Preventive Medicine Reports 45 (2024) 102830

Contents lists available at ScienceDirect

Preventive Medicine Reports

journal homepage: www.elsevier.com/locate/pmedr

Nonlinear associations between dietary zinc intake and cardiovascular disease risk, a National cross-sectional study based on the NHANES 2005–2018

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ARTICLE INFO

Keywords:
Cardiovascular diseases
Cerebrovascular disorders
Heart disease risk factors
NHANES
Zinc

ABSTRACT

Objective: To explore the associations between dietary zinc intake and cardiovascular diseases (CVDs), including congestive heart failure (CHF), coronary heart disease (CHD), angina, heart attack, and cerebrovascular accident (CVA), this study was performed.

Setting: Data from the National Health and Nutrition Examination Survey (2005–2018) were used in this study. Dietary zinc intake was stratified into quartiles. Restricted cubic splines were constructed to assess nonlinear associations and identify cut-off values based on the type of nonlinearity. Binary logistic regressions were performed using the cut-offs.

Results: Positive associations were detected between the second, third, and fourth quantiles of dietary zinc intake and decreased risks of overall CVDs (Q2: OR = 0.83, 95 % CI = 0.72–0.96; Q3: OR = 0.83, 95 % CI = 0.71–0.96; Q4: OR = 0.79, 95 % CI = 0.67–0.93). The second, third, and fourth quantiles were significantly associated with decreased risks of various CVDs (all $P < 0.05$), except for CHD and angina (all $P > 0.05$). Restricted cubic spline regression revealed significant nonlinear trends for associations of dietary zinc intake with the risk of developing CVDs and CHF (both P for nonlinear <0.05), whereas those for heart attack and CVA were marginally significant (P for nonlinear = 0.072, and 0.075, respectively).

Conclusions: This study revealed that high dietary zinc intake is associated with reduced risks of developing CVDs, CHF, heart attack, and CVA, but not CHD or angina.

1. Background

Cardiovascular diseases (CVDs) are a group of disorders that affect the heart and blood vessels. It includes various conditions such as congestive heart failure (CHF), and coronary heart disease (CHD), which consists of angina, heart attack, and cerebrovascular accident (CVA). CVDs are a leading cause of morbidity and mortality worldwide, with an estimated 17.9 million deaths in 2019 (Benjamin et al., 2019). The incidence and prevalence of CVDs vary with age, sex, and other risk factors. In the United States, the number of CHF patients is estimated to be approximately6.5 million, while CHD affects approximately18.2 million adults (Mozaffarian et al., 2016). Angina pectoris affects approximately 9.1 million individuals, whereas CVA affects approximately 795,000 people per year. The health burden of CVDs is significant, as it can lead to a range of complications, including disability, decreased quality of life, and premature death (Yancy et al., 2013). Therefore, prevention and management of CVDs are crucial for improving public health.

Some studies have examined the risk factors and treatment options for CVDs. Lifestyle modifications such as regular exercise, a healthy diet, and smoking cessation have been shown to reduce the risk of developing CVDs (Sharma et al., 2015; Shan et al., 2020; Shields and Wilkins, 2013). Medications such as statins, antihypertensive agents, and antiplatelet drugs have also been found to be effective in reducing the risk factors strongly associated with CVDs (Low Wang et al., 2016). Among these factors, few studies have investigated the role of trace elements such as zinc in the occurrence and progression of cardiovascular diseases. Milton et al. (2018) reported that high dietary zinc intake and high zinc-iron ratio could increase the risk of developing CVDs in women (aged 50–61 years), which is in line with the findings of De Oliveira Otto et al. (2012). However, in contrast to their conclusions, Kwon et al. (2023) analyzed 143,050 adult participants and reported that dietary zinc intake was

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https://doi.org/10.1016/j.pmedr.2024.102830
Received 11 January 2024; Received in revised form 11 July 2024; Accepted 13 July 2024
Available online 16 July 2024

inversely associated with all-cause and cardiovascular mortality. These inconsistent results may be explained by differences in sex, age, and race. In addition, the dose–response associations between dietary zinc intake and CVDs, especially their subtypes, remain unclear. Therefore, further investigations with ample sample sizes in the overall population are needed to clarify the unclear associations between dietary zinc intake and the risk of developing CVDs and its subtypes.

To explore the associations between dietary zinc intake and the risk of developing CVDs, including CHF, CHD, angina, heart attack, and CVA, datasets from the National Health and Nutrition Examination Surveys (NHANES) were used. Clarifying the dose–response associations of zinc intake with CVDs and its subtypes may be beneficial for determining appropriate intervention strategies for CVDs patients.

2. Methods

2.1. Study design and population

This study is based on the NHANES in the United States, which is a nationally representative survey conducted since 1998. The NHANES website (https://www.cdc.gov/nchs/nhanes/index.htm) provides detailed information about the survey design and past studies. The NHANES uses a stratified, multistage probability sampling technique to obtain representative samples. Prior to participating in the survey, all the participants signed an informed consent form indicating their willingness to participate in the study. The questionnaires were completed by participants in their homes, and physical examinations and laboratory tests were conducted at a mobile testing center. On the day of their examination, trained personnel collected information via standardized questionnaires, including demographic characteristics, work history, personal and family medical history, and lifestyle behaviors such as smoking and alcohol consumption. For this study, data were extracted from seven survey cycles conducted between 2005 and 2018, with a total of 70,190 participants. Data from 18,377 participants whose complete information was available were used for analysis (Fig. S1). The NHANES institutional review board approved the NHANES protocol and obtained signed informed consent from all participants. Thus, this study was exempt from ethical review and approval. This study met the data curator's guidelines for protection of human subjects concerning safety and privacy.

2.2. Assessment of cardiovascular disease

During the personal interviews, the participants were asked a set of standardized medical condition questions, which included inquiries about CHF, CHD, angina pectoris, heart attack, and CVA. Specifically, participants were asked "Has a doctor or other health professional ever informed you that you have CHF/CHD/angina pectoris/heart attack/stroke?" If a participant answered "yes" to any of these questions, they were classified as having cardiovascular disease (CVD). Patients with stroke were defined as having CVA. This set of five questions was asked with exact phrasing for consistency across all participants.

2.3. Assessment of zinc intake

In the NHANES, dietary intake data were collected through interviews conducted on two distinct occasions: the initial interview was in-person, followed by a subsequent telephone interview. To ascertain dietary zinc intake, the collected dietary data, which were based on 24-h dietary recall interviews, were cross-referenced with the United States Department of Agriculture's Food and Nutrient Database for Dietary Studies (Ahluwalia et al., 2016). This database provides detailed nutrient compositions, including zinc content, of consumed foods. Researchers then computed each participant's total zinc intake by aggregating the zinc contents of all reported foods and beverages within the 24-h recall timeframe. Owing to substantial missing data in the second interview, the analysis in this study relied solely on the dietary data from the initial in-person interview.

2.4. Covariates

Structured questionnaires were used to collect sociodemographic information including age (in years), sex (male/female), educational level, race, smoking status, drinking status, the ratio of family income to poverty, body mass index (BMI), hypertension and diabetes, during household interviews. Sex was categorized as male or female. Race was grouped into Mexican American, non-Hispanic Black, non-Hispanic White, other Hispanic, and other races. Educational level was classified into three categories: less than high school, high school, and above high school. The ratio of family income to poverty was used as an income index to estimate household socioeconomic status, which was categorized as <1.5, 1.5–3.5, or >3.5 (Rahman et al., 2022). Alcohol intake was classified into three categories: non-drinker, moderate, and binge (Naimi et al., 2003; Phillips, 2021). Smoking status was categorized as never, former, and current, with never smokers defined as those who smoked <100 cigarettes in their lifetime, former smokers defined as those who had smoked >100 cigarettes in their lifetime but currently did not smoke, with a cessation period of at least 30 days, and current smokers defined as those who had smoked >100 cigarettes in their lifetime and currently smoked some days or every day. Alcohol consumption was categorized into three groups: non-drinkers, moderate drinkers (frequency of drinking is less than 0.5 times per day), and binge drinkers (frequency of drinking is 0.5 times per day or more). Hypertension was defined as either self-reported hypertension diagnosed by a physician or meeting the NHANES criteria for hypertension, which are a mean value of $\geq$130 mmHg for systolic blood pressure or $\geq$80 mm Hg for diastolic blood pressure. BMI was classified as underweight ($<$18.5 kg/m^2), normal ($\geq$18.5 kg/m^2 to $<$25 kg/m^2), overweight ($\geq$25 kg/m^2 to $<$30 kg/m^2), or obese ($\geq$30 kg/m^2) (Seidell et al., 1987). Diabetes mellitus was defined as reporting a diabetes diagnosis, glycohemoglobin HbA1c (%) $>$6.5, fasting glucose (mmol/L) $\geq$ 7.0, random blood glucose (mmol/L) $\geq$ 11.1, two-hour OGTT blood glucose (mmol/L) $\geq$ 11.1, or the use of diabetes medication or insulin (Harreiter and Roden, 2019). Based on this definition, all subtypes of diabetes including type-I diabetes, type-II diabetes, juvenile diabetes, and gestational diabetes were included.

2.5. Statistical analysis

The Kolmogorov-Smirnov test was used to determine whether continuous variables exhibited a normal distribution. For normally distributed continuous and categorical variables, analysis of variance and Chi-square tests were conducted to investigate variations in participant characteristics by quantiles of total zinc (Q1, (0,6.48]; Q2, (6.48,9.52]; Q3, (9.52,13.7]; Q4, (13.7,33.4]). Chi-square tests were used to compare the frequencies of categorical variables.

Firstly, quartile logistic regression was used to evaluate the associations between zinc intake and the risk of developing CVD, as well as five individual diseases. In addition, subgroup and interaction analyses were adopted to explore the potential interactive effects of covariates. Subsequently, restricted cubic splines (RCS) were used to assess the nonlinear association between zinc intake and diseases, and cut-off points were identified based on the type of nonlinear association (L-shaped or U-shaped). Based on these results, the nonlinear association in this study more closely resembled an L-shaped or linear pattern. Therefore, we have based our determination of cut-off points on an L-shaped fit. To obtain these cut-off points, we adopted a two-stage strategy. Initially, we identified potential cut-off point ranges through graphical analysis. Within these ranges, we subsequently divided the data into multiple nodes at intervals of 0.01. At each node, we segmented the data into two parts, fitting linear models for values less than and greater than the cut-off points. The optimal cut-off points were

determined based on the R^2 value of the models, indicating the most significant change in data trends before and after the cut-off points.

Finally, based on the cut-off points, the associations between zinc intake and the risk of developing CVD, as well as the five individual diseases, were evaluated separately for the two parts before and after the cut-off point. All models were adjusted for age, educational level, race, the ratio of family poverty, BMI status, smoking status, drinking status, hypertension, and diabetes.

Sensitivity analyses were conducted. We incorporated the intake of additional trace elements as covariates to control for potential confounding factors. The covariate analysis included the following elements: caffeine, calcium, copper, iron, magnesium, phosphorus, potassium, selenium, sodium, and theobromine.

All the analyses were performed using the R 3.5.6 software (R Foundation for Statistical Computing, Vienna, Austria). A two-tailed *P* value <0.05 was considered the significance threshold for statistical analysis.

3. Results

3.1. Characteristics of participants

The study included a total of 18,377 participants who were at least 18 years old, with 8,493 males (46.2 %) and 9,884 females (53.8 %). The average ages of the four groups were 49.71 (SD = 18.72), 49.20 (SD = 18.24), 46.78 (SD = 17.88), and 44.08 (SD = 17.23) years, respectively, as presented in Table 1. Significant differences ($P < 0.05$) were observed between the zinc groups in terms of age, sex, educational level, race, family poverty rate, smoking and drinking habits, hypertension, and cardiovascular diseases (including CHF, CHD, angina, heart attack, and CVA), as indicated in Table 1. Males generally had higher zinc intake than females did, individuals with a college education or higher had higher zinc intake, and never smokers and non-drinkers had lower zinc intake. Overall, zinc intake varied significantly among different populations, and was influenced by sociodemographic factors and lifestyle habits.

3.2. Association of zinc with specific CVDs

The associations between zinc intake and the prevalence of five specific CVDs are shown in Table 2. In the quantile analysis, the second, third, and fourth quantiles were significantly associated with a decreased risk of developing various CVDs, except for CHD and angina. A positive association was found for the second, third, and fourth quantiles of zinc intake and decreased risk of overall CVDs (Q2: OR = 0.83, 95 % CI = 0.72–0.96; Q3: OR = 0.83, 95 % CI = 0.71–0.96; Q4: OR = 0.79, 95 % CI = 0.67–0.93). A decreased risk of developing CHF, heart attack, and CVA was significantly associated with increased zinc intake. However, the association between zinc intake and the risk of developing CVDs does not appear to be linear, so we further performed a nonlinear analysis.

3.3. Nonlinear associations of zinc with specific CVDs

As shown in Fig. 1, a nonlinear association between zinc intake and the risk of developing CVDs was observed. Using two-step linear regression analysis, we calculated an inflection point of 10.55. To the left of the inflection point, effect size and 95 % CI were 0.94 (0.92–0.97), and 1.00 (0.98–1.02), respectively.

Among the specific CVDs examined, no significant nonlinear associations were observed between zinc intake and CHD or angina. However, a significant nonlinear association was found between zinc intake and CHF, whereas heart attack and CVA exhibited significant inflection points at 10.50 and 10.37, respectively, despite the nonlinear association being insignificant (with an inflection point at 10.39). The effect values of zinc intake before the inflection point for CHF, heart attack,

Table 1
Characteristics distribution of the participants in NHANES 2005–2018 across dietary zinc intake.

Groups	Q1 (N = 4598)	Q2 (N = 4602)	Q3 (N = 4587)	Q4 (N = 4590)	Total (N = 18377)	*P*
Age group (%)						<0.001
20–39 years	1594 (22.1)	1621 (22.5)	1842 (25.5)	2159 (29.9)	7216 (39.3)	
40–65 years	1859 (25.0)	1915 (25.8)	1896 (25.5)	1765 (23.7)	7435 (40.5)	
66–85 years	1145 (30.7)	1066 (28.6)	849 (22.8)	666 (17.9)	3726 (20.3)	
Sex (%)						<0.001
Female	3203 (32.4)	2775 (28.1)	2340 (23.7)	1566 (15.8)	9884 (53.8)	
Male	1395 (16.4)	1827 (21.5)	2247 (26.5)	3024 (35.6)	8493 (46.2)	
Educational levels (%)						<0.001
Less high school	1399 (28.3)	1265 (25.6)	1166 (23.6)	1113 (22.5)	4943 (26.9)	
High school	1172 (25.5)	1143 (24.8)	1096 (23.8)	1194 (25.9)	4605 (25.1)	
College or above	2027 (23.0)	2194 (24.9)	2325 (26.3)	2283 (25.9)	8829 (48.0)	
Race (%)						<0.001
Mexican American	696 (21.5)	758 (23.4)	874 (27.0)	907 (28.0)	3235 (17.6)	
Non-Hispanic Black	1256 (30.5)	1058 (25.7)	932 (22.6)	873 (21.2)	4119 (22.4)	
Non-Hispanic White	1735 (22.8)	1864 (24.5)	1904 (25.0)	2114 (27.8)	7617 (41.5)	
Other Hispanic	509 (27.6)	499 (27.0)	465 (25.2)	374 (20.3)	1847 (10.1)	
Other Race	402 (25.8)	423 (27.1)	412 (26.4)	322 (20.7)	1559 (8.5)	
The ratio of family poverty (%)						<0.001
0–1.5	2215 (27.8)	2019 (25.3)	1866 (23.4)	1877 (23.5)	7977 (43.4)	
1.5–3.5	1752 (23.9)	1821 (24.8)	1891 (25.8)	1873 (25.5)	7337 (39.9)	
>3.5	631 (20.6)	762 (24.9)	830 (27.1)	840 (27.4)	3063 (16.7)	
BMI status (%)						0.075
Underweight	78 (26.4)	66 (22.4)	60 (20.3)	91 (30.9)	295 (1.6)	
Normal	1215 (24.3)	1246 (24.9)	1277 (25.5)	1268 (25.3)	5006 (27.2)	
Overweight	1456 (24.5)	1523 (25.6)	1493 (25.1)	1476 (24.8)	5948 (32.4)	
Obese	1849 (25.9)	1767 (24.8)	1757 (24.7)	1755 (24.6)	7128 (38.8)	
Smoking status (%)						<0.001
Never smokers	2665 (26.0)	2609 (25.5)	2528 (24.7)	2434 (23.8)	10,236 (55.7)	
Former smokers	858 (21.8)	997 (25.3)	1037 (26.3)	1053 (26.7)	3945 (21.5)	
Current smokers	1078 (25.6)	999 (23.8)	1024 (24.4)	1104 (26.3)	4205 (22.9)	
Alcohol consumption (%)						<0.001

(*continued on next page*)

Table 1 (*continued*)

Groups	Q1 (N = 4598)	Q2 (N = 4602)	Q3 (N = 4587)	Q4 (N = 4590)	Total (N = 18377)	*P*
Non-drinker	2016 (31.7)	1646 (25.9)	1499 (23.6)	1200 (18.9)	6361 (34.6)	
Moderate	2250 (21.8)	2529 (24.5)	2647 (25.6)	2899 (28.1)	10,325 (56.2)	
Binge	335 (19.7)	430 (25.3)	443 (26.1)	492 (28.9)	1700 (9.3)	
Hypertension (%)						<0.001
Yes	2805 (23.2)	2939 (24.3)	3089 (25.5)	3274 (27.0)	12,107 (65.9)	
No	1793 (28.6)	1663 (26.5)	1498 (23.9)	1316 (23.0)	6270 (34.1)	
Diabetes (%)						<0.001
No	3724 (24.3)	3785 (24.7)	3855 (25.2)	3933 (25.7)	15,297 (83.2)	
Diabetes	874 (28.4)	817 (26.5)	732 (23.8)	657 (21.3)	3080 (16.8)	
Diseases (%)						
CVD	561 (31.9)	454 (25.8)	401 (22.8)	346 (19.6)	1763 (9.6)	<0.001
CHF	187 (35.0)	140 (26.2)	103 (19.3)	104 (19.5)	534 (2.9)	0.008
CHD	189 (29.3)	169 (26.2)	159 (24.6)	129 (20.0)	646 (3.5)	0.004
Angina	124 (29.0)	121 (28.3)	105 (24.6)	77 (18.0)	427 (2.3)	<0.001
Heart attack	207 (32.5)	155 (24.3)	139 (21.8)	137 (21.5)	638 (3.5)	<0.001
CVA (stroke)	213 (35.1)	150 (24.7)	140 (23.1)	104 (17.1)	607 (3.3)	<0.001

The participants were categorized into four groups according to the quartiles of dietary zinc intake. The dietary zinc levels were 0–6.48 mg/day for the Q1 group, 6.48–9.52 mg/day for the Q2 group, 9.52–13.73 mg/day for the Q3 group, and 13.73–33.41 mg/day for the Q4 group. Data are presented as n (%) for categorical measures. The differences of covariates across quartiles were tested using Chi-square test. CHF: congestive heart failure; CHD: coronary heart disease; CVA: cerebrovascular accident; Less high school: Less than a high school education; Other Race: Including Multi-Racia.

and CVA were 0.94 (95 % CI: 0.90–0.99), 0.93 (95 % CI: 0.89–0.98), and 0.95 (95 % CI: 0.91–0.99), respectively (Table 3).

3.4. Associations of zinc with specific CVDs by subgroup

Given that factors are associated with CVDs, we conducted stratified analyses among people with different characteristics to identify factors that may affect the relationship between zinc intake and the risk of developing CVDs. As shown in Supplementary Table 4 and Tables S1–S5, most subgroup analyses of age, sex, race, education level, BMI, smoking status, hypertension, and diabetes, revealed that these factors had an impact on the association between zinc intake and the risk of developing CVDs (Table 4). Our stratified analysis for CVDs revealed differential associations of zinc intake across sociodemographic characteristics. For instance, females in the third and fourth quartiles showed a significant reduction in CVD risk compared to the first quartile, while in males, a notable risk reduction was observed in the second quartile. The associations between zinc intake and individual CVDs varied across sociodemographic groups. For example, the relationship between zinc intake and heart attack was similar across different groups, but for CVA, a significant association was observed only in females (Tables S4 and S5). The sensitivity analysis results showed that when the intake of other ingredients was considered, the associations remained consistent (Table S6).

4. Discussion

In this study, higher dietary zinc intake was associated with a decreased risk of developing CVDs including CHF, heart attack, and CVA. The marginally significant associations of zinc intake with CHD and angina also suggested possible protective effects of zinc intake on CHD and angina. However, further verification is needed. Of note, our study revealed nonlinear associations of dietary zinc intake with the risk of developing CVDs and CHF. The results of this study provide more evidence for the association between dietary zinc intake and the risk of developing CVDs.

Zinc is an essential mineral that plays a vital role in many biological functions, including the immune response, protein synthesis, and DNA synthesis (Roohani et al., 2013). The recommended daily intake of zinc varies by age and sex, with adult men requiring 11 mg/day and adult women requiring 8 mg/day (Mocchegiani et al., 2013). Foods rich in zinc include oysters, red meat, poultry, beans, nuts, and whole grains (Mocchegiani et al., 2013). Zinc deficiency, which is considered to be less than the recommended daily intake, can lead to a variety of health problems, including impaired immune function (Mocchegiani et al., 2013), loss of appetite (Aranha et al., 2012), and delayed sexual maturation (Onukwuli et al., 2018). Conversely, significantly elevated serum zinc concentrations can lead to adverse health effects, such as the development of type-II diabetes (Fernández-Cao et al., 2019) and reductions in leukocyte telomere length (Xing et al., 2023). These data suggest that moderate zinc intake is crucial as both high and low zinc intake are harmful to health.

The protective effects of high dietary zinc intake on cardiovascular health may be explained by the following mechanisms. First, zinc deficiency can lead to dysregulated oxidative stress. Zinc deficiency reportedly increases the accumulation of reactive oxygen species (ROS) in various cells such as human fibroblasts, and epithelial cells (Eide, 2011). The accumulated ROS can trigger the formation of the NLRP3 inflammasome and subsequently induce the proptosis of human aortic endothelial cells, leading to the impairment of cardiovascular health (Wu et al., 2018). In addition, zinc deficiency can also result in chronic inflammation. In mice, Beattie et al. (2012) reported that suboptimal dietary zinc intake could increase the concentrations of circulating interleukin-1β, interleukin-6 and soluble vascular adhesion molecule-1,

Table 2
Association between dietary zinc intake and CVD in NHANES 2005–2018.

Quartiles	CVD OR (95 % CI)	CHF OR (95 % CI)	CHD OR (95 % CI)	Angina OR (95 % CI)	Heart attack OR (95 % CI)	CVA (stroke) OR (95 % CI)
Q1	reference	reference	reference	reference	reference	reference
Q2	0.83 (0.72–0.96)	0.83 (0.65–1.04)	0.91 (0.72–1.14)	1.03 (0.79–1.34)	0.76 (0.61–0.95)	0.78 (0.62–0.97)
Q3	0.83 (0.71–0.96)	0.69 (0.53–0.89)	0.92 (0.73–1.16)	1.00 (0.76–1.31)	0.74 (0.58–0.93)	0.84 (0.67–1.06)
Q4	0.79 (0.67–0.93)	0.81 (0.62–1.05)	0.79 (0.61–1.02)	0.80 (0.59–1.08)	0.78 (0.62–1.00)	0.72 (0.56–0.93)
P for trend	0.005	0.030	0.094	0.186	0.034	0.020

The participants were categorized into four groups according to the quartiles of dietary zinc intake. The dietary zinc levels were 0–6.48 mg/day for the Q1 group, 6.48–9.52 mg/day for the Q2 group, 9.52–13.73 mg/day for the Q3 group, and 13.73–33.41 mg/day for the Q4 group. All models were adjusted for age, educational level, race, the ratio of family poverty, BMI status, smoking status, drinking status, hypertension, and diabetes. CHF, congestive heart failure; CHD, coronary heart disease; CVA: cerebrovascular accident.

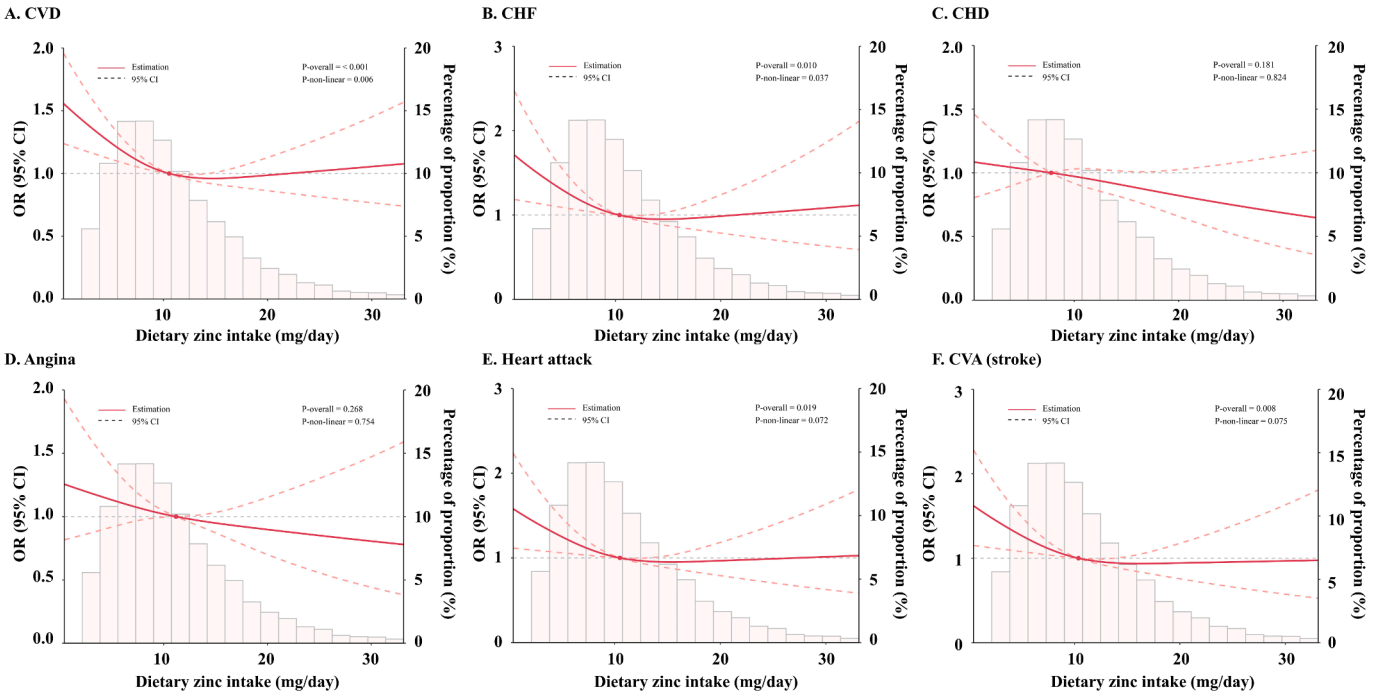

Fig. 1. Non-linear relationship between dietary zinc intake and CVDs in NHANES 2005–2018. CHF, congestive heart failure; CHD, coronary heart disease; CVA: cerebrovascular accident.

Table 3
Linear relationship between dietary zinc intake and CVD (less and greater than cutoff point).

Diseases	Cutoff point	Less than cutoff point OR (95 % CI)	Greater than cutoff point OR (95 % CI)	Continuous OR (95 % CI)
CVD	10.55	0.94 (0.92–0.97)*	1.00 (0.98–1.02)	0.98 (0.97–1.00)*
CHF	10.39	0.94 (0.90–0.99)*	1.01 (0.98–1.04)	0.98 (0.96–1.00)*
CHD	7.79	1.03 (0.95–1.12)	0.99 (0.97–1.01)	0.98 (0.97–1.00)
Angina	11.18	0.96 (0.92–1.01)	0.98 (0.94–1.02)	0.98 (0.97–1.00)
Heart attack	10.50	0.93 (0.89–0.98)*	1.00 (0.97–1.03)	0.98 (0.97–1.00)*
CVA (stroke)	10.37	0.95 (0.91–0.99)*	1.00 (0.97–1.03)	0.98 (0.96–1.00)*

Note: All models were adjusted for age, educational level, race, the ratio of family poverty, BMI status, smoking status, drinking status, hypertension, and diabetes. *, $P < 0.05$; CHF, congestive heart failure; CHD, coronary heart disease; CVA: cerebrovascular accident.

suggesting the presence of inflammation. The plasma total cholesterol and total protein levels were also significantly elevated. These inflammatory factors and "bad lipids" are well-known risk factors for cardiovascular health (Silveira Rossi et al., 2022; Soppert et al., 2020). Notably, that the cross-talk of dysregulated oxidative stress, chronic inflammation, and dyslipidemia can aggravate this pathologic progress.

The associations between zinc intake and the risk of developing CVDs have been inconsistent across studies. Some studies suggest that high zinc intake contributes to suppressing the incidence and progression of CVDs. In Korea, Kwon et al. (2023) initiated a prospective, 10-year, community-based cohort with 143,050 adult participants. They reported that higher dietary zinc intake could decrease cardiovascular mortality, suggesting potential protective effects of zinc. One study from Japan involving 965, 970 person-years of follow-up between 1989–2009 revealed that higher dietary zinc was associated with a decrease risk of developing CHD in males, but not in females (Eshak et al., 2018). In China, one case-control study by Yang et al. (2022) showed that high zinc intake during gestation could significantly reduce the risk of congenital heart defects. Similar findings have also been reported among Finns, and Americans (Reunanen et al., 1996; Lee et al., 2005). Overall, these clinical studies suggest that adequate dietary zinc intake or supplementation may be beneficial for improving cardiovascular health. In contrast, other studies have shown that high zinc intake increases the risk of developing CVDs. Milton et al. (2018) recruited 9,264 females in Australia. After six years of follow-up, they reported that increased dietary zinc intake and high zinc-iron ratio were associated with increased CVDs risks. Afridi et al. (2011) revealed that low Zn levels were associated with an increased risk of developing CVDS, independent of cigarette consumption. The results of the previous surveys were discordant. Our study provides novel evidence that high zinc intake reduces the risk of developing CHF, heart attack, and CVA, but not CHD or angina. The definitions of CVDs in different studies may lead to this discrepancy. Diagnoses based on self-reports (Milton et al., 2018) or objective examinations such as coronary angiography (Soppert et al., 2020) were used in previous surveys. Similarly, the present study was based on a set of standardized medical condition questions. It is difficult to balance the accuracy of diagnosis and the sample size concurrently, especially for CVD patients. In future research, investigators should take this information into consideration to further validate the findings of the present study.

Of note, significant nonlinear associations were identified between dietary zinc intake, and the risk of developing CHF and CVDs. The cut-off values of dietary zinc intake were 10.55 and 10.39 mg for CVDs and CHF patients, respectively. This finding discloses the threshold effects of dietary zinc intake. In addition, the nonlinear associations of dietary zinc intake with the risk of heart attack and CVA occurrence were marginally significant, with cut-off values of 10.50, and 10.37 respectively. These data indicate that additional dietary zinc intake beyond the

Table 4
Subgroup analysis of association between dietary zinc intake and CVDs among U.S. adults in NHANES 2005–2018.

Groups	*P* interaction	<cutoff point OR (95 % CI)	>cutoff point OR (95 % CI)	Q2 OR (95 % CI)	Q3 OR (95 % CI)	Q4 OR (95 % CI)
Sex	0.841					
Female		0.94 (0.91–0.98)*	1.03 (0.99–1.06)	0.90 (0.75–1.08)	0.78 (0.63–0.97)*	0.77 (0.60–0.99)*
Male		1.03 (0.99–1.06)	0.95 (0.90–0.99)*	0.75 (0.60–0.96)*	0.86 (0.69–1.08)	0.80 (0.64–1.01)
Educational level	0.414					
Less high school		0.94 (0.90–0.99)*	0.99 (0.96–1.03)	0.88 (0.69–1.12)	0.82 (0.63–1.07)	0.74 (0.55–1.00)*
High school		0.99 (0.96–1.03)	0.94 (0.88–1.00)*	0.72 (0.54–0.96)*	0.78 (0.58–1.05)	0.78 (0.57–1.06)
College or above		0.94 (0.88–1.00)*	1.01 (0.97–1.05)	0.88 (0.69–1.12)	0.86 (0.67–1.10)	0.83 (0.65–1.07)
Race	0.570					
Mexican American		0.95 (0.87–1.04)	0.99 (0.93–1.05)	0.93 (0.60–1.44)	0.66 (0.41–1.06)	0.75 (0.46–1.21)
Non-Hispanic Black		0.99 (0.93–1.05)	0.95 (0.90–1.01)	0.94 (0.71–1.25)	0.88 (0.64–1.20)	0.87 (0.62–1.21)
Non-Hispanic White		0.95 (0.90–1.01)	0.99 (0.95–1.03)	0.76 (0.61–0.93)*	0.82 (0.66–1.02)	0.75 (0.60–0.94)*
Other Hispanic		0.99 (0.95–1.03)	0.93 (0.89–0.97)*	0.75 (0.46–1.22)	0.83 (0.49–1.41)	0.91 (0.50–1.63)
Other Race		0.93 (0.89–0.97)*	1.00 (0.97–1.02)	0.98 (0.52–1.84)	1.00 (0.52–1.92)	0.68 (0.30–1.57)
The ratio of family poverty	0.337					
0–1.5		0.96 (0.92–1.00)*	1.02 (0.99–1.05)	0.89 (0.72–1.10)	0.80 (0.64–1.00)	0.90 (0.71–1.14)
1.5–3.5		1.02 (0.99–1.05)	0.94 (0.89–0.98)*	0.84 (0.66–1.06)	0.90 (0.71–1.14)	0.69 (0.53–0.89)*
>3.5		0.94 (0.89–0.98)*	0.97 (0.94–1.01)	0.60 (0.39–0.94)*	0.67 (0.43–1.04)	0.74 (0.47–1.16)
BMI status	0.336					
Underweight		0.92 (0.78–1.08)	1.08 (0.98–1.19)	0.96 (0.43–2.14)	0.57 (0.23–1.39)	0.73 (0.31–1.72)
Normal		1.08 (0.98–1.19)	0.93 (0.86–0.99)*	0.79 (0.56–1.11)	0.95 (0.67–1.33)	0.66 (0.45–0.97)*
Overweight		0.93 (0.86–0.99)*	0.99 (0.94–1.04)	0.72 (0.55–0.94)*	0.81 (0.62–1.07)	0.70 (0.51–0.94)*
Obese		0.99 (0.94–1.04)	0.92 (0.87–0.97) *	0.92 (0.74–1.14)	0.80 (0.63–1.00)	0.93 (0.74–1.18)
Smoking status	0.583					
Never smokers		0.94 (0.90–0.98)*	1.02 (0.98–1.05)	0.83 (0.67–1.02)	0.73 (0.58–0.92)*	0.78 (0.61–1.00)
Former smokers		1.02 (0.98–1.05)	0.95 (0.90–1.00)	0.84 (0.64–1.10)	1.04 (0.80–1.36)	0.81 (0.61–1.08)
Current smokers		0.95 (0.90–1.00)	0.97 (0.94–1.00)	0.83 (0.61–1.13)	0.72 (0.52–0.99)*	0.83 (0.59–1.15)
Drinking status	0.432					
Non-drinker		0.95 (0.91–1.00)*	1.00 (0.96–1.04)	0.94 (0.76–1.16)	0.86 (0.68–1.08)	0.90 (0.69–1.16)
Moderate		1.00 (0.96–1.04)	0.93 (0.89–0.97)*	0.75 (0.60–0.94)*	0.74 (0.59–0.93)*	0.68 (0.54–0.86)*
Binge		0.93 (0.89–0.97)*	1.00 (0.98–1.03)	0.74 (0.46–1.19)	0.99 (0.62–1.59)	0.98 (0.60–1.58)
Hypertension	0.143					
Yes		0.96 (0.93–1.00)*	1.00 (0.97–1.02)	0.90 (0.76–1.06)	0.90 (0.75–1.08)	0.86 (0.70–1.04)
No		1.00 (0.97–1.02)	0.89 (0.84–0.94)*	0.68 (0.52–0.89)*	0.64 (0.48–0.85)*	0.65 (0.49–0.88)*
Diabetes	0.649					
Yes		0.97 (0.92–1.02)	1.01 (0.98–1.04)	0.72 (0.60–0.87)*	0.80 (0.66–0.96)*	0.78 (0.64–0.95)*
No		0.93 (0.89–0.96)*	0.99 (0.97–1.02)	1.01 (0.80–1.28)	0.85 (0.66–1.10)	0.78 (0.59–1.02)

Notes: In the multivariable logistic regression models, covariates were adjusted as Table 2 in previous analyses except for subgroup variables. The Q1 group was set as the reference group. *P* interaction was calculated based on the Continuous of zinc intake. *, $P < 0.05$.

cut-off values may not be beneficial for the general population. Thus, individuals are not advised to engage in excessive zinc supplementation, which may lead to additional risks. This information should be considered when developing a public intervention strategy for CVDs.

This study has some merits and demerits that need to be addressed in future studies. First, the cross-sectional design is a major limitation, as it cannot provide causal evidence linking dietary zinc intake to CVDs. A randomized controlled trial can be considered in future studies. In addition, we adopted a well-designed questionnaire to investigate dietary zinc intake. However, further verification of circulating zinc levels is still lacking. Besides, the diagnosis of CVDs is based mainly on self-reports, which may introduce bias. However, previous studies also disclosed that self-reported CVDs are reliable for identifying nonfatal events. The major strength of this study is the adequate sample size, providing ample power for statistical inference (Barr et al., 2009; Engstad et al., 2000). Moreover, in this study, we analyzed the associations between dietary intake and the risk of developing specific CVDs including total CVDs, CHF, heart attack, CHD, angina, and CVA. Nonlinear associations were also detected, which provides more evidence.

5. Conclusions

In conclusion, this study provides new evidence that higher dietary zinc intake is associated with a lower risk of total CVDs, CHF, heart attack, and CVA, with the exception of CHD and angina. Obvious threshold effects are identified with different cut-off values. In addition, there were a significant nonlinear association of dietary zinc intake, with the risk of developing CHF and overall CVDs. For the general population, appropriate dietary zinc intake is beneficial for cardiovascular health.

6. Ethics approval and consent to participate

This study was exempt from ethical review and approval.

7. Consent for publication

Not applicable.

8. Authors' contributions

WH. Z and H.Y performed the data analyses; WH, Z, and YM. L wrote the manuscript; WH. Z and K. Z revised the manuscript; WH. Z, YM. L, and YJ. L participated in the study design and helped draft the manuscript; H.Y conceived and supervised this study.

Funding

This work was supported by the Guizhou Science and Technology Program (No. gzwkj2021-192) and Key Discipline Construction Fund for Neurosurgery at the Affiliated Hospital of Guizhou Medical University (ZDPT-2023-01).

CRediT authorship contribution statement

Weihao Zhang: Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Conceptualization. **Yuming Li:** Writing – review & editing, Conceptualization. **Kai Zheng:** Writing – review & editing. **Yuanjing Li:** Writing – review & editing. **Hua Yang:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The datasets analysed during the current study are available in the website: https://www.cdc.gov/nchs/nhanes/index.htm.

Acknowledgements

We thank the NHANES team who share the datasets used in this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pmedr.2024.102830.

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