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Association between dietary selenium intake and the risk of cardiovascular disease in US adults: a population-based study

Dan Liang[1,3], Chang Liu[2,3]✉ & Xingyu Zhang[1]✉

The relationship of dietary selenium intake and CVD remains unestablished. Our study aimed to investigate the relationship between dietary selenium intake and the risk of CVD in American adults. This cross-sectional study used data of 39,372 participants from the NHANES 2003–2018. We employed multivariable logistic regression and restricted cubic splines (RCS) to explore the association between dietary selenium intake and CVD risk. Subgroup analysis and interaction tests were also conducted to assess the influence of various covariates. For 39,372 individuals recruited in this study. The overall prevalence of CVD was 8.57%, and this prevalence decreased with increasing dietary selenium intake across tertiles. In the fully adjusted models, Tertile 2 of dietary selenium intake showed a 16% reduced risk of CVD. Subgroup analysis revealed that the association between dietary selenium intake and CVD risk remained consistent across different status. However, notably, the negative association between dietary selenium intake and the risk of ASCVD was significantly influenced by hypertension status. Dietary selenium intake could reduce the risk of CVD. A nonlinear association of dietary selenium intake with CVD risk was also revealed. These findings have important implications for establishing recommended dietary selenium intake levels to benefit public cardiovascular health.

Keywords Selenium intake, CVD, ASCVD, Cardiovascular health, NHANES, Cross-section study

Cardiovascular disease (CVD) remains the leading cause of global mortality, contributing to approximately 46% of non-communicable disease-related deaths worldwide[1,2]. In the United States alone, an estimated 85.6 million individuals live with some form of CVD, and this number is steadily increasing[3]. It's worth noting that the burden of CVD is even more pronounced in low- and middle-income countries when compared to high-income counterparts[4]. Common risk factors for CVD encompass hypertension, diabetes mellitus, hyperlipidemia, as well as several adverse lifestyle choices such as smoking, physical inactivity, and excessive consumption of processed foods[5–7].

Selenium (Se), an essential micronutrient, naturally exists in a variety of foods, including grains, nuts, seafood, red meat, and dairy products[8]. This trace element is crucial for the enzymatic functions of selenoproteins, and selenium deficiency impairs the ability of cells and tissues to produce these proteins in sufficient amounts, leading to various health issues associated with inadequate selenium intake[9].

Previous research has shed light on the multifaceted impact of dietary selenium intake on various aspects of health. For example, a cross-sectional study found that intake of dietary selenium reduced the incidence of kidney stones in adults aged 60 and older[10]. Moreover, selenium's role in reducing the risk of rheumatoid arthritis and arthritis, as well as its positive influence on bone density, has been documented[11,12]. Dietary selenium intake also improved cognitive function in older adults[13]. Interestingly, a nonlinear, inverse association between dietary selenium intake and the risk of stroke in adults has also been observed[14]. However, it's essential to recognize that the relationship between dietary selenium intake and health outcomes may vary across different populations. Another study of Brazilian adolescents found no significant association between dietary selenium intake and CVD-related risk factors such as high blood pressure, high blood glucose, and high cholesterol[15]. Despite these valuable insights, there is a lack of large-scale studies examining the specific impact of dietary selenium intake on CVD in the general population. Consequently, there is a pressing need for further research in this area,

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aiming to elucidate the relationship between dietary selenium intake and CVD incidence. Such studies could help determine optimal dietary selenium levels for promoting cardiovascular health.

Therefore, our study aimed to investigate the association between dietary selenium intake and the risk of CVD based on the American National Health and Nutrition Examination Survey (NHANES). Our findings may provide evidence supporting a potential inverse association between dietary selenium intake and the risk of CVD.

Materials and methods

Survey description

The National Health and Nutrition Examination Survey (NHANES) is a nationally representative, serial cross-sectional survey conducted in the United States. NHANES employs a complex, stratified, multistage probability cluster design to gather comprehensive health and nutritional data from the noninstitutionalized civilian population. Detailed information regarding survey methods and analytical guidelines is publicly accessible. Data collection for NHANES includes home interviews, physical examinations, and laboratory assessments. The survey interview covered a wide range of topics, including demographics, socioeconomic status, dietary habits, and health-related inquiries. The examination component involved thorough medical, dental, and physiological evaluations, all conducted by highly trained medical professionals. The NHANES study protocol received ethical approval from the National Center for Health Statistics (NCHS) Research Ethics Review Board, and all participants provided written informed consent as a prerequisite for their involvement.

Study population

We utilized continuous NHANES data from survey cycles 2003–2018, collected at 2-year intervals, for our initial sample. These survey cycles provided comprehensive information on dietary selenium intake and various cardiovascular conditions, including CVD, congestive heart failure, coronary heart disease, atherosclerotic cardiovascular disease, heart attack, angina, and stroke. Initially, our study enrolled 80,312 participants. After exclusions for individuals under 20 years of age (n = 35,522) and those with missing data on dietary selenium intake (n = 5,033) or with missing data on specific cardiovascular conditions (CVD: n = 6, congestive heart failure: n = 106, coronary heart disease: n = 118, atherosclerotic cardiovascular disease: n = 0, heart attack: n = 43, angina: n = 74, stroke: n = 38), the final analysis included 39,372 participants (Fig. 1).

Assessment of dietary selenium intake

All NHANES participants were eligible for two 24-h dietary recall interviews. The initial interview was conducted in person at the Mobile Examination Center (MEC), while the subsequent interview was completed via telephone within 3 to 10 days. Dietary selenium intake was assessed using the University of Texas Food Intake Analysis System and the US Department of Agriculture Survey Nutrient Database. Nutrients obtained from dietary supplements or medications were excluded from the nutrient estimates. This methodology ensured

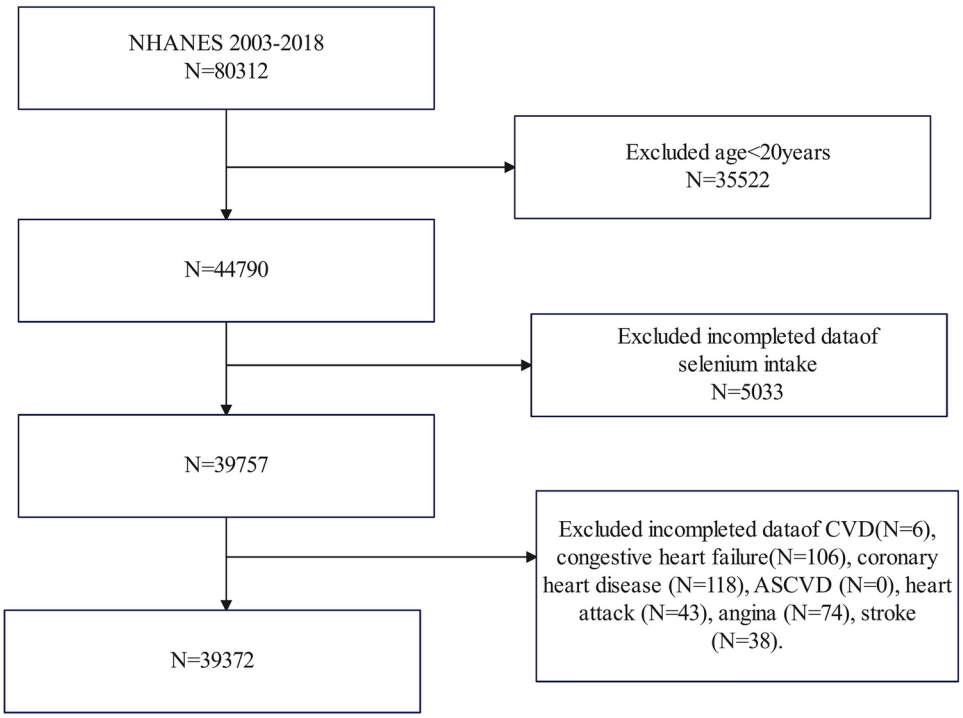


Fig. 1. Flowchart of the sample selection from National Health and Nutrition Examination Survey (NHANES) 2003–2018.

a comprehensive and accurate evaluation of dietary selenium intake from natural food sources, eliminating any potential confounding effects from supplementary sources.

Assessment of cardiovascular disease

The medical conditions section, identified by the variable name prefix MCQ, comprises self- and proxy-reported data from personal interviews, covering a wide range of health conditions and medical history for both children and adults. This section includes questions such as 'Has a doctor or other health professional ever told you/SP that you/him/her… had congestive heart failure, coronary heart disease, angina (also called angina pectoris), heart attack (also called myocardial infarction). stroke, etc.?' These questions were designated as MCQ160B-F in the household questionnaires administered through home interviews. Participants responding 'yes' to any of these questions were considered to have a history of cardiovascular disease (CVD). We established a composite endpoint for CVD, encompassing coronary heart disease (CHD), atherosclerotic cardiovascular disease (ASCVD), angina, stroke, and congestive heart failure (CHF) as primary outcomes. Additionally, we separately analyzed events related to CHD, ASCVD, angina, stroke, and CHF as secondary outcomes.

Selection of covariates

During household interviews, a range of variables were collected, including age, gender, race, educational levels, family income-to-poverty ratio (PIR), and alcohol consumption history. Body Mass Index (BMI) was computed by dividing weight (in kilograms) by the square of height (in meters). Participants were classified as normal weight (< 25 kg/ m^2), overweight (25–29.9 kg/m^2), or obese (≥ 30 kg/ m^2) based on their BMI. The LE8 scoring algorithm encompasses eight cardiovascular health (CVH) metrics, which are categorized into two groups: four health behaviors (diet, physical activity, nicotine exposure, and sleep duration) and four health factors (body mass index [BMI], non-high-density-lipoprotein cholesterol, blood glucose, and blood pressure). Detailed algorithms for calculating the LE8 scores for each metric using NHANES data have been previously published. Additionally, we summarized other covariates such as total energy intake, diabetes (DM), and hypertension. Blood pressure measurements were obtained by physicians using mercury sphygmomanometers following a standard protocol in the MEC. DM was defined as either treatment or medical diagnosis of hyperglycemia with hemoglobin A1c $\geq 6.5\%$, fasting blood glucose ≥ 126 mg/dL, or a 2-h blood glucose ≥ 200 mg/dL[16]. Hypertension was defined as the use of antihypertensive medications, a medical diagnosis of hypertension, or three consecutive measurements of systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg[17].

Statistical analysis

All statistical analyses were conducted following the guidelines established by the CDC. Given that NHANES employs a complex probability sample design and oversamples certain populations to ensure representativeness, we applied sample weights to combine data from multiple survey cycles and estimate means and standard deviations. Continuous variables were presented as means ± standard deviations, while categorical variables were expressed as percentages. To assess differences in the descriptive analyses, we employed the weighted student's t-test for continuous variables and the weighted chi-square test for categorical variables. Multivariate logistic regression was employed to examine the correlation between dietary selenium intake (dependent variable) and the risk of cardiovascular disease (CVD) (independent variable) using three different models for statistical inference. Model 1 was unadjusted, while Model 2 corrected for age, gender, and race. Model 3 included adjustments for age, gender, race, education level, body mass index (BMI), total energy intake, diabetes (DM), hypertension, drinking status, and the LE8 score. Sensitivity analyses were conducted by categorizing dietary selenium intake into tertiles to evaluate the robustness of the results and assess the risk of CVD across these tertiles. To further investigate the association between dietary selenium intake and the risk of CVD, restricted cubic splines (RCS) with 3 knots at the 10th, 50th, and 90th percentiles were performed[18,19]. For subgroup analysis of the association between dietary selenium intake and the likelihood of CVD, we stratified the data by gender (male/female), age ($< 60 / \geq 60$ years), BMI (normal weight/overweight/obesity), hypertension (yes/no), DM (yes/no), and alcohol use (yes/no). These stratified factors were also considered as potential effect modifiers. A significance level of $P < 0.05$ was used to indicate statistical significance. All analyses were conducted using R version 4.3.2 (http://www.R-project.org, The R Foundation).

Results

Participants characteristics at baseline

Table 1 presents the clinical characteristics of the 39,372 participants categorized into tertiles based on their dietary selenium intake. The mean age of the participants was 47.27 ± 0.23 years, with 51.79% female and 48.21% male. The average dietary selenium intake was 114.67 ± 0.53 μg/d. The overall prevalence of CVD was 8.57%, and this prevalence decreased as dietary selenium intake increased across tertiles (Tertile 1: 11.10%, Tertile 2: 8.12%, Tertile 3: 6.75%). Participants in the highest dietary selenium intake tertile exhibited a reduced risk of stroke, CHF, CHD, ASCVD, heart attack, and angina compared to those in the lowest tertile. Factors such as age, total energy intake, LE8 score, gender, race, PIR, educational levels, BMI, DM, hypertension, and alcohol use significantly differed among the dietary selenium intake tertiles (all $P < 0.05$). Compared to those in the lowest tertile of dietary selenium intake, participants in the highest tertile tended to be younger, had higher LE8 scores and total energy intake, were more likely to be male and alcohol users, had normal weight, and had a higher proportion of Mexican Americans and also higher income and educational levels. Additionally, they had a lower prevalence of hypertension and DM.

Dietary selenium intake	All participants	Tertiles 1	Tertiles 2	Tertiles 3	P value
Age (year)	47.27 (0.23)	49.67 (0.29)	47.80 (0.26)	44.65 (0.30)	**< 0.0001**
Total energy (Kcal/d)	2177.15 (8.21)	1445.07 (7.69)	2050.98 (7.78)	2945.09 (12.92)	**< 0.0001**
Selenium intake (μg/d)	114.67 (0.53)	55.58 (0.22)	100.89 (0.17)	180.07 (0.85)	**< 0.0001**
LE8	67.76 (0.23)	67.16 (0.29)	67.87 (0.27)	68.18 (0.29)	**0.003**
Gender (%)					**< 0.0001**
Female	51.79 (0.01)	69.48 (0.48)	56.03 (0.61)	32.10 (0.53)	
Male	48.21 (0.01)	30.52 (0.48)	43.97 (0.61)	67.90 (0.51)	
Races (%)					**< 0.0001**
Mexican American	8.35 (0.01)	7.38 (0.59)	8.19 (0.68)	9.37 (0.77)	
Non-Hispanic Black	11.20 (0.01)	12.98 (0.84)	10.51 (0.71)	10.27 (0.60)	
Non-Hispanic White	67.64 (0.03)	67.42 (1.39)	68.89 (1.30)	66.66 (1.31)	
Others	12.81 (0.00)	12.22 (0.64)	12.41 (0.61)	13.71 (0.63)	
PIR (%)					**< 0.0001**
< 1	12.96 (0.00)	16.11 (0.62)	12.99 (0.55)	12.82 (0.60)	
1–4	34.22 (0.01)	52.46 (0.91)	49.38 (0.86)	46.79 (1.01)	
> 4	46.09 (0.01)	31.44 (0.99)	37.64 (0.95)	40.39 (1.18)	
Educational levels (%)					**< 0.0001**
Less than 9th grade	5.33 (0.00)	6.73 (0.39)	4.81 (0.27)	4.58 (0.28)	
9-11th grade	10.46 (0.00)	11.66 (0.47)	10.06 (0.47)	9.78 (0.44)	
High school graduate	23.40 (0.01)	25.11 (0.60)	22.90 (0.65)	22.36 (0.65)	
Some college or AA degree	31.39 (0.01)	31.73 (0.70)	31.37 (0.63)	31.12 (0.66)	
College graduate or above	29.42 (0.01)	24.77 (0.95)	30.87 (0.89)	32.17 (1.15)	
BMI (%)					**< 0.001**
Normal weight	29.61 (0.01)	28.63 (0.70)	29.21 (0.67)	32.25 (0.64)	
Overweight	32.24 (0.01)	33.22 (0.65)	32.80 (0.63)	31.71 (0.56)	
Obesity	37.02 (0.01)	38.15 (0.76)	38.00 (0.74)	36.04 (0.60)	
DM (%)	13.79 (0.00)	14.92 (0.50)	14.30 (0.44)	12.30 (0.47)	**< 0.001**
Hypertension (%)	37.48 (0.01)	39.81 (0.71)	37.83 (0.60)	35.08 (0.71)	**< 0.0001**
CVD (%)	8.57 (0.01)	11.10 (0.43)	8.12 (0.27)	6.75 (0.36)	**< 0.0001**
Stroke (%)	2.97 (0.02)	4.41 (0.25)	2.72 (0.16)	1.92 (0.17)	**< 0.0001**
Congestive heart faliure (%)	2.29 (0.01)	3.12 (0.20)	2.,20 (0.13)	1.64 (0.17)	**< 0.0001**
Coronary heart disease (%)	3.39 (0.01)	4.10 (0.23)	3.32 (0.20)	2.83 (0.24)	**< 0.0001**
ASCVD (%)	7.84 (0.01)	10.11 (0.42)	7.42 (0.27)	6.22 (0.34)	**< 0.0001**
Heart attack (%)	3.31 (0.01)	4.06 (0.23)	3.09 (0.18)	2.87 (0.25)	**< 0.001**
Angina (%)	2.13 (0.01)	2.75 (0.19)	1.94 (0.17)	1.77 (0.17)	**< 0.001**
Alcohol user (%)	80.19 (0.02)	76.75 (0.55)	80.91 (0.53)	82.56 (0.48)	**< 0.0001**

Table 1. Baseline characteristics of the study population. *Tertiles 1, 2, 3* dietary selenium intake tertiles, *PIR* ratio of family income to poverty, *LE8* Life's essential 8, *BMI* body mass index, *DM* diabetes, *CVD* cardiovascular disease, *ASCVD* atherosclerotic cardiovascular disease. Continuous variables were presented as means ± standard deviations, while categorical variables were expressed as percentages. The values in parentheses in Table 1 represent the standard deviations (SD) for the included variables.

Association between dietary selenium intake and CVD risk

Table 2 displays the relationship between dietary selenium intake and the risk of CVD. In the crude model, when compared to the reference level (Tertile 1), a significant inverse association was observed between dietary selenium intake and the likelihood of CVD (OR = 0.71, 95%CI: 0.64–0.78, p < 0.0001 for Tertile 2; OR = 0.58, 95%CI: 0.50–0.67, p < 0.0001 for Tertile 3). After adjusting for age, sex, and race in Model 2, higher dietary selenium intake tertiles were associated with decreased CVD risk compared to the lowest tertile (OR = 0.76, 95%CI: 0.68–0.85, p < 0.0001 for Tertile 2; OR = 0.73, 95%CI: 0.63–0.86, p < 0.0001 for Tertile 3). In the fully adjusted models, Tertile 2 of dietary selenium intake showed a 16% reduced risk of CVD (OR = 0.84, 95%CI: 0.74–0.96, p = 0.01). However, this association was not significant for the highest tertile of dietary selenium intake (OR = 0.96, 95%CI: 0.78–1.17, p = 0.66).

Supplemental Fig. 1–6 show the relationship between dietary selenium intake and the risk of CHD, ASCVD, CHF, stroke, heart attack, and angina. A significantly negative association was only observed between dietary selenium intake and CHD (Model 1: OR = 0.80, 95%CI: 0.69–0.94, p = 0.01 for Tertile 2, OR = 0.68, 95%CI: 0.57–0.81, p < 0.0001 for Tertile 3; Model 2: OR = 0.82, 95%CI: 0.70–0.97, p = 0.02 for Tertile 2, OR = 0.78, 95%CI: 0.64–0.95, p = 0.01 for Tertile 3.), CHF (Model 1: OR = 0.70, 95%CI: 0.60–0.81, p < 0.0001 for Tertile 2, OR = 0.52, 95%CI: 0.41–0.66, p < 0.0001 for Tertile 3; Model 2: OR = 0.80, 95%CI: 0.67–0.94, p = 0.01 for Tertile 2, OR = 0.72,

CVD	OR (95%CI)		
	Model 1	Model 2	Model 3
Tertile 1	Reference	Reference	Reference
Tertile 2	0.71 (0.64, 0.78), p < 0.0001	0.76 (0.68, 0.85), p < 0.0001	0.84 (0.74, 0.96), p = 0.01
Tertile 3	0.58 (0.50, 0.67), p < 0.0001	0.73 (0.63, 0.86), p < 0.0001	0.96 (0.78, 1.17), p = 0.66

Table 2. Multivariate logistic regression models of CVD with dietary selenium intake. Model 1: No covariates were adjusted. Model 2: Age, gender, and race were adjusted. Model 3: Further adjusted for PIR, BMI, total energy intake, alcohol consumption and the American Heart Association's Life's Essential 8 cardiovascular health score (LE8).

95%CI: 0.56–0.93, p = 0.01 for Tertile 3.), heart attack (Model 1: OR = 0.75, 95%CI: 0.64–0.88, p < 0.001 for Tertile 2; OR = 0.70, 95%CI: 0.57–0.86, p < 0.001 for Tertile 3; Model 2: OR = 0.78, 95%CI: 0.66–0.92, p = 0.004 for Tertile 2) and angina (Model 1: OR = 0.70, 95%CI: 0.55–0.88, p = 0.003 for Tertile 2, OR = 0.64, 95%CI: 0.50–0.81, p < 0.001 for Tertile 3; Model 2: OR = 0.75, 95%CI: 0.60–0.95, p = 0.02 for Tertile 2) in both Model 1 and Model 2. Supplement Fig. 2 and 4 clearly illustrate a significant risk reduction in ASCVD and stroke for participants in the higher tertile of dietary selenium intake. Specifically, in fully adjusted Model 3, the tertile 2 of dietary selenium intake demonstrated a reduced risk for both ASCVD (Model 3: OR = 0.85, 95%CI: 0.74–0.98, p = 0.02 for Tertile 2) and stroke (Model 3: OR = 0.82, 95%CI: 0.67–0.99, p = 0.04 for Tertile 2).

When dietary selenium intake was considered as a continuous variable, we found a negative correlation between dietary selenium intake and the risk of CVD (Model 3: OR = 0.96, 95%CI: 0.94–0.99, p < 0.0001), stroke (Model 3: OR = 0.96, 95%CI: 0.93–0.98, p = 0.04) and ASCVD (Model 3: OR = 0.97, 95%CI: 0.93–0.99, p < 0.0001) (Supplemental Table 1).

Nonlinear association between dietary selenium intake and CVD risk

We also performed restricted cubic spline (RCS) analysis to explore the relationship between dietary selenium intake and the risk of CVD, stroke, and ASCVD. As shown in Fig. 2, the RCS analysis revealed a significant association between dietary selenium intake and CVD risk, exhibiting a clear nonlinear trend (P overall = 0.0002, P nonlinear = 0.0001). As dietary selenium intake increased, the risk of CVD gradually decreased to a certain threshold. However, beyond the inflection point (135.28 μg/d), this protective effect weakened, and in fact, higher selenium intake may even increase the risk of CVD.

Figures 3 and 4 further illustrate the nonlinear relationships between dietary selenium intake and the risks of stroke and ASCVD. For stroke, we found that as dietary selenium intake increased, the risk of stroke significantly decreased. However, when intake exceeded the inflection point (100.3 μg/d), this protective effect seemed to plateau, suggesting a potential saturation effect at higher levels of selenium intake for stroke risk (P overall = 0.0009, P nonlinear = 0.0057). Similarly, we observed a significant nonlinear relationship between dietary selenium intake and ASCVD risk (P overall = 0.0008, P nonlinear = 0.0002). When selenium intake was below a certain threshold (135.28 μg/d), it was negatively associated with ASCVD risk. However, beyond this threshold, a positive correlation emerged between higher selenium intake and increased ASCVD risk, indicating a potential risk for adverse outcomes at higher selenium levels.These findings suggest that while moderate dietary selenium intake may be beneficial for reducing cardiovascular risk, excessive intake beyond specific thresholds may reverse these protective effects.

Subgroup analysis

We conducted subgroup analyses and interaction tests to investigate the consistency of the relationship between dietary selenium intake and the risks of CVD, stroke, and ASCVD across different population subgroups, including age, gender, BMI, hypertension, DM, and alcohol consumption. The risk of CVD reduced in participants who were female (OR = 0.687, 95%CI: 0.577–0.819, p < 0.0001 for Tertile 2), age < 60 years (OR = 0.763, 95%CI: 0.613–0.948, p = 0.015 for Tertile 2) and > = 60 years (OR = 0.841, 95%CI: 0.724–0.976, p = 0.023 for Tertile 2) and obese (OR = 0.743, 95%CI: 0.601–0.919, p = 0.007 for Tertile 2). Both alcohol users (OR = 0.830, 95%CI: 0.696–0.991, p = 0.039) and non-alcohol users (OR = 0.762, 95%CI: 0.586–0.992, p = 0.043) in the middle dietary selenium tertile also experienced a decreased risk of CVD. Individuals with hypertension (OR = 0.757, 95%CI: 0.657–0.873, p < 0.001) and DM (OR = 0.768, 95%CI: 0.615–0.960, p = 0.021) also benefited from a middle dietary selenium intake tertile, which was associated with a lower risk of CVD (Table 3).

For the risk of stroke, a negative association was observed in participants who were female (OR = 0.768, 95%CI: 0.589–1.000, p = 0.045 for Tertile 2), under 60 years old (OR = 0.691, 95%CI: 0.485–0.985, p = 0.041 for Tertile 2) and overweight (OR = 0.583, 95%CI: 0.345–0.984, p = 0.044 for Tertile 2), and with a history of hypertension (OR = 0.775, 95%CI: 0.621–0.968, p = 0.025 for Tertile 2) and DM (OR = 0.727, 95%CI: 0.565–0.937, p = 0.014 for Tertile 2, OR = 0.657, 95%CI: 0.449–0.962, p = 0.031 for Tertile 3) (Table 4).

Regarding ASCVD, our analysis showed that dietary selenium intake was associated with a reduced risk. Statistically significant correlations were observed in females (OR = 0.701, 95%CI: 0.579–0.848, p < 0.001 for Tertile 2), individuals under 60 years old (OR = 0.783, 95%CI: 0.617–0.993, p = 0.044 for Tertile 2), those with obesity (OR = 0.758, 95%CI: 0.607–0.947, p = 0.015 for Tertile 2), DM (OR = 0.785, 95%CI = 0.628–0.982, P = 0.034 for Tertile 2), and hypertension (OR = 0.738, 95%CI: 0.633–0.859, p < 0.001).

However, interaction tests did not reveal any significant influence of gender, age, BMI, DM, or hypertension on the association between dietary selenium intake and the risk of CVD and stroke. Notably, our results

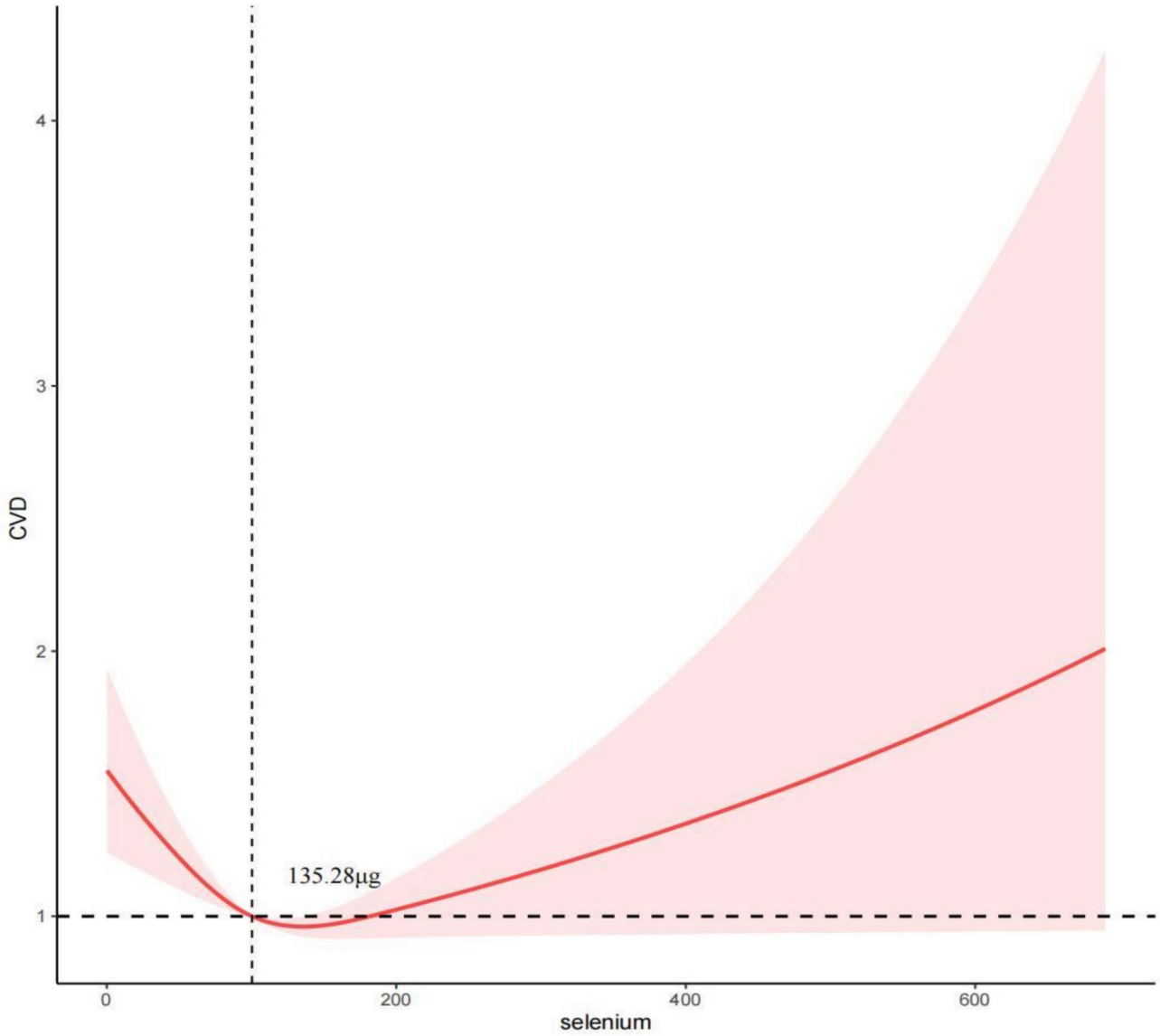


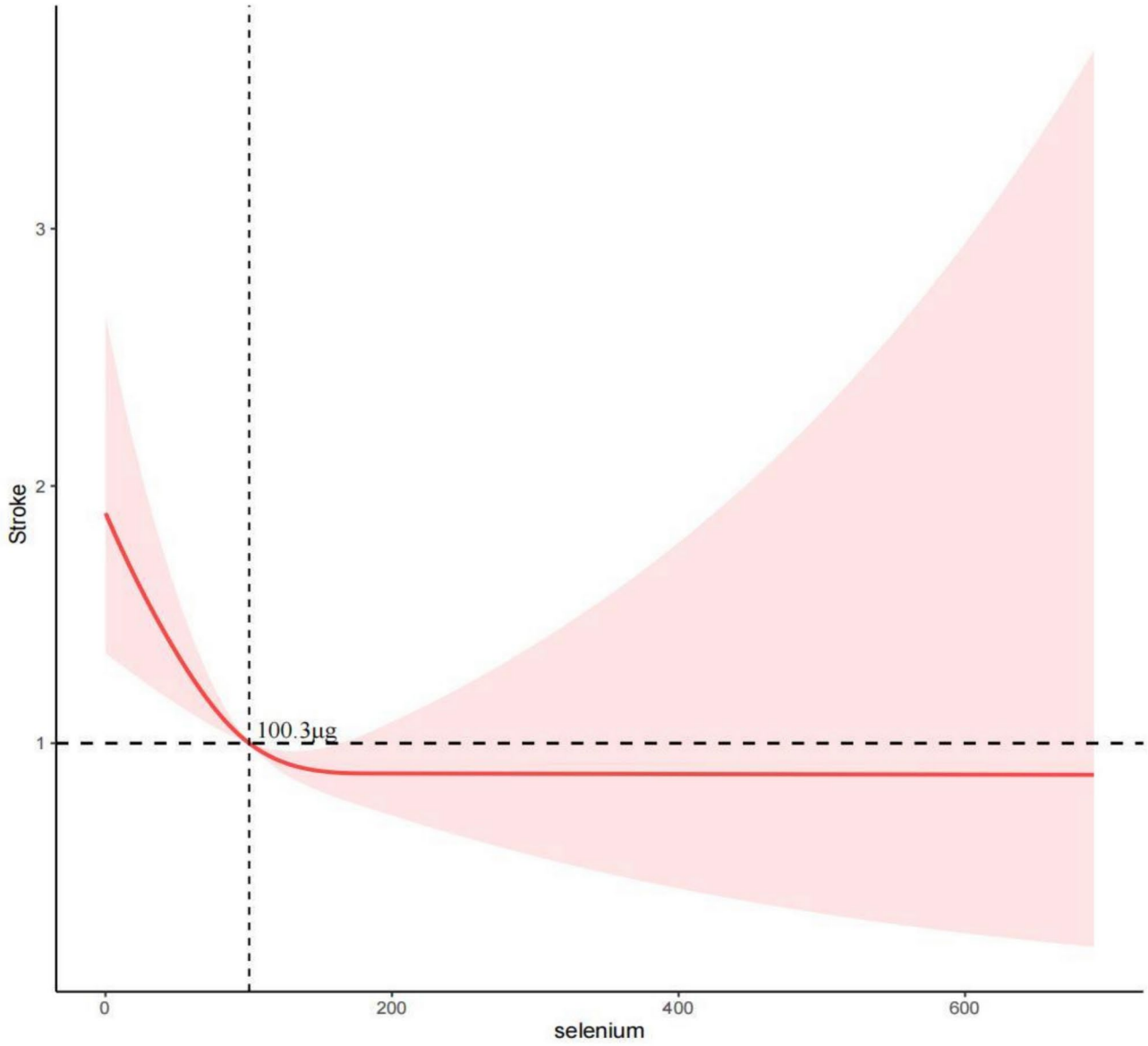
Fig. 2. The restricted cubic spline (RCS) analysis between dietary selenium intake and the risk of CVD.

indicated that the negative association between dietary selenium intake and the risk of ASCVD was significantly influenced by hypertension status (P for interaction = 0.034) (Table 5).

Furthermore, when dietary selenium intake was analyzed as a continuous variable (Supplemental Table 2, 3 and 4), we observed a significant negative correlation between selenium intake and the risk of CVD (OR = 0.994, 95%CI: 0.990–0.998, p = 0.004), stroke (OR = 0.991, 95%CI: 0.986–0.996, p = 0.001), and ASCVD (OR = 0.994, 95%CI: 0.990–0.999, p = 0.010) in women specifically. Additionally, we found that dietary selenium intake was particularly effective in reducing the risk of stroke in individuals with obesity (OR = 0.993, 95%CI: 0.988–0.999, p = 0.016). However, interaction tests did not reveal any significant influence of gender, age, BMI, diabetes (DM), or hypertension on the relationship between dietary selenium intake and the risk of CVD, stroke, or ASCVD (P for interaction > 0.05). This suggests that while dietary selenium intake may play a role in reducing the risk of these cardiovascular events, factors such as gender, age, and metabolic conditions do not appear to significantly modify this association.

Discussion

Based on NHANES data spanning from 2003 to 2018, this study demonstrated that higher dietary selenium intake was associated with a decreased risk of CVD. Subgroup analysis and interaction tests revealed that the association between dietary selenium intake and CVD risk remained consistent across gender, age, BMI, DM,



The restricted cubic spline (RCS) analysis between dietary selenium intake and the risk of Stroke (P overall=0.0009, P nonlinear=0.0057)

Fig. 3. The restricted cubic spline (RCS) analysis between dietary selenium intake and the risk of stroke.

and hypertension status. However, notably, the inverse association between dietary selenium intake and the risk of ASCVD was significantly influenced by hypertension status. These findings suggested that clinicians should prioritize monitoring and managing dietary selenium intake, especially in patients at risk for CVD.

The association between selenium and cardiovascular disease (CVD) risk has yielded mixed results across various studies. Some investigations have shown promising outcomes, while others have presented inconclusive findings. Gutiérrez-Bedmar M et al. found that higher serum selenium concentrations were linked to a reduced incidence of initial CVD in a high-risk cardiovascular population[20]. Existing studies have shown a nonlinear relationship between selenium concentration in the blood and the risk of cardiovascular disease (CVD), particularly within the range of 30–165 μg/L[21]. In this narrow range of 55–145 μg/L, the risk of cardiovascular disease is significantly reduced, highlighting the health benefits of an optimal selenium level[21]. However, in the aforementioned studies, the assessment of selenium status was primarily based on selenium concentrations in the serum, rather than on dietary selenium intake. This approach overlooks the fact that diet is the primary source of selenium for the human body, with approximately 80% of dietary selenium being effectively absorbed[22]. Given this, evaluating the risk of CVD based on selenium intake from dietary sources seems to be a more practical and meaningful approach. A study by Gharipour et al. did not observe significant changes in the expression levels of key enzymes associated with oxidative stress, namely cyclooxygenase-2 (COX-2) and matrix metallopeptidase-9

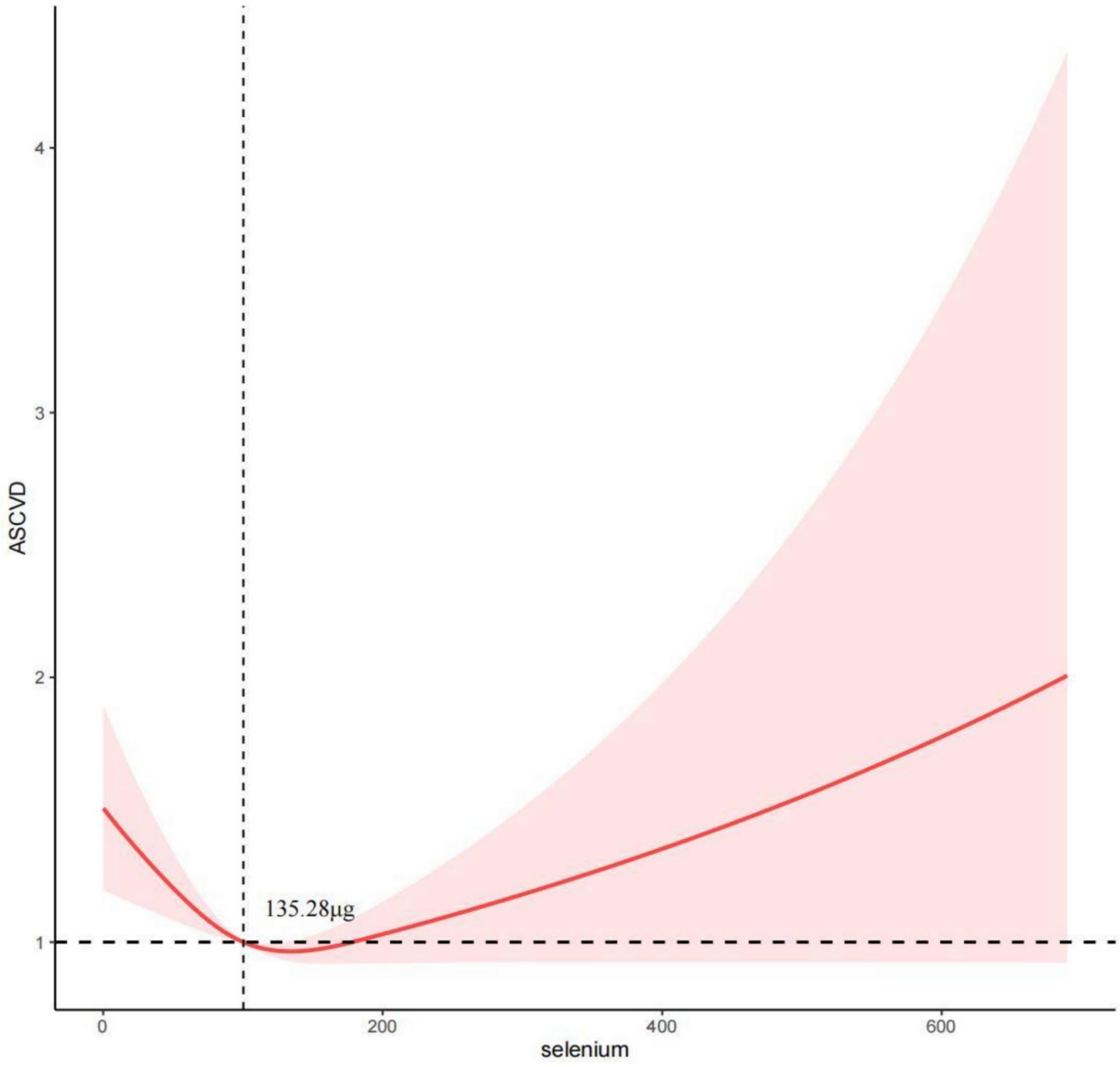


Fig. 4. The restricted cubic spline (RCS) analysis between dietary selenium intake and the risk of ASCVD.

(MMP-9), in CVD patients following selenium supplementation[23]. These enzymes are considered pivotal factors in CVD development. Additional research by Kuria et al. found that individuals with high selenium status experienced a 34% and 31% reduction in CVD morbidity and all-cause mortality, respectively, compared to those with low selenium status[24]. Moreover, several studies have reported positive outcomes, demonstrating that selenium supplementation can reduce cardiovascular mortality[25–28]. However, the precise impact of selenium on CVD risk remains a subject of debate. One meta-analysis revealed a significant negative association between selenium status and CVD risk within a narrow range of selenium levels in prospective studies. However, it found no substantial effect of selenium supplementation on cardiovascular disease risk in randomized controlled trials[21]. In our study, we revealed a significant association between dietary selenium intake and CVD risk, exhibiting a clear nonlinear trend. As dietary selenium intake increased, the risk of CVD gradually decreased to a certain threshold. However, beyond the inflection point (135.28 μg/d), this protective effect weakened, and in fact, higher selenium intake may even increase the risk of CVD. The results of another meta-analysis found that selenium supplementation reduced the risk of CVD by 11% in randomized controlled trials compared to the placebo group, but the validity of this association is uncertain because of the small sample sizes in most of

Subgroup	OR (95%CI)	P for trend	P for interaction
Sex			0.111
Female (N = 20,317)			
Tertile 1	Reference	Reference	
Tertile 2	0.687 (0.577, 0.819)	**< 0.0001**	
Tertile 3	0.734 (0.530, 1.017)	0.063	
Male (N = 19,055)			
Tertile 1	Reference	Reference	
Tertile 2	0.959 (0.793, 1.160)	0.663	
Tertile 3	1.063 (0.819, 1.380)	0.642	
Age			0.203
< 60 (N = 26,185)			
Tertile 1	Reference	Reference	
Tertile 2	0.763 (0.613, 0.948)	**0.015**	
Tertile 3	0.811 (0.594, 1.107)	0.185	
> = 60 (N = 13,187)			
Tertile 1	Reference	Reference	
Tertile 2	0.841 (0.724, 0.976)	**0.023**	
Tertile 3	0.924 (0.728, 1.173)	0.511	
BMI			0.807
Normal weight (N = 11,832)			
Tertile 1	Reference	Reference	
Tertile 2	0.884 (0.641,1.221)	0.451	
Tertile 3	0.946 (0.658, 1.361)	0.764	
Overweight (N = 12,822)			
Tertile 1	Reference	Reference	
Tertile 2	0.847 (0.655, 1.095)	0.202	
Tertile 3	0.911 (0.682, 1.216)	0.521	
Obesity (N = 14,718)			
Tertile 1	Reference	Reference	
Tertile 2	0.743 (0.601, 0.919)	**0.007**	
Tertile 3	0.839 (0.633, 1.112)	0.218	
DM			0.859
Yes (N = 7039)			
Tertile 1	Reference	Reference	
Tertile 2	0.768 (0.615, 0.960)	**0.021**	
Tertile 3	0.854 (0.633, 1.153)	0.300	
No (N = 32,333)			
Tertile 1	Reference	Reference	
Tertile 2	0.838 (0.699, 1.005)	0.057	
Tertile 3	0.915 (0.721, 1.162)	0.462	
Hypertension			0.127
Yes (N = 16,638)			
Tertile 1	Reference	Reference	
Tertile 2	0.757 (0.657, 0.873)	**< 0.001**	
Tertile 3	0.868 (0.679, 1.111)	0.258	
No (N = 22,734)			
Tertile 1	Reference	Reference	
Tertile 2	0.985 (0.745, 1.303)	0.916	
Tertile 3	0.957 (0.674, 1.360)	0.806	
Continued			

Subgroup	OR (95%CI)	P for trend	P for interaction
Alcohol use			0.759
Yes (N = 29,936)			
Tertile 1	Reference	Reference	
Tertile 2	0.830 (0.696, 0.991)	**0.039**	
Tertile 3	0.924 (0.730, 1.171)	0.511	
No (N = 9436)			
Tertile 1	Reference	Reference	
Tertile 2	0.762 (0.586, 0.992)	**0.043**	
Tertile 3	0.819 (0.554, 1.211)	0.314	

Table 3. Subgroup analysis for the association between dietary selenium intake and the risk of CVD. Bold means the result is of statistical significance.

the included trials and the combination of selenium with other vitamins in many of them[29]. Furthermore, a cross-sectional study involving 120 women discovered a negative association between dietary selenium intake and cardiovascular risk indices, such as waist-to-hip ratio, non-high-density lipoprotein (non-HDL), and low-density lipoprotein (LDL-c)[30]. However, the study by Bley et al. did not find a significant correlation between selenium levels and cardiovascular disease mortality[31]. The sample sizes in the aforementioned epidemiological studies were relatively small. In contrast, our study included a total of 39,372 participants, ensuring a sufficiently large sample size to enhance the reliability and validity of the findings. The discrepancies in the relationship between selenium levels and cardiovascular events across different studies may be attributed to variations in selenium intake among different populations. As a result, further high-quality research is needed to more clearly validate the specific relationship between selenium intake and CVD. This would provide more precise guidance for clinical practice and help improve dietary recommendations. In our study, we identified inflection points in the correlation between dietary selenium intake and CVD/ASCVD at 135.28 μg/d, and between dietary selenium intake and stroke at 100.3 μg/d. Beyond these threshold values, the protective effect of dietary selenium intake on cardiovascular events appeared to weaken, and in some cases, a positive correlation emerged. Based on these findings, we do not recommend relying solely on selenium supplementation to prevent cardiovascular events. It is essential to consider the broader context of a balanced diet and overall health to develop more comprehensive strategies for CVD prevention.

The mechanism by which selenium influences CVD risk remains unclear. Selenium is a vital component of common selenoproteins, such as glutathione peroxidases (GPx) and thioredoxin reductases (TrxR), which possess antioxidant properties. These selenoproteins play a crucial role in protecting cells from oxidative stress by neutralizing reactive oxygen species (ROS), an imbalance between ROS production and endogenous antioxidant defenses is an important pathophysiological pathway in the onset and progression of CVD[8,32]. GPx enzyme activity was significantly decreased at the cardiac site in patients with heart failure compared to healthy controls[33]. Similarly, cardiac tissue from patients with ischemic heart disease exhibited a notable decline in TrxR activity[34]. Moreover, selenium deficiency can lead to changes in lipid structures, such as elevated total cholesterol and triglycerides levels. These lipid changes are established risk factors for the development and progression of CVD[35,36]. Emerging research suggests that selenium may have anti-thrombotic properties by influencing platelet function and coagulation factors[37,38]. Through modulating platelet aggregation and coagulation pathways, dietary selenium may reduce the risk of thrombotic events, thereby protecting against CVD. Intriguingly, the endoplasmic reticulum (ER) stress response, a cellular mechanism for protein quality control within the ER, plays a role in vascular and cardiac diseases due to the accumulation of misfolded proteins[39]. SELENOT, a selenoprotein expressed in the heart, has a protective role against oxidative stress, apoptosis, and myocardial ischemia–reperfusion injury[40]. However, it's essential to note that both selenium deficiency and over-supplementation can have detrimental effects. While selenium deficiency is associated with increased protein misfolding within cells, excessive selenium supplementation can lead to the saturation of selenoproteins and the accumulation of selenium-containing reactive oxygen species, which ultimately exacerbates oxidative stress[41,42].

This study has several notable strengths. Firstly, it utilizes HANES data, which provides a nationally representative, population-based sample, distinguished by its large sample size and careful participant selection. Secondly, we conducted thorough covariate adjustments to minimize confounding bias, enhancing the credibility of our findings.

This study also has some limitations to consider. Firstly, although we adjusted for a range of potential confounding factors, there is still a possibility that other unmeasured variables could influence the observed associations. These factors were not adequately captured in the NHANES dataset, which limits the comprehensiveness of our analysis. Additionally, the study's cross-sectional design prevents us from examining changes in participants' dietary patterns over time. Dietary habits can evolve throughout an individual's life, and such changes may have significant implications for the relationship between selenium intake and CVD. As a result, the temporal aspect of dietary influence on CVD risk remains unclear. Secondly, our reliance on self-reported data for CVD diagnosis introduces the potential for recall bias. Participants' reports of their medical history may not be entirely accurate, and misclassification of CVD status could occur. However, it is important to

Subgroup	OR (95%CI)	P for trend	P for interaction
Sex			0.957
Female (N = 20,317)			
Tertile 1	Reference	Reference	
Tertile 2	0.768 (0.589, 1.000)	**0.045**	
Tertile 3	0.788 (0.522, 1.190)	0.254	
Male (N = 19,055)			
Tertile 1	Reference	Reference	
Tertile 2	0.812 (0.592, 1.115)	0.195	
Tertile 3	0.790 (0.514, 1.214)	0.279	
Age			0.624
< 60 (N = 26,185)			
Tertile 1	Reference	Reference	
Tertile 2	0.691 (0.485, 0.985)	**0.041**	
Tertile 3	0.663 (0.399, 1.099)	0.110	
> = 60 (N = 13,187)			
Tertile 1	Reference	Reference	
Tertile 2	0.856 (0.680, 1.078)	0.183	
Tertile 3	0.864 (0.619, 1.208)	0.389	
BMI			0.427
Normal weight (N = 11,832)			
Tertile 1	Reference	Reference	
Tertile 2	0.821 (0.551,1.222)	0.327	
Tertile 3	0.745 (0.418, 1.325)	0.312	
Overweight (N = 12,822)			
Tertile 1	Reference	Reference	
Tertile 2	0.764 (0.512, 1.141)	0.186	
Tertile 3	0.583 (0.345, 0.984)	**0.044**	
Obesity (N = 14,718)			
Tertile 1	Reference	Reference	
Tertile 2	0.789 (0.570, 1.092)	0.152	
Tertile 3	0.953 (0.631, 1.440)	0.818	
DM			0.452
Yes (N = 7039)			
Tertile 1	Reference	Reference	
Tertile 2	0.727 (0.565, 0.937)	**0.014**	
Tertile 3	0.657 (0.449, 0.962)	**0.031**	
No (N = 32,333)			
Tertile 1	Reference	Reference	
Tertile 2	0.928 (0.698, 1.234)	0.604	
Tertile 3	1.121 (0.732, 1.717)	0.595	
Hypertension			0.207
Yes (N = 16,638)			
Tertile 1	Reference	Reference	
Tertile 2	0.775 (0.621, 0.968)	**0.025**	
Tertile 3	0.813 (0.602, 1.098)	0.174	
No (N = 22,734)			
Tertile 1	Reference	Reference	
Tertile 2	0.825 (0.563, 1.208)	0.319	
Tertile 3	0.686 (0.353, 1.332)	0.262	
Continued			

Subgroup	OR (95%CI)	P for trend	P for interaction
Alcohol use			
Yes (N = 29,936)			
Tertile 1	Reference	Reference	
Tertile 2	0.775 (0.580, 1.037)	0.085	
Tertile 3	0.782 (0.526, 1.162)	0.221	0.816
No (N = 9436)			
Tertile 1	Reference	Reference	
Tertile 2	0.733 (0.555, 0.968)	0.054	
Tertile 3	0.666 (0.438, 1.105)	0.058	

Table 4. Subgroup analysis for the association between dietary selenium intake and the risk of Stroke. Bold means the result is of statistical significance.

note that self-reported CVD data in NHANES is a useful tool for estimating the prevalence of CVD, as it has been validated in previous studies[43]. While recall bias may still be a concern, the self-report methodology remains a widely accepted approach in epidemiological studies of this nature. Finally, the cross-sectional nature of our study design limits our ability to draw causal conclusions between dietary selenium intake and CVD. While we have observed associations, we cannot infer causality due to the absence of temporal data. Longitudinal studies with larger, more diverse cohorts are needed to confirm our findings and establish a causal relationship. Such studies would help elucidate whether changes in selenium intake over time directly influence the development of CVD, providing more robust evidence for public health recommendations.

Conclusion

This study demonstrated a nonlinear relationship between dietary selenium intake and the prevalence of cardiovascular disease among U.S. adults. It suggested that maintaining an optimal level of selenium intake may contribute to a reduced risk of cardiovascular disease. However, exceeding a certain threshold of selenium intake could lead to the opposite effect. Furthermore, our research highlighted the influence of hypertensive status on the negative association between dietary selenium intake and ASCVD. Given the substantial global burden of cardiovascular disease, these findings could play a crucial role in shaping recommended selenium intake levels for public cardiovascular health. Further research is needed to validate these results and explore the underlying mechanisms in greater detail.

Subgroup	OR (95%CI)	P for trend	P for interaction
Sex			0.075
Female (N = 20,317)			
Tertile 1	Reference	Reference	
Tertile 2	0.701 (0.579, 0.848)	**< 0.001**	
Tertile 3	0.735 (0.532, 1.016)	0.062	
Male (N = 19,055)			
Tertile 1	Reference	Reference	
Tertile 2	0.968 (0.793,1.181)	0.745	
Tertile 3	1.113 (0.852, 1.453)	0.428	
Age			0.122
< 60 (N = 26,185)			
Tertile 1	Reference	Reference	
Tertile 2	0.783 (0.617, 0.993)	**0.044**	
Tertile 3	0.822 (0.604, 1.119)	0.210	
> = 60 (N = 13,187)			
Tertile 1	Reference	Reference	
Tertile 2	0.839 (0.716, 0.982)	**0.029**	
Tertile 3	0.954 (0.749, 1.215)	0.699	
BMI			0.818
Normal weight (N = 11,832)			
Tertile 1	Reference	Reference	
Tertile 2	0.915 (0.657,1.274)	0.596	
Tertile 3	0.902 (0.621, 1.310)	0.583	
Overweight (N = 12,822)			
Tertile 1	Reference	Reference	
Tertile 2	0.832 (0.631, 1.097)	0.190	
Tertile 3	0.940 (0.692, 1.277)	0.688	
Obesity (N = 14,718)			
Tertile 1	Reference	Reference	
Tertile 2	0.758 (0.607, 0.947)	**0.015**	
Tertile 3	0.891 (0.673, 1.180)	0.417	
DM			0.612
Yes (N = 7039)			
Tertile 1	Reference	Reference	
Tertile 2	0.785 (0.628, 0.982)	**0.034**	
Tertile 3	0.899 (0.668, 1.210)	0.478	
No (N = 32,333)			
Tertile 1	Reference	Reference	
Tertile 2	0.842 (0.690, 1.028)	0.090	
Tertile 3	0.931 (0.728, 1.190)	0.563	
Hypertension			**0.034**
Yes (N = 16,638)			
Tertile 1	Reference	Reference	
Tertile 2	0.738 (0.633, 0.859)	**< 0.001**	
Tertile 3	0.878 (0.684, 1.126)	0.302	
No (N = 22,734)			
Tertile 1	Reference	Reference	
Tertile 2	1.100 (0.816, 1.483)	0.527	
Tertile 3	1.043 (0.740, 1.471)	0.806	
Continued			

Subgroup	OR (95%CI)	P for trend	P for interaction
Alcohol use			0.683
Yes (N = 29,936)			
Tertile 1	Reference	Reference	
Tertile 2	0.836 (0.690, 1.013)	0.067	
Tertile 3	0.937 (0.731, 1.191	0.592	
No (N = 9436)			
Tertile 1	Reference	Reference	
Tertile 2	0.774 (0.585, 1.025)	0.073	
Tertile 3	0.870 (0.584, 1.297)	0.491	

Table 5. Subgroup analysis for the association between dietary selenium intake and the risk of ASCVD. Bold means the result is of statistical significance.

Data availability

Publicly available datasets were analyzed in this study. This data can be found here: https://www.cdc.gov/nchs/nhanes/index.htm.

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DL and CL contributed to the interpretation of the data, CL and DL drafted the article. XYZ reviewed the article. All authors critically revised the article, agreed to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final article.

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Declarations

Competing interests
The authors declare no competing interests.

Ethics statement
The studies involving human participants were reviewed and approved by NCHS Research Ethics Review Board (ERB). Written informed consent for participation was required for this study in accordance with the national legislation and the institutional requirements.

Consent for publication
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