyrethroids could cause repeated firing of sensory nerve endings, resulting in abnormal sensation and irritation of the human respiratory tract [36].

We for the first time reported a significant association between urinary 3-PBA and sleep problems among adolescents. The study also has several limitations in this study. First, the cross-sectional nature of this study does not allow for inferring causality. Second, some potential confounders/covariates are not available for analysis, such as genetic factors. Third, the half-life of pyrethroids in the body of humans is short, so one-time measurement could not reflect long-term exposure [25]. Fourth, there may have recall bias in self-reported sleep problems. Fifth, urinary creatinine excretion fluctuated greatly due to specific internal and external factors such as gender, age and race. The adjustment of urinary creatinine to correct chemical concentrations in urine will not necessarily improve the correlation with all chemical exposure doses (it may worsen the result) [7]. Finally, extrapolating the results to other populations should be cautious.

Conclusions

There were sex differences regarding the associations between 3-PBA exposure and sleep problems with a stronger association in male adolescents. We still need more research to confirm our findings and explore the underlying mechanisms.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12302-023-00753-0.

Additional file 1: Table S1. Associations between urinary 3-PBA level and sleep disorders. **Table S2.** Associations between urinary 3-PBA level and trouble sleeping. **Table S3.** Associations between pyrethroids exposure and sleep health (using a multiple imputation approach). **Table S4.** Comparison of main characteristics between those included in the analyses and those excluded due to missing data. **Table S5.** Associations between urinary 3-PBA level and sleep problem (not excluding participants with missing data on covariates). **Table S6.** Associations between urinary 3-PBA level and sleep problem (using the covariate-adjusted standardization method). **Table S7.** Associations between sum of pyrethroid metabolites levels and sleep problem (using unsupervised summary scores of pyrethroid metabolites). **Table S8.** Associations between urinary 3-PBA level and sleep problem (not using complex survey design). **Table S9.** Associations between urinary 3-PBA level and sleep problem (excluding poor health status participants, and further controlling for dietary factors and cotinine).

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Author contributions
The manuscript was drafted and revised by all authors. GH, HYC and SHP were responsible for the conceptualization, supervision, and editing sections. LZ and GZL were tasked with the data collection, formal analysis, investigation, and original draft writing sections. XC, LZ, MLL, LC and CXJ critically reviewed and helped to prepare the methods sections. LZ and GZL contributed equally to this paper. GH, HYC and SHP will act as guarantors for the paper.

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Availability of data and materials
The datasets analyzed in the current study are available in the NHANES [https://www.cdc.gov/nchs/nhanes/].

Declarations

Ethics approval and consent to participate
The National Center for Health Statistics Ethics Review Board has approved the protocol and written consent was provided for all participants.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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