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Association between ultra-processed food and osteoporosis: a cross-sectional study based on the NHANES database

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Abstract

Aim Nutritional characteristics and additives in ultra-processed foods (UPF) are directly related to bone health. Physical activity as a modifiable lifestyle intervention also plays a possible role in bone mineral density (BMD), but effect of physical activity on association between UPF and osteoporosis is not fully understood. Herein, this study aims to explore the association of UPF with osteoporosis, and assess the potential mediating effects of some related factors on this pathway.

Methods Data of adults were extracted from the National Health and Nutrition Examination Survey (NHANES) database in this cross-sectional study. Associations of unprocessed/minimally processed food (MPF), processed culinary ingredient (PCI), processed foods (PF) and UPF with femur neck BMD, total femur BMD and osteoporosis were investigated using linear regression and weighted univariate and multivariate logistic regression analyses respectively. Subgroup analyses of age, gender, physical activity, poverty income ratio (PIR), hypertension, diabetes mellitus (DM), cardiovascular disease (CVD), and dyslipidemia were performed. The potential mediating and interaction effects of physical activity and related factors on association of UPF with osteoporosis were also assessed. The evaluation indexes were β, odds ratios (ORs) and 95% confidence intervals (CIs).

Results Among 10,678 eligible persons, 454 had osteoporosis. After adjusting for covariates, elevated UPF intake was associated with decreased demur neck and total femur BMD (β=-0.003). A higher UPF intake level (> 57.51%) was linked to higher odds of osteoporosis (OR = 1.789). These relationships were also significant in different subgroups. Physical activity had a potential mediating effect on the association between UPF and osteoporosis (OR = 0.47, mediating proportion = 21.54%).

Conclusion UPF intake levels were associated with BMD and osteoporosis. Physical activity had an interaction effect with UPF, and had a potential mediating effect on relationship between UPF and osteoporosis.

Keywords Ultra-processed food, Osteoporosis, Physical activity, Interaction effect, Mediating effect, Cross-sectional study

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Introduction

Osteoporosis is a systemic bone disease characterized by reduced bone mineral density (BMD), impaired bone strength, and an increased risk of fragility fractures [1]. The World Health Organization (WHO) considers osteoporosis to be the second leading health problem (rank only second to cardiovascular disease) worldwide [2]. In 2019, global cases of osteoporosis are 41.5 million, and the total number is expected to reach 263.2 million between 2030 and 2034 [3]. Osteoporosis increases the risk of fractures. Among individuals at the age of 50, about one in two women and one in three men will have a fracture in the rest of their lives [4]. Fractures lead to reduced quality of life, hospitalization, disability and increased mortality, especially for susceptible populations such as postmenopausal women and cancer patients [5, 6]. Besides, with a rapidly aging population and dramatic changes in lifestyle, such as dietary habit, reduced physical activity, and increased sedentary behavior, osteoporosis may become more common in the near future [1, 3, 7]. Therefore, promoting healthy habits is important to reduce the risk of osteoporosis.

The supply and consumption of ultra-processed foods (UPF), characterized by foods of low nutritional quality and high energy density, has increased significantly in many countries over the past two decades, and are replacing traditional diets based on unprocessed/minimally processed food (MPF) [8–10]. According to the NOVA classification, UPF are foods that have undergone intensive industrial physical, chemical or biological processes (such as hydrogenation, forming, extrusion, frying pretreatment) or contain industrial substances not commonly found in home kitchens (such as maltodextrin, hydrogenated oil or modified starch), cosmetic additives (such as dyes, emulsifiers, artificial sweeteners) or flavoring agents [11]. Studies have found that nutritional characteristics (higher fat and added sugar) [12, 13] and additives (phosphate, etc.) in UPF are directly related to bone health [14, 15]. Among them, phosphate additives have many key functions in food manufacturing, including pH stabilization, fermentation and bactericidal action [14, 15]. However, due to the wide diversity application of phosphorus-based food additives, a growing body of research suggests that consuming phosphorus (P) in excess of the nutritional requirements of healthy people may significantly disrupt the hormonal regulation of phosphate, calcium (Ca), and vitamin D (VD), which can lead to mineral metabolism disorders and bone loss [16, 17]. Physical activity as a modifiable lifestyle intervention has been shown to have a possible role in the prevention and treatment of low BMD [18]. Also, researches suggested in adolescent girls with high levels of physical activity, eating UPF is more detrimental to bone health [19]. However, roles of physical activity, serum P, serum VD and serum Ca in association between UPF and osteoporosis, as well as their pathogenesis are not fully understood.

Herein, this study aims to explore the association of UPF with osteoporosis, and assess the potential mediating effects of physical activity, serum P, serum VD and serum Ca on the pathways associated with UPF and osteoporosis, in order to provide some multi-dimension ideas in osteoporosis prevention.

Methods

Study design and participants

In this cross-sectional study, data of participants were obtained from the National Health and Nutrition Examination Survey (NHANES) database in 2005–2010 and 2013–2014. The NHANES is conducted by the Centers for Disease Control and Prevention (CDC) and the National Center for Health Statistics (NCHS) with the aim of assessing nutritional and health status of the noninstitutionalized population in the United States. NHANES uses a complex, multistage stratified probability sample based on selected counties, blocks, households, and persons within households. Interviews conducted by the NCHS well trained professionals in individuals' homes, and extensive physical examinations were conducted at mobile exam centers (MECs). More information is shown elsewhere: https://www.cdc.gov/nchs/nhanes/index.htm.

Initially, there were 41,209 adults in the database. We included those who aged > 20 years old with information on dietary intake and bone densitometry. The exclusion criteria were without information on education level, smoking status, marital status, body mass index (BMI), cardiovascular disease (CVD), dyslipidemia, serum Ca, or P. Finally, 10,678 were eligible. NHANES has obtained ethical approval from the institutional review board (IRB) of NCHS. All extracted data were de-identified, and the participants have provided informed consent. Since this database is publicly available, ethical approval has been waived from the IRB of Chinese People's Liberation Army General Hospital.

Assessment of food consumption

Food items recorded in the NHANES were allocated into 4 mutually exclusive food groups, including MPF, processed culinary ingredient (PCI), processed foods (PF) and UPF, basing on the NOVA framework, which classifies food items according to the extent and purpose of food processing [20]. Dietary intake information from participants were collected and recorded by NHANES interviewers via two 24-hour dietary recalls. The first 24-hour recall interview was conducted in person in the MEC, and the second interview was performed through telephone or mail 3 to 10 days later [21]. We further

categorized these foods in detail according to What We Eat in America (WWEIA), and used food code energy values provided by NHANES to calculate energy intake with quartiles or medians. More details on the cut-off values of different ingredients were shown in the Figure S1.

Diagnosis of osteoporosis and measurement of BMD

BMD was measured using dual-energy X-ray absorptiometry (DXA). More information on DXA examination protocol could be found in the Body Composition Procedure Manual of the NHANES. BMD at the total femur and femur neck was used to calculate the T-score, with the following formula: respondent's BMD – reference group mean BMD / reference group standard deviation (SD) [22, 23]. The reference group consisted of non-Hispanic White women aged 20–29 years from NHANES. Osteoporosis was defined as femur neck or total femur BMD T-score ≤ -2.5.

Variables selection

We also selected variables as potential covariates from the database, including age, gender, education level, race, marital status, poverty income ratio (PIR), smoking, drinking, BMI, physical activity, P, vitamin D, Ca, diabetes mellitus (DM), hypertension, CVD and dyslipidemia.

During the NHANES household interview, participants who had a positive response to the question "smoked at least 100 cigarettes in life" were categorized into smoking [24]. Similarly, the pattern of alcohol consumption was captured by questionnaires with the unit of times per week [25, 26]. Physical activity was converted into weekly energy expenditure through the formula: weekly energy expenditure (MET·min/week)=recommended metabolic equivalent (MET) × weekly exercise time of corresponding activity (min).

Hypertension was defined as self-reported high blood pressure or systolic blood pressure (SBP)≥140 mmHg or diastolic blood pressure (DBP)≥90 mmHg or taking hypotensive drugs. Dyslipidemia referred to total cholesterol (TC)≥200 mg/dL (5.2 mmol/L) or triglyceride (TG)≥150 mg/dL (1.7 mmol/L) or low-density lipoprotein cholesterol (LDL-C)≥130 mg/dL (3.4 mmol/L) or high-density lipoprotein cholesterol (HDL-C)≤40 mg/dL (1.0 mmol/L) or self-reported hypercholesterolemia or lipid-lowering therapy [27]. Participants with fasting blood glucose≥126 mg/dL or glycosylated hemoglobin (HbAlc)≥6.5% or 2-hour oral glucose tolerance test (OGTT)≥200 or self-reported DM or receiving hypoglycemic therapy were considered as DM patients [28]. Self-reported CVDs (including coronary heart disease, stenocardia, heart failure, heart attack and stroke) as well as cardiovascular drugs were used for CVD diagnosis.

Statistical analysis

Continuous data were described by mean±standard error (mean±SE). T test was used for comparation between osteoporosis group and non-osteoporosis group. Categorical data were expressed as frequency and constituent ratio [N (%)]. Chi-square test (χ^2) was utilized for comparison. According to the NHANES recommendation, the special sample weights "Full Sample 2 Year MEC Exam Weight (WTMEC2YR)" should be utilized due to the combination of data from 4 cycles. Linear regression was utilized to explore the associations of MPF, PCI, PF and UPF with femur neck BMD and total femur BMD respectively. Weighted univariate and multivariate logistic regression analyses were employed to investigate the associations of MPF, PCI, PF and UPF with osteoporosis. Also, subgroup analyses of age, gender, physical activity, PIR, hypertension, DM, CVD, and dyslipidemia were performed. We further investigated the potential mediating effect of physical activity, serum P, serum VD and serum Ca on the pathways associated with UPF and osteoporosis, including four pathways (effect A: from UPF to intermediary factors; effect B: from intermediary factors to osteoporosis; effect C': from UPF to osteoporosis with adjustment of intermediary factors; effect C: from UPF to osteoporosis without adjustment of intermediary factors) (Figure S2). The interaction effects of physical activity, serum P, serum VD and serum Ca with UPF on osteoporosis were also assessed. Heat map and three-dimensional diagram were drawn to reflect these potential interaction effects. The evaluation indexes were β, odds ratios (ORs) and 95% confidence intervals (CIs). Two-sided $P<0.05$ was considered significant. Statistical analysis was performed using SAS 9.4 (SAS Institute, Cary, NC, USA).

Results

Characteristics of participants

Figure 1 showed the participants screening process. There are a total of 41,209 individuals in the NHANES database in 2005–2010 and 2013–2014. We included those who aged>20 years old and with information on dietary intake ($n=11311$). Then, persons missing information on education level ($n=12$), smoking ($n=2$), marital status ($n=48$), BMI ($n=46$), CVD ($n=7$), dyslipidemia ($n=328$), Ca ($n=119$), or P ($n=71$) were excluded. Finally, 10,678 were eligible.

Comparation on characteristics of participants between non-osteoporosis and osteoporosis were shown in the Table 1. Among eligible persons, 454 had osteoporosis. The average age of total population was 49.82 years old. The mean physical activity level in non-osteoporosis group was significantly higher than that in osteoporosis group (2535.90 MET·min/week vs. 1033.79 MET·min/week). Average serum P concentrations were significantly

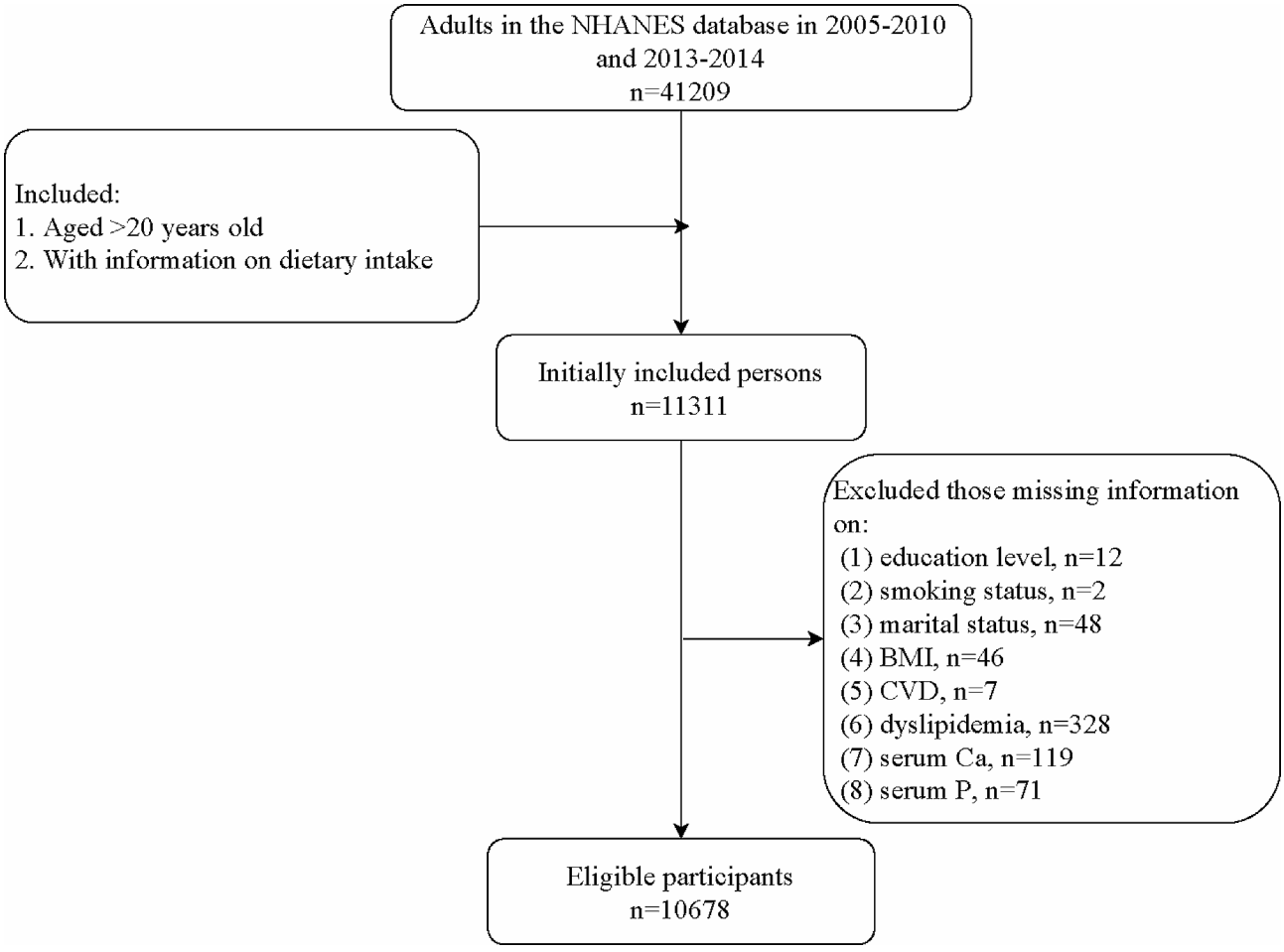

Fig. 1 Flow chart of study process

lower in non-osteoporosis group than that in osteoporosis group (1.22 mg/dL vs. 1.27 mg/dL). However, no significant difference of vitamin D or serum Ca concentrations were found between these two groups (all $P>0.05$). The average consumptions of MPF and UPF were significantly different between these two groups, whereas PCI and PF had no difference. In addition, gender, education level, race, marital status, drinking, DM, hypertension, CVD and dyslipidemia were also significantly different between non-osteoporosis group and osteoporosis group.

Associations of MPF, PCI, PF and UPF with femur neck BMD, total femur BMD and osteoporosis

Firstly, we screened the covariates associated with osteoporosis (Table S1). The results showed that age, gender, education level, race, marital status, drinking, BMI, physical activity, P, DM, hypertension, CVD, and dyslipidemia were all significantly linked to osteoporosis (all $P<0.05$), and therefore, they were included in adjustment of multivariate models.

As it shown in the Table 2, after adjusting for covariates, elevated UPF intake was associated with both decreased demur neck BMD and total femur BMD (β= -0.003, 95%CI: -0.006, -0.000). Also, UPF intake had a positive association with osteoporosis (OR=1.167, 95%CI: 1.028, 1.325), and persons who had UPF intake levels>57.51% seemed to have higher odds of osteoporosis (OR=1.789, 95%CI: 1.064, 3.007) compared to those had UPF intake levels≤57.51%. Besides, when categorizing different types of food other than UPF as non-UPF, no significant association has been observed between non-UPF and BMD or osteoporosis (Table S2).

We also assessed the associations of MPF, PCI, PF and UPF with osteoporosis in subgroups of age, gender, physical activity, PIR, hypertension, DM, CVD, and dyslipidemia (Fig. 2). Both higher levels of MPF and PCI intake were associated with lower odds of osteoporosis in persons with physical activity levels<450 MET·min/week. PCI had a negative association with osteoporosis in non-hypertension subgroup. Also, a higher level of UPF was significantly associated with higher odds of osteoporosis in age≥65 years old, female, physical activity level<450

Table 1 Characteristics of participants between osteoporosis group and non-osteoporosis group

Variables	Total (*n* = 10678)	Non-osteoporosis (*n* = 10224)	Osteoporosis (*n* = 454)	Statistics	*P*
Age, years, Mean (S.E)	49.82 (0.34)	49.14 (0.33)	68.31 (0.82)	$t = 24.739$	**< 0.001**
Gender, *n* (%)				χ^2=94.178	**< 0.001**
Male	5461 (50.06)	5323 (50.96)	138 (25.66)		
Female	5217 (49.94)	4901 (49.04)	316 (74.34)		
Education level, *n* (%)				χ^2=24.197	**< 0.001**
Less than 9th grade	1194 (5.66)	1131 (5.56)	63 (8.53)		
9-11th grade	1574 (11.06)	1492 (10.91)	82 (14.90)		
High school grad/GED or equivalent	2464 (23.12)	2357 (23.07)	107 (24.46)		
Some college or AA degree	2995 (30.32)	2883 (30.26)	112 (31.99)		
College graduate or above	2451 (29.84)	2361 (30.20)	90 (20.13)		
Race, *n* (%)				χ^2=38.478	**< 0.001**
Mexican American	1918 (7.93)	1878 (8.10)	40 (3.27)		
Other Hispanic	833 (4.25)	807 (4.33)	26 (2.09)		
Non-Hispanic White	5285 (72.19)	4974 (71.76)	311 (83.72)		
Non-Hispanic Black	1938 (9.62)	1906 (9.84)	32 (3.60)		
Other Race - including multi-racial	704 (6.02)	659 (5.97)	45 (7.32)		
Marital status, *n* (%)				χ^2=386.331	**< 0.001**
Married	6015 (61.04)	5810 (61.48)	205 (48.98)		
Widowed	890 (6.08)	744 (5.23)	146 (29.05)		
Divorced	1253 (11.27)	1196 (11.19)	57 (13.51)		
Separated	336 (2.22)	325 (2.25)	11 (1.35)		
Never married	1428 (12.63)	1400 (12.93)	28 (4.62)		
Living with partner	756 (6.76)	749 (6.92)	7 (2.50)		
PIR, *n* (%)				χ^2=4.353	0.163
≤ 1	1851 (10.91)	1767 (10.82)	84 (13.14)		
> 1	8083 (83.75)	7747 (83.89)	336 (79.93)		
Unknown	744 (5.35)	710 (5.29)	34 (6.93)		
Smoking, *n* (%)				χ^2=0.434	0.579
Yes	5078 (47.10)	4865 (47.04)	213 (48.76)		
No	5600 (52.90)	5359 (52.96)	241 (51.24)		
Drinking, *n* (%)				χ^2=66.624	**< 0.001**
No	1300 (9.70)	1190 (9.25)	110 (21.85)		
Yes	8971 (87.14)	8645 (87.57)	326 (75.52)		
Unknown	407 (3.15)	389 (3.17)	18 (2.63)		
BMI, Mean (S.E)	28.15 (0.11)	28.29 (0.11)	24.25 (0.23)	$t = -15.730$	**< 0.001**
Physical activity, MET·min/week, Mean (S.E)	2482.24 (74.27)	2535.90 (76.89)	1033.79 (113.69)	$t = -10.868$	**< 0.001**
P, mg/dL, Mean (S.E)	1.22 (0.00)	1.22 (0.00)	1.27 (0.01)	$t = 3.805$	**< 0.001**
Vitamin D, nmol, Mean (S.E)	23.96 (1.19)	24.06 (1.20)	21.52 (2.19)	$t = -1.267$	0.210
Ca, nmol, Mean (S.E)	9.47 (0.01)	9.47 (0.01)	9.50 (0.02)	$t = 1.279$	0.206
DM, *n* (%)				χ^2=5.119	**0.027**
No	9003 (88.54)	8639 (88.68)	364 (84.92)		
Yes	1675 (11.46)	1585 (11.32)	90 (15.08)		
Hypertension, *n* (%)				χ^2=77.264	**< 0.001**
No	4555 (46.65)	4451 (47.47)	104 (24.60)		
Yes	6123 (53.35)	5773 (52.53)	350 (75.40)		
CVD, *n* (%)				χ^2=74.479	**< 0.001**
No	9519 (91.27)	9176 (91.72)	343 (79.02)		
Yes	1159 (8.73)	1048 (8.28)	111 (20.98)		
Dyslipidemia, *n* (%)				χ^2=5.626	**0.034**
No	3101 (29.60)	2997 (29.80)	104 (24.15)		
Yes	7577 (70.40)	7227 (70.20)	350 (75.85)		
MPF, %, Mean (S.E)	9.61 (0.20)	9.54 (0.21)	11.56 (0.67)	$t = 2.874$	**0.006**
PCI, %, Mean (S.E)	2.62 (0.09)	2.63 (0.09)	2.48 (0.34)	$t = -0.436$	0.665

Table 1 (continued)

Variables	Total ($n=10678$)	Non-osteoporosis ($n=10224$)	Osteoporosis ($n=454$)	Statistics	*P*
PF, % Mean (S.E)	5.84 (0.14)	5.86 (0.15)	5.27 (0.51)	t=-1.054	0.296
UPF, %, Mean (S.E)	27.12 (0.33)	27.02 (0.33)	29.90 (1.19)	t=2.463	**0.017**

t: t test, χ^2: chi-square test

SE: standard error, PIR: poverty income ratio, BMI: body mass index, P: phosphorus, Ca: calcium, DM: diabetes mellitus, CVD: cardiovascular disease, MPF: minimally processed food, PCI: processed culinary ingredient, PF: processed foods, UPF: ultra-processed foods

Table 2 Associations of MPF, PCI, PF and UPF with femur neck BMD, total femur BMD and osteoporosis

Variables	Femur neck BMD		Total femur BMD		Osteoporosis*	
	β (95% CI)	*P*	β (95% CI)	*P*	OR (95% CI)	*P*
MPF	-0.001 (-0.004, 0.003)	0.766	-0.001 (-0.004, 0.003)	0.653	0.982 (0.864, 1.116)	0.783
PCI	0.002 (-0.001, 0.004)	0.261	0.001 (-0.002, 0.004)	0.436	0.864 (0.725, 1.028)	0.108
PF	0.001 (-0.002, 0.003)	0.642	0.001 (-0.001, 0.004)	0.298	1.002 (0.848, 1.184)	0.979
UPF	-0.003 (-0.006, -0.000)	**0.033**	-0.003 (-0.006, -0.000)	**0.035**	1.167 (1.028, 1.325)	**0.023**
MPF level						
≤ 9.49	Ref		Ref		Ref	
> 9.49	-0.000 (-0.007, 0.006)	0.892	-0.000 (-0.006, 0.005)	0.874	0.897 (0.676, 1.192)	0.459
PCI level						
≤ 0.21	Ref		Ref		Ref	
> 0.21	0.002 (-0.004, 0.008)	0.600	0.000 (-0.006, 0.006)	0.934	0.847 (0.593, 1.210)	0.366
PF level						
≤ 2.03	Ref		Ref		Ref	
> 2.03	0.003 (-0.002, 0.009)	0.270	0.005 (-0.001, 0.011)	0.099	0.829 (0.606, 1.133)	0.247
UPF level						
≤ 57.51	Ref		Ref		Ref	
> 57.51	-0.005 (-0.012, 0.002)	0.209	-0.004 (-0.011, 0.003)	0.264	1.789 (1.064, 3.007)	**0.035**

MPF: minimally processed food, PCI: processed culinary ingredient, PF: processed foods, UPF: ultra-processed foods, BMD: bone mineral density, CI: confidence interval, OR: odds ratio, Ref: reference

*Adjusted for age, gender, education level, race, marital status, drinking, BMI, physical activity, P, DM, hypertension, CVD, and dyslipidemia

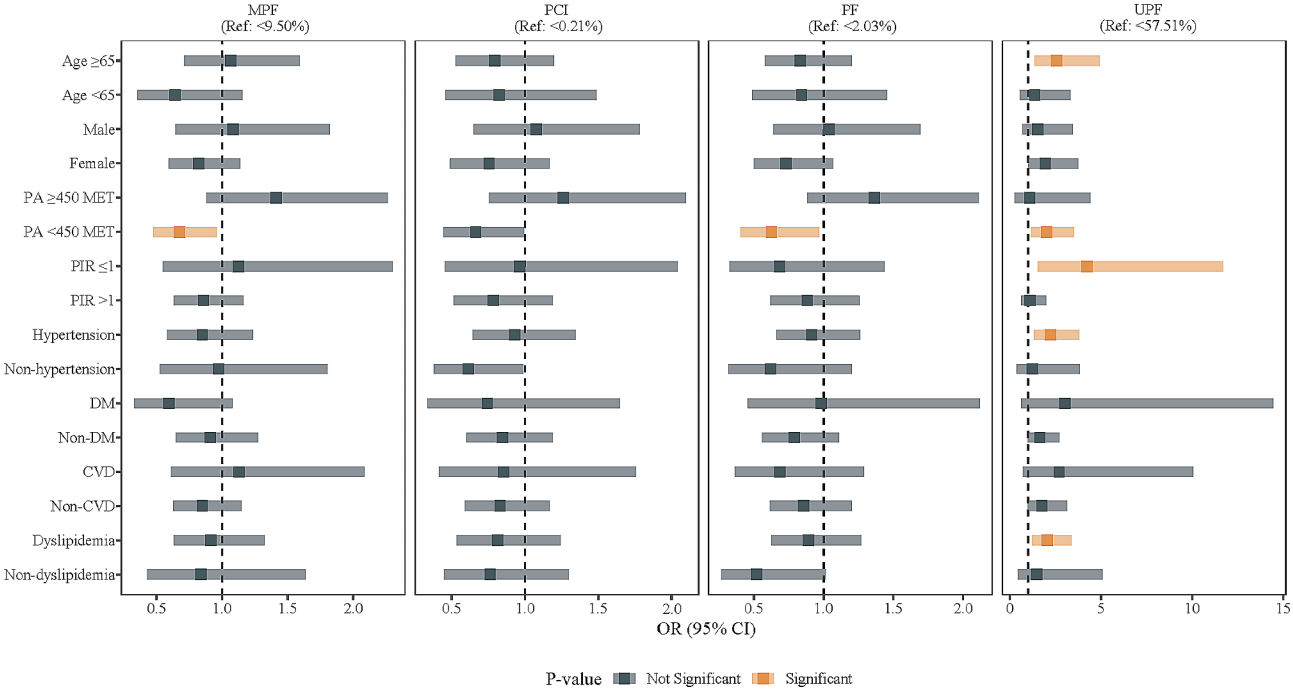

Fig. 2 Associations of MPF, PCI, PF and UPF with osteoporosis in subgroups of age, gender, physical activity, PIR, hypertension, DM, CVD, and dyslipidemia

MET·min/week, PIR≤1, hypertension, non-MD, CVD, non-CVD, and dyslipidemia subgroups (all $P<0.05$).

Mediating and interaction effects of physical activity, P, vitamin D, and Ca on association between UPF and osteoporosis

The mediating effects of physical activity, P, vitamin D, and Ca on association between UPF and osteoporosis were further evaluated (Table 3). It seemed that only physical activity had a potential mediating effect on the association between UPF and osteoporosis (OR=0.47, 95%CI: 0.26, 0.69), with the mediating proportion of 21.54%.

In addition, we respectively investigated the potential interaction effects between UPF and different factors on osteoporosis (Table 4). Comparing to individuals with low UPF intake level combined with high physical activity level, those who had low UPF intake level combined with low physical activity level (OR=1.662, 95%CI: 1.248, 2.214) or had high UPF intake level combined with low physical activity level (OR=4.225, 95%CI: 2.447, 7.295) both seemed to have higher odds of osteoporosis. Low UPF intake level combined with low serum *P* level or high UPF intake level combined with low serum *P* level were linked to higher odds of osteoporosis, compared to low UPF intake combined with high serum *P* level (all $P<0.05$). High UPF intake level combined with low serum vitamin D level was associated with higher odds of osteoporosis (OR=2.924, 95%CI: 1.683, 5.080). High UPF intake level combined with high serum Ca level and high UPF intake level combined with low serum Ca level were both linked to higher odds of osteoporosis (all $P<0.05$).

Besides, we further draw heat map (Fig. 3) and three-dimensional diagram (Fig. 4) to reflect the interaction effect between UPF and physical activity on osteoporosis. In brief, in the Fig. 3, color band represented the effect of physical activity level or UPF on the probability of osteoporosis, where the deep the yellow color, the stronger the positive correlation, and the deep the blue color, the stronger the negative correlation. It suggested that the association between UPF intake and osteoporosis probability is affected by physical activity, and conversely, the association between physical activity and osteoporosis probability is also influenced by UPF level. Additionally, Fig. 4 clearly showed that along with physical activity level increased, odds of osteoporosis associated with UPF intake was decreased.

Discussion

The current study explored the associations of UPF intake with BMD and osteoporosis, and assessed the relationship between UPF and osteoporosis in age, gender, physical activity, PIR, hypertension, DM, CVD and dyslipidemia subgroups. Also, potential interaction effect of

Table 3 Mediating effects of physical activity, P, vitamin D, and ca on association between UPF and osteoporosis

Variables	Effect A OR (95% CI)	*P*	Effect B OR (95% CI)	*P*	Effect C OR (95% CI)	*P*	Effect C′ OR (95% CI)	*P*	Mediating effects OR (95% CI)	Proportion (%)
Physical activity	0.756 (0.607, 0.941)	**0.016**	0.534 (0.402, 0.709)	**<0.001**	2.257 (1.430, 3.562)	**0.001**	2.132 (1.350, 3.368)	**0.002**	0.47 (0.26, 0.69)	21.54
P	0.820 (0.643, 1.045)	0.117	1.282 (0.962, 1.708)	0.098	2.038 (1.302, 3.190)	**0.004**	2.042 (1.299, 3.211)	**0.004**	0.20 (0, 0.41)	6.94
Vitamin D	0.867 (0.683, 1.101)	0.249	0.713 (0.519, 0.979)	**0.044**	2.042 (1.299, 3.211)	**0.004**	2.042 (1.299, 3.211)	**0.004**	0.29 (0.1, 0.48)	6.77
Ca	0.982 (0.766, 1.258)	0.886	0.937 (0.682, 1.289)	0.693	2.042 (1.299, 3.211)	**0.004**	2.042 (1.299, 3.211)	**0.004**	0.06 (-0.12, 0.25)	0.17

P: phosphorus, Ca: calcium, UPF: ultra-processed foods, OR: odds ratio, CI: confidence interval

Effect A: from UPF to intermediary factors; Effect B: from intermediary factors to osteoporosis; Effect C: from UPF to osteoporosis without adjustment of intermediary factors; Effect C′: from UPF to osteoporosis with adjustment of intermediary factors

Table 4 Interaction effects of UPF with physical activity, P, vitamin D, and ca on osteoporosis

Interaction effects	OR (95% CI)	*P*
UPF*physical activity		
Low UPF & High physical activity	Ref	
Low UPF & Low physical activity	1.662 (1.248, 2.214)	**0.001**
High UPF & High physical activity	1.116 (0.459, 2.716)	0.810
High UPF & Low physical activity	4.225 (2.447, 7.295)	**<0.001**
UPF*serum P		
Low UPF & High serum P	Ref	
Low UPF & Low serum P	1.380 (1.020, 1.869)	**0.044**
High UPF & High serum P	2.971 (1.708, 5.168)	**<0.001**
High UPF & Low serum P	1.682 (0.794, 3.560)	0.183
UPF*serum vitamin D		
Low UPF & High serum vitamin D	Ref	
Low UPF & Low serum vitamin D	1.356 (0.971, 1.893)	0.083
High UPF & High serum vitamin D	1.618 (0.692, 3.786)	0.275
High UPF & Low serum vitamin D	2.924 (1.683, 5.080)	**<0.001**
UPF*serum Ca		
Low UPF & High serum Ca	Ref	
Low UPF & Low serum Ca	1.091 (0.765, 1.555)	0.633
High UPF & High serum Ca	2.721 (1.241, 5.966)	**0.017**
High UPF & Low serum Ca	1.978 (1.064, 3.680)	**0.038**

P: phosphorus, Ca: calcium, UPF: ultra-processed foods, OR: CI: confidence interval, Ref: reference

physical activity on association between UPF and osteoporosis, and mediating effects between UPF and physical activity, P, vitamin C, and Ca on osteoporosis were investigated. According to the study results, higher UPF intake was linked to higher odds of both femur neck and total femur BMD and osteoporosis. The positive association between UPF and osteoporosis were also observed in age≥65 years old, female, physical activity level<450 MET·min/week, PIR≤1, hypertension, non-MD, CVD, non-CVD, and dyslipidemia subgroups. Also, physical activity had a potential mediating effect on the relationship between UPF and osteoporosis. There were possible interaction effects between UPF and different influencing factors on osteoporosis.

With the wide application of UPF, the negative implications for health have been recognized, but their effect on skeletal development has little been explored. Zaretsky et al. [12] showed that BMD decreases significantly in young rats fed UPF rich in fat and sugar. Gutiérrez et al. [29] performed a feeding study of 10 healthy individuals and found that the enhanced *P* content of PF can disturb bone and mineral metabolism in humans. Results in the present study similarly suggested a negative association between UPF and femur neck/total femur BMD, and a higher level of UPF intake was linked to higher odds of osteoporosis. Information of our study participants were extracted from the NHANES database that includes large samples of representative populations in the United States, which may further verify the associations of UPF intake with BMD and osteoporosis. However, comparing to Gutiérrez's research, no significant association between PF and BMD/osteoporosis was observed in our research. A possible reason may be the large size and representative subjects we included from the NHANES database. Meanwhile, we have adjusted covariates (including serum *P* level) significantly associated with osteoporosis in the multivariate models, and if serum *P* level was not included in the adjustment, the associations of PF with BMD/osteoporosis are still not significant (Table S3). These findings also indicating that whether *P* plays a major role in association between PF and bone health still need further clarification by large-sample prospective cohort study. Besides, we also divided participants into different groups according to the proportion of UPF in total dietary intake, including UPF percentage of <17.8%, 17.8-32.3% and >32.3% (Table S4). It could be found that difference in education level and race was significant among three groups, indicating the difference of race, lifestyle habits, and awareness and knowledge of health may influence UPF intake level. Also, the proportion of persons who smoking, with hypertension or with osteoporosis was all the highest in UPF percentage>32.3% group, suggesting multiple health conditions in individuals with different UPF intake percentages. The further association analysis similarly showed negative association between UPF percentage and BMD, and that positive association between UPF percentage and osteoporosis (Table S5). Overall, taking steps to reduce UPF intake and the proportion of UPF in total dietary intake through health promotion, correcting unhealthy habits or health examination, may reduce the potential risk of bone mineral density loss and osteoporosis. Nevertheless, the causal associations of UPF with BMD and osteoporosis are still needed to be clarified.

Besides, we investigated the association of UPF intake with osteoporosis in different subgroups. The results showed that this positive association was significant in age≥65 years old, female, physical activity<450 MET·min/week, PIR≤1, hypertension, non-DM, CVD/non-CVD, and dyslipidemia subgroups. It is well known that osteoporosis is the most common bone disease in adults and confers significant morbidity and mortality in older persons and women [30, 31]. Estrogen deficiency, aging processes including inflammatory processes, increased parathyroid hormone levels, Ca and vitamin D insufficiency, or osteoblast dysfunction were all risk factors for osteoporosis [32, 33]. A cross-sectional study in Korean adults showed that in women aged≥65 years, a decreased frequency of performing strengthening exercises was associated with a higher risk of osteosarcopenia after adjusting for several confounding factors and protein intake [34]. Also, another cross-sectional study from the NHANES 2007–2018 found physical activity ranging

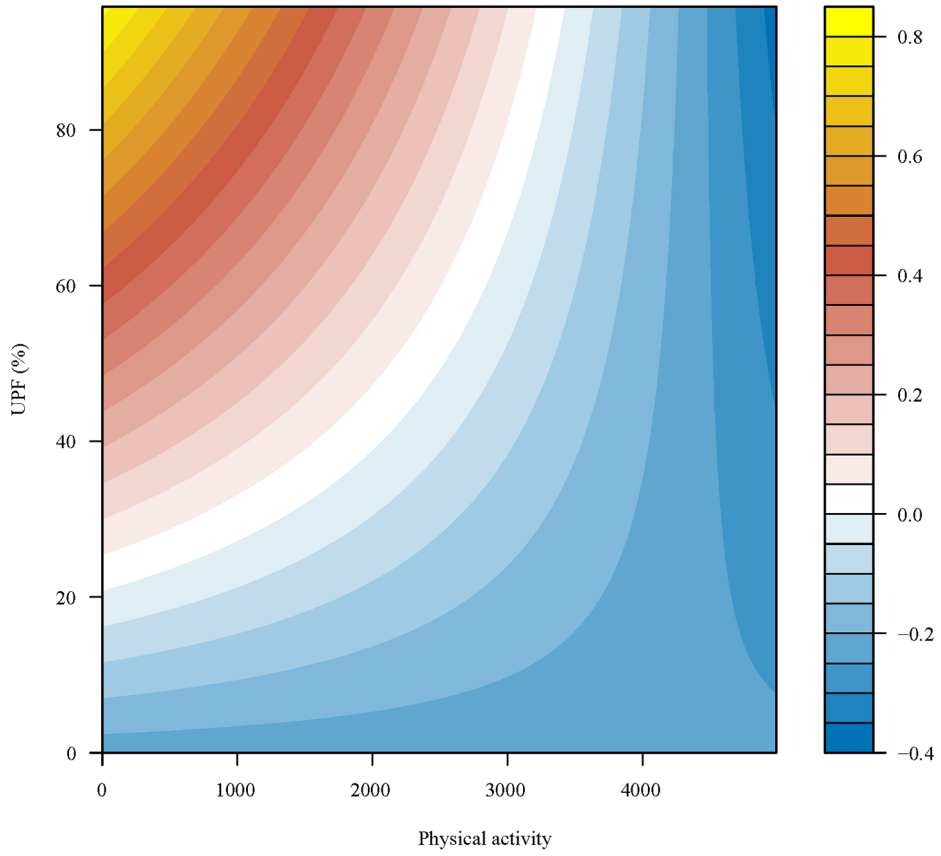

Fig. 3 Heat map of potential interaction effect between UPF and physical activity on osteoporosis. The color band represents the effect of physical activity level or UPF on the probability of osteoporosis. The deep the yellow color, the stronger the positive correlation; the deep the blue color, the stronger the negative correlation

from moderate to vigorous was linked to higher total spine BMD in postmenopausal women [35]. Min et al. [36] considered that the higher the intensity of physical activity is, the lower the rate of occurrence of each osteoporotic fracture. In this study, we categorized the physical activity level into with cut-off value of 450 MET·min/week, and found that higher level of physical activity had potential mediating effect on association between UPF and osteoporosis. Epidemiological evidence suggested that higher consumption of UPF is associated with increased risk of CVD, and main biological pathways include altered serum lipid concentrations, modified gut microbiota and host-microbiota interactions, obesity, inflammation, oxidative stress, dysglycemia, insulin resistance, and hypertension [37]. Therefore, our findings indicated that no matter individuals have a chronic disease, UPF consumption should be concerned about, to reduce the potential risk of osteoporosis.

In addition to old age and postmenopausal period, other risk factors, such as endocrine disorders, inflammatory arthropathy, and nutrition disorders, can also be involved in pathogenesis of osteoporosis [38]. Adequate protein intake is essential for bone matrix formation and maintenance, and high fat intake can directly interfere with intestinal Ca absorption. UPF are energy-dense, nutritionally unbalanced products, low in fiber but high in saturated fat, salt, and sugar [39]. Increased fat accumulation and obesity that results from a high intake of fat and/or refined carbohydrates, may decrease osteoblast differentiation and bone formation [40]. Sodium is also associated with calciuria, which leads to increased bone remodeling and bone loss [41]. In the current study, high UPF intake combined with high or low serum Ca level was associated with higher odds of osteoporosis comparing to the idea situation (low UPF intake combined with high serum Ca level). *P* intake in excess of the nutrient needs of healthy adults is thought to disrupt hormonal regulation of P, Ca, and vitamin D, contributing to impaired peak bone mass, bone resorption, and greater risk of fracture [42]. Similarly, we observed that serum levels of *P* and vitamin D had potential interaction effects with UPF on osteoporosis. In Gutiérrez's study, consumption of a diet rich in P-based food additives but stable for Ca increased circulating fibroblast growth factor 23, osteopontin, and osteocalcin concentrations relative to baseline values and decreased mean sclerostin

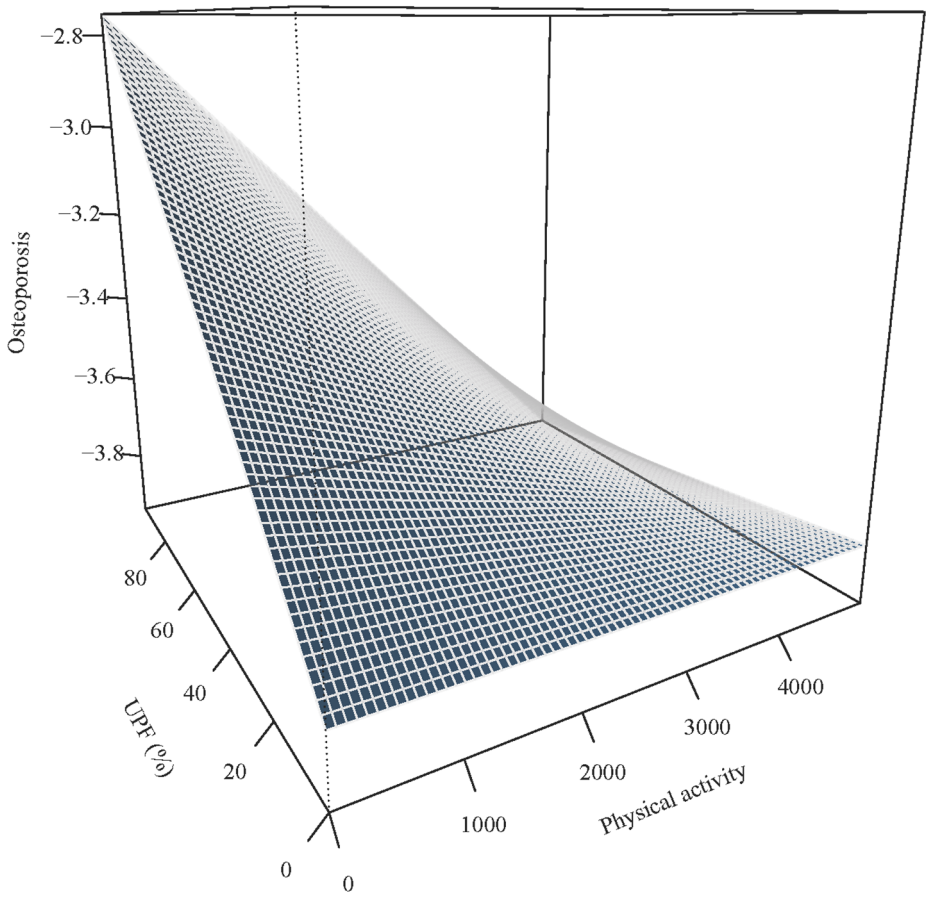

Fig. 4 Three-dimensional diagram of potential interaction effect between UPF and physical activity on osteoporosis

concentrations in healthy individuals [29]. Also, vitamin D may be involved in the UPF-associated osteoporosis process by regulating obesity and metabolic related diseases [43]. However, the specific mechanisms that interaction effects between UPF and different influencing factors on osteoporosis require further exploration.

Physical activity is considered an excellent support for bone health. Researchers considered during physical exercise, the forces transmitted through the skeleton on the bone generate mechanical signals that are recognized by osteocytes, and in turn, trigger a cascade of biochemical responses that lead to an increase in bone turnover and net to bone deposition [44]. Marty et al. [45] suggested that physical activities improve muscle mass, strength and function. The combination of exercise and proper nutrition induces mitochondrial biogenesis and function and increases the number/function of satellite cells, while inhibits inflammatory cytokines, leading to increased protein synthesis and decreased protein degradation [46]. According to our findings, physical activity have a potential mediating effect on the pathway of UPF intake and osteoporosis, and low physical activity level combined with UPF intake (low/high level) was associated with higher odds of osteoporosis. We speculated that appropriate physical activity may work by alleviating oxidative stress associated with high level of UPF intake, mitochondrial dysfunction, regulating inflammation, and promoting the balance of nutrients such as vitamin D, Ca, fat, and protein. Various scientific societies have published various guidelines and recommendations that the best option in the patient already suffering from osteopenia or osteoporosis is a combined training program. For example, the Osteoporosis Canada: Too Fit to Fracture recommend two or more times a week progressive resistance training, daily balance exercises, and 150 min a week of aerobic physical activity [47]. Similarly, individuals who expose to high levels of UPF may also apply to these exercise guidelines to reduce potential osteoporosis risk.

This study explored the mediating effect of physical activity in association between UPF intake and osteoporosis, as well as the potential interactions between UPF and different influencing factors on osteoporosis based on the NHANES database. The study results may provide some new idea for lifestyle intervention in prevention of osteoporosis in general adult population. However, there

are also some limitations. This is a cross-sectional study that is unable to clarify causal associations of UPF with BMD/osteoporosis. Information on dietary was self-reported that the information bias was inevitable, and the 24-hour dietary recalls could only reflected recent dietary trends. Therefore, further prospective long-term cohort studies are needed to verify the causal association between UPF intake and osteoporosis, as well as the mediating role of physical activity in this pathway.

Conclusion

A higher level of UPF intake was associated with higher odds of osteoporosis, and physical activity may play a potential regulating role in this association. However, the causal association between UPF and osteoporosis, and the mediating effect of physical activity on UPF-associated osteoporosis needs further clarification.

Abbreviations

BMD	Bone mineral density
WHO	World Health Organization
UPF	Ultra-processed foods
MPF	Minimally processed food
P	Phosphorus
Ca	Calcium
VD	Vitamin D
NHANES	National Health and Nutrition Examination Survey
CDC	Centers for Disease Control and Prevention
NCHS	National Center for Health Statistics
MECs	Mobile exam centers
BMI	Body mass index
CVD	Cardiovascular disease
PCI	Processed culinary ingredient
PF	Processed foods
WWEIA	What We Eat in America
DXA	X-ray absorptiometry
SD	Standard deviation
PIR	Poverty income ratio
DM	Diabetes mellitus
MET	Metabolic equivalent
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
TC	Total cholesterol
TG	Triglyceride
LDL-C	Low-density lipoprotein cholesterol
HDL-C	High-density lipoprotein cholesterol
HbAlc	Glycosylated hemoglobin
OGTT	Oral glucose tolerance test
ORs	Odds ratios
CIs	Confidence intervals

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12986-024-00843-7.

Supplementary Material 1: Figure 1. The cut-off values of classification of MPF, PCI, PF, UPF, serum VD, serum P, serum Ca and physical activity. The blue columns represent distribution of points with values lower than the cut-off values; the orange columns represent distribution of points with values higher than the cut-off values

Supplementary Material 2: Figure 2. Potential mediating effect of physical activity, serum P, serum VD and serum Ca on the pathways associated with UPF and osteoporosis. Effect A: from UPF to intermediary factors; effect B: from intermediary factors to osteoporosis; effect C': from UPF to osteoporosis with adjustment of intermediary factors; effect C: from UPF to osteoporosis without adjustment of intermediary factors

Supplementary Material 3: Table S1. Covariates associated with osteoporosis. **Table S2.** Associations of non-UPF with femur neck BMD, total femur BMD and osteoporosis. **Table S3.** Associations of MPF, PCI, PF and UPF with BMD/osteoporosis. **Table S4.** Characteristics of participants in different UPF percentage groups. **Table S5.** Associations of different UPF levels with femur neck BMD, total femur BMD and osteoporosis

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None.

Author contributions

SFW designed the study and wrote the manuscript. SFW, JSX, DDZ, ZW and HXQ collected, analyzed, and interpreted the data. MHD critically reviewed, edited, and approved the manuscript. All authors read and approved the final manuscript.

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Data availability

The datasets used and analyzed during the current study are available from the NHANES database: https://www.cdc.gov/nchs/nhanes/index.htm.

Declarations

Ethics approval and consent to participate

The NHANES has obtained ethical approval from the institutional review board (IRB) of NCHS. All extracted data were de-identified, and the participants have provided informed consent. Since this database is publicly available, ethical approval has been waived from the IRB of Chinese People's Liberation Army General Hospital.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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