Original Article

Dietary and serum selenium in coronary heart disease and all-cause mortality: An international perspective

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Background and Objectives: The objective of this study was to explore the associations of dietary selenium and serum selenium concentration with coronary heart disease (CHD) prevalence and all-cause mortality among participants in United States. **Methods and Study Design:** Using data collected from the National Health and Nutrition Examination Survey (NHANES) 1999–2006, 17867 individuals were included. Logistic regression analyses were used to explore the associations between dietary selenium intake and serum selenium concentration and prevalent of CHD. Multivariable Cox regression was used to identify the association between dietary selenium intake and all-cause mortality. The nonlinear relationships were assessed using generalized additive models. **Results:** A U-shaped association between dietary intake of selenium and all-cause mortality was observed. Compared with the lowest quartile, the second quartile of dietary intake of selenium was inversely associated with all-cause mortality (Hazard ratio [HR]: 0.802, 95% confidence interval [CI]: 0.658, 0.977, p=0.029). There was no evidence of association between dietary selenium intake and CHD risk (Odds ratio [OR]: 1.001, 95% CI: 0.999, 1.003, p=0.206). Furthermore, serum selenium concentration was negatively associated with CHD risk (OR: 0.989, 95% CI: 0.981, 0.997, p=0.006). Comparing with the lowest quartile, participants with the highest serum selenium concentration had a statistically significant decreased prevalence of CHD, with OR (95% CI) of 0.417 (0.259, 0.669) (p<0.001). The smoothing curve also showed a non-linear relationship between serum selenium and risk of CHD. **Conclusions:** This analysis suggested that a higher serum selenium concentration was associated with reduced risk of CHD, and that the relationship was non-linear. In addition, an appropriate dietary selenium intake might reduce all-cause mortality.

Key Words: dietary selenium, serum selenium, coronary heart disease, all-cause mortality, NHANES

INTRODUCTION

Selenium, an essential trace element, plays a key role in antioxidant, immune, and anti-inflammatory processes through glutathione peroxidase (GSH-Px) and other selenoproteins.[1-3] Selenium deficiency in humans is associated with acute and chronic pathological conditions, such as systemic inflammation, cardiovascular disease, autoimmune disease, diabetes, and various cancers.[4,5] Foods such as meat, intestines, and seafood are primary sources of selenium.[6] Selenium is also a component of many popular dietary supplements.

Although numerous studies have provided evidence supporting the importance of meeting the recommended intake of selenium to maintain proper bodily function and homeostasis, findings regarding selenium exposure and its health outcomes are conflicting. As early as the 1950s, selenium deficiency had been proved to be the main cause of Keshan disease, which was first occurred in the Keshan county of Heilong-jiang province. Clinically, this disease showed acute or chronic episode of a heart disease characterized by cardiogenic shock, enlarged heart, and congestive heart failure.[7] Furthermore, selenium was discovered to play a crucial role in regulating glucose homeostasis.[8,9] Low serum selenium concentrations are associated with future cardiovascular death in patients with acute coronary syndrome.[10] Animal and basic scientific studies have shown that selenium deficiency may be associated with an increased risk of atherosclerotic cardiovascular disease.[11] However, among studies, no consensus has been reached regarding the safe range of exposure to selenium, which may improve or damage human health according to the dose used.[12-14] Higher selenium intake is associated with lower insulin resistance when the total selenium intake is less than 1.6 μg/kg/day, but this negative correlation is no longer significant when the selenium intake is more than 1.6 μg/kg/day.[15] Furthermore, several cross-sectional studies have revealed that serum selenium concentration is correlated with concentrations of blood lipid parameters.[6,16]

Coronary heart disease (CHD) is a leading cause of morbidity and mortality worldwide.[17] Few studies with a large sample size have comprehensively examined the associa-

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tions of dietary intake of selenium and serum selenium concentration with CHD prevalence. Furthermore, little research has investigated whether dietary and circulating selenium concentrations are nonlinearly related to CHD prevalence and whether a threshold effect exists for these relationships. We conducted this study to address this research gap by analyzing the associations of dietary intake of selenium and serum selenium concentration with CHD prevalence and all-cause mortality among participants older than 18 years in the National Health and Nutrition Examination Survey (NHANES).

METHODS

Study population

All participants were from the NHANES 1999-2006 database.[18] The National Center for Health Statistics of the Centers for Disease Control and Prevention (CDC) conducted this cross-sectional study among nationally representative US population. In NHANES 1999-2006, there were a total of 41,474 individuals and our study limited the participants aged 18 years and older who were provide dietary and serum selenium data and self-reported personal data on CHD. In the end, we included a total of 17867 and 2883 individuals to explore the associations between dietary and serum selenium and risk of CHD respectively. The procedures involving human subjects were approved by the national center for health statistics research ethics review board and informed consent was obtained from every participant.

Coronary heart disease

The NHANES database provided self-reported personal interview data on a broad range of health conditions for both children and adults. A standardized questionnaire and measurements were provided to basic characteristics of all participants. Furthermore, the medical conditions section from the questionnaire data provides self-reported personal interview information on the diagnosed health status, including CHD, diabetes, and hypertension. The questions were asked using the Computer-Assisted Personal Interviewing system. The CHD status in all participants was based on their answers to the question, "Has a doctor or other health professional ever told you that you had CHD?" The data were reviewed and edited for completeness, consistency, and illogical values.

Dietary intake and serum selenium concentration

Dietary intake information was obtained from dietary interview which was conducted in the NHANES Mobile Examination Centers (MECs). The participants were asked to recall all the types and amounts of foods and beverages consumed in two inconsecutive 24-hour period before the interview. Based on the dietary intake data, intakes of energy, total fat, dietary fiber, nutrients, and other food components were estimated. The selenium intake of each participants was calculated as microgram per day (μg/day). To ensure the quality and completeness of questionnaire, one-week training course and written guidelines have been developed for all dietary investigators to complete the required procedures. The nutrient intake data reported in NHANES do not include those obtained from dietary supplements, medications, or plain drinking water. The serum selenium was measured by atomic absorption spectrometry.

Follow-up and ascertainment of deaths

Mortality information was collected from the date of the survey participation through 31 December 2006. NHANES 1999–2000 and 2001-2002 survey data have been linked to death certificate records from the National Death Index (NDI). Overall, 4754 and 5260 participants were followed in the 1999–2000 and 2001–02, respectively, with 445 and 325 assumed death events, respectively.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD). The 4th percentile of dietary and serum selenium concentration were calculated. Odds ratios (ORs) and 95% confidence intervals (CIs) for CHD were estimated by multivariate logistic regression analysis. We used multivariable Cox proportional hazard models to estimate the risk of all-cause mortality. The multivariate adjusted model was adjusted for age (continuous), sex, race (non-Hispanic white, black, Mexican American, other Hispanic, other race/ethnicity, or missing), education (less than high school, high school, more than high school, or missing), body mass index (BMI) (<18.5, 18.5-24.9, 25-29.9, >30, or missing), current cigarette smoker (yes, no, or missing), alcohol use (yes, no, or missing), intake energy (continuous), total fat (continuous) and dietary fiber (continuous), and hypertension (yes, no, or missing). In addition, we used generalized additive model (GAM) with a spline smoothing function to identify the non-linear relationship between dietary and serum selenium and CHD and all-cause mortality. The subgroup analyses were conducted and stratified by age, sex, BMI, current alcohol use, cigarette smoker, and status of diabetes and hypertension. All the statistical analyses were conducted using EmpowerStats software (www.empowerstats.com, X&Y solutions, Inc. Boston MA) and R version 3.3.2. Two-sided p values <0.05 were considered as statistical significance.

RESULTS

The role of selenium in coronary heart disease

We reviewed 14 studies in different countries and regions to discussion on the role of selenium for CHD (Table 1). Of these, 7 were prospective cohort study,[10,19-24] 6 were case-control study,[25-30] and 1 was nested case-control study.[31] Data on first author, publication year, country, study design, exposure details, selenium concentration, and outcomes were extracted. The current observational studies mainly evaluated the associations of selenium concentration in whole blood, serum, plasm, erythrocyte, toenails and urine with CHD. Most studies show that low circulating selenium concentrations are inversely associated with incidence or mortality of CHD. However, at present, few observational studies have explored the association between dietary selenium intake and risk of CHD.

A pathway analysis diagram shows how selenium is involved (Figure 1). Increasing the intake of selenium through diet or supplement can improve the plasma selenium concentration. Different chemical forms (organic and

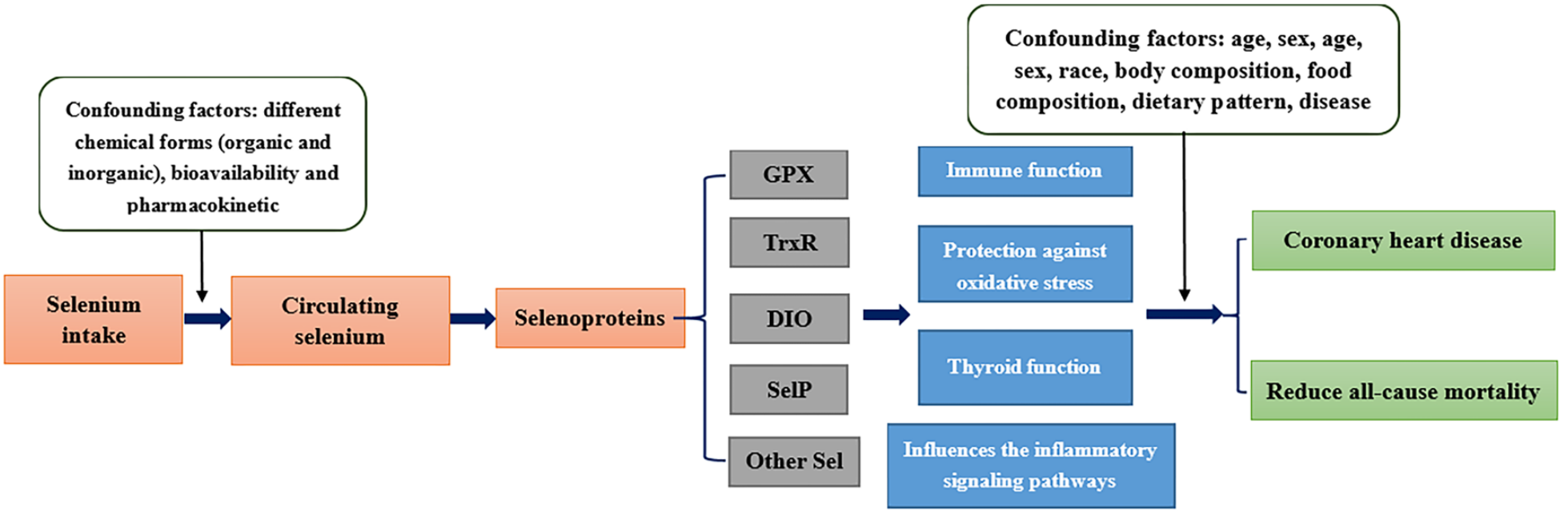

Figure 1. Role of selenium in the CHD. GPX: glutathione peroxidases; TrxR; thioredoxin reductase; DIO: thyroid hormone deiodinases; SelP; selenoprotein P.

Table 1. Comparison of research in different countries and regions of the association of selenium status with CHD

First author, year	Country	Design	Exposure details	Selenium concentration, μg/L		Outcome
				Case subjects	Non-case/control subjects	
Yuan, 2017[31]	China	Nested case-control	Plasma	67.48 (57.67-78.69)	65.85 (56.88-76.87)	Plasma selenium was negatively associated with CHD incidence
Kilander, 2001[19]	Sweden	Prospective cohort study	Serum	NA	NA	Serum selenium was negatively with CVD mortality
Kok, 1987[20]	Netherlands	Prospective cohort study	Serum	125.1±28.4	126.5±28.5	Low serum selenium (below 105 μg/L) is not clearly associated with an excess risk of CVD death
Ringstad, 1986[21]	Norway	Nested case-control	Serum	130.7± 21.2	125.9± 22.0	Low serum selenium is not associated with an excess risk of myocardial infarction.
Akbaraly, 2005[22]	France	Prospective cohort study	Serum	83.7±15.7	86.0±15.7	No significant association between serum selenium concentration and cardiovascular diseases
Yoshizawa, 2003[23]	USA	Prospective cohort study	Toenails	0.95±0.43†	0.93±0.29†	No significant association between serum selenium concentration and incidence of CHD
Lubos, 2009[10]	Germany	Prospective cohort study	Serum	61.0±22.5	71.5±22.3	Low selenium concentration was associated with CVD mortality
Wei, 2004[24]	China	Prospective cohort study	Serum	NA	NA	A nearly significant protective association was observed between selenium concentration and heart disease mortality
Salonen, 1982[25]	Finland	Case-control study	Serum	51.8±13.8	55.3±14.7	Serum selenium of less than 45 μg/L was associated with an increased risk of CHD mortality
Oster, 1986[26]	Germany	Case-control study	Serum	56.0±15.0	78.0±11.0	No relationship was found between the serum selenium concentration and the severity of myocardial infarction
Kardinaal, 1997[27]	Eight European countries and Israel	Case-control study	Whole blood	86.8±15.8	105.8±13.4	No relationship was found between the serum selenium concentration and AMI incidence
Bor, 1999[28]	Turkey	Case-control study	Plasma, erythrocyte, and urinary	63.7±12	82.2±14.6	AMI exhibit lower plasma, erythrocyte and urinary selenium than the controls.
Beaglehole, 1990[29]	New Zealand	Case-control study	Whole blood	82.7±20.2	88.2±20.7	Low selenium concentration was associated with increased risk of AMI incidence
Zachara, 2001[30]	Poland	Case-control study	Whole blood and Plasma	53.8±18.3	52.5±13.6	No significant alterations were noticed in whole blood and plasma concentrations of selenium, among AMI patients compared with the control group

IHD: ischaemic heart disease; CHD: coronary heart disease; AMI: acute myocardial in fraction; CVD: cardiovascular disease.

†Measured in μg/g.

inorganic selenocompounds) in foods and dietary supplements, and bioavailability and pharmacokinetic profiles of selenium can affect the biological function of selenium. Selenium is incorporated into selenoproteins as selenocysteine. At present, over 25 selenoproteins have been identified that play diverse roles in the regulation of cellular redox processes. Serum selenium concentrations are positively correlated with the activities of GPX and other antioxidant selenoproteins, which are crucial for maintenance of redox homeostasis and optimal antioxidant defense. Meanwhile, oxidative stress plays an important role in the chronic and acute phase of CHD.

Baseline characteristics of the participants in this study

The baseline characteristics of the participants are shown in Table 2. This cross-sectional study included 17867 individuals with a mean age of 49.24±18.98 years, 8485 (47.49%) of them were males. The mean BMI was 28.48±6.39 kg/m^2. There was a higher proportion of non-Hispanic white among participants with CHD. Participants with CHD also appeared to have higher systolic blood pressure, BMI, plasma glucose, and triglyceride.

Association between dietary intake of selenium and serum selenium concentration and CHD

The relationships between dietary intake of selenium and serum selenium concentration and CHD were performed by univariable and multivariable logistic regression analysis. As shown in Table 3, univariable analysis showed that dietary intake of selenium was negatively associated with CHD (p<0.001). Those in the highest quartile of dietary selenium intake had the lowest odds of CHD prevalent (OR: 0.653, 95% CI: 0.530, 0.805, p<0.001). However, we did not observe the same trend after fully adjusting for confounding (p=0.206). In multivariate adjusted models, serum selenium concentration was negatively associated with CHD (OR: 0.989, 95% CI: 0.981, 0.997, p=0.006). Comparing with the lowest quartile, participants with higher serum selenium concentration had a statistically significant decreased prevalent of CHD, with ORs (95% CIs) of 0.427 (0.252, 0.722) (p=0.002), 0.561 (0.353, 0.890) (p=0.014) and 0.417 (0.259, 0.669) (p<0.001). The same trend in sensitivity analysis were also observed (p for trend was 0.009).

Figure 2 and 3 shows the results of non-linear relationship analysis. The smoothing curve showed that the relationship between serum selenium concentration and prevalent of CHD was non-linear after multivariable adjustment (Figure 3). With further increase of concentration of serum selenium, the prevalent of CHD reduces slowly.

Subgroup analysis

Associations of dietary intake of selenium and serum selenium concentration and CHD by subgroup analysis are shown in Table 4. There were no interactions between age, BMI, current alcohol use, cigarette smoker, and status of diabetes and hypertension and dietary selenium intake for prevalent of CHD (all p>0.05). The associations between serum selenium concentration and CHD remained significant in participants aged ≥60 years old, BMI ≥30 kg/m^2 and suffered from hypertension (p<0.05). Serum selenium concentration was also associated with decreased prevalent of CHD in participants without alcohol and smoke use (p<0.05).

Associations between dietary intake of selenium and all-cause mortality

A total of 770 deaths occurred during the follow-up period. The results of the Cox proportional hazards models for

Table 2. Characteristics of the participants

Characteristics	Total population	No CHD	CHD
N	17867	17083	784
Age (years)	49.2±19.0	48.3±18.7	69.1±12.0
Male (%)	8485 (47.5)	7962 (46.6)	523 (66.7)
Race (%)			
Non-Hispanic white	9011 (50.4)	8475 (49.6)	536 (68.4)
Black	3544 (19.8)	3439 (20.1)	105 (13.4)
Mexican American	3915 (21.9)	3814 (22.3)	101 (12.9)
Other Hispanic	750 (4.20)	735 (4.30)	15 (1.91)
Other race/ethnicity	647 (3.62)	620 (3.63)	27 (3.44)
Body mass index (kg/m^2)	28.5±6.39	28.5±6.42	28.9±5.79
Some college or college graduate (%)	8058 (45.2)	7759 (45.5)	299 (38.2)
SBP (mmHg)	119±15.2	119±15.2	122±15.8
DBP (mmHg)	69.6±13.1	69.7±13.0	66.0±15.2
Current cigarette smoker	5536 (54.0)	5382 (55.6)	154 (27.6)
Alcohol use (gm)	5013 (28.1)	4838 (28.3)	175 (22.3)
Glucose, plasma (mg/dL)	105±35.4	104±34.9	117±43.3
Total cholesterol (mg/dL)	203±43.4	203±43.1	191±48.9
Triglyceride (mg/dL)	151±131	150±132	170±104
LDL-cholesterol (mg/dL)	120±36.6	120±36.4	107±37.9
HDL-Cholesterol (mg/dL)	52.7±16.0	52.9±16.0	47.6±14.5
Selenium (μg)	106±59.1	106±59.5	95.8±48.0
Selenium (ng/mL)	137±19.7	137±19.6	134±20.0
Energy (kcal)	2086±944	2100±952	1778±688
Total fat (gm)	77.3±42.5	77.9±42.8	65.2±33.5
Dietary fiber (gm)	15.9±9.58	15.9±9.59	15.7±9.22

SBP: systolic blood pressure; DBP: diastolic blood Pressure; CHD: coronary heart disease.
Data are expressed as mean±SD/n (%).

Table 3. Associations of dietary selenium intake and serum selenium concentration with CHD

	Non-adjusted	*p*-value	Adjusted for age and sex	*p*-value	Multivariate adjusted model†	*p*-value
Dietary selenium	0.996 (0.995, 0.998)	<0.001***	0.999 (0.997, 1.00)	0.135	1.001 (0.999, 1.003)	0.206
Quartile of dietary selenium (μg)						
Q1	Reference		Reference		Reference	
Q2	0.867 (0.703, 1.070)	0.184	0.885 (0.711, 1.102)	0.274	0.975 (0.776, 1.225)	0.829
Q3	0.806 (0.656, 0.990)	0.040*	0.924 (0.743, 1.149)	0.475	1.119 (0.877, 1.426)	0.366
Q4	0.653 (0.530, 0.805)	<0.001***	0.922 (0.734, 1.158)	0.485	1.321 (0.990, 1.763)	0.058
p for trend	<0.001		0.625		0.0388	
Serum selenium	0.994 (0.987, 1.001)	0.103	0.991 (0.984, 0.999)	0.021*	0.989 (0.981, 0.997)	0.006**
Quartile of selenium (ng/mL)						
Q1	Reference		Reference		Reference	
Q2	0.460 (0.283, 0.747)	0.002**	0.494 (0.299, 0.816)	0.006**	0.427 (0.252, 0.722)	0.002**
Q3	0.662 (0.435, 1.007)	0.054	0.643 (0.416, 0.995)	0.047*	0.561 (0.353, 0.890)	0.014*
Q4	0.530 (0.345, 0.815)	0.004**	0.489 (0.313, 0.765)	0.002**	0.417 (0.259, 0.669)	<0.001***
p for trend	0.091		0.0231		0.009	

†Adjusted for age (continuous), sex, race (non-Hispanic white, black, Mexican American, other Hispanic, other race/ethnicity, or missing), education (less than high school, high school, more than high school, or missing), body mass index (<18.5, 18.5-24.9, 25-29.9, >30, or missing), current cigarette smoker (yes, no, or missing), alcohol use (yes, no, or missing), intake energy (continuous), total fat (continuous) and dietary fiber (continuous), and hypertension (yes, no, or missing).
*p<0.05, **p<0.01, ***p<0.001

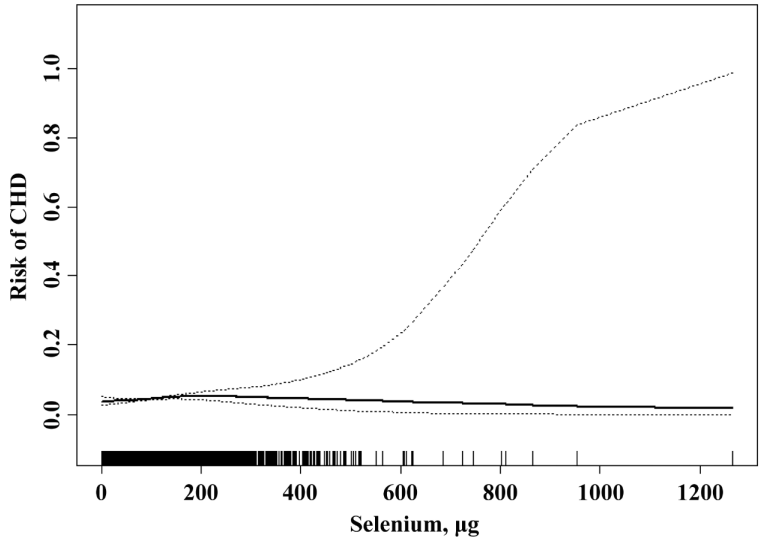

Figure 2. Multivariate adjusted smoothing spline plots of CHD by dietary intake of selenium. Adjusted for age (continuous), sex, race (non-Hispanic white, black, Mexican American, other Hispanic, other race/ethnicity, or missing), education (less than high school, high school, more than high school, or missing), body mass index (<18.5, 18.5-24.9, 25-29.9, >30, or missing), current cigarette smoker (yes, no, or missing), alcohol use (yes, no, or missing), intake energy (continuous), total fat (continuous) and dietary fiber (continuous), and hypertension (yes, no, or missing).

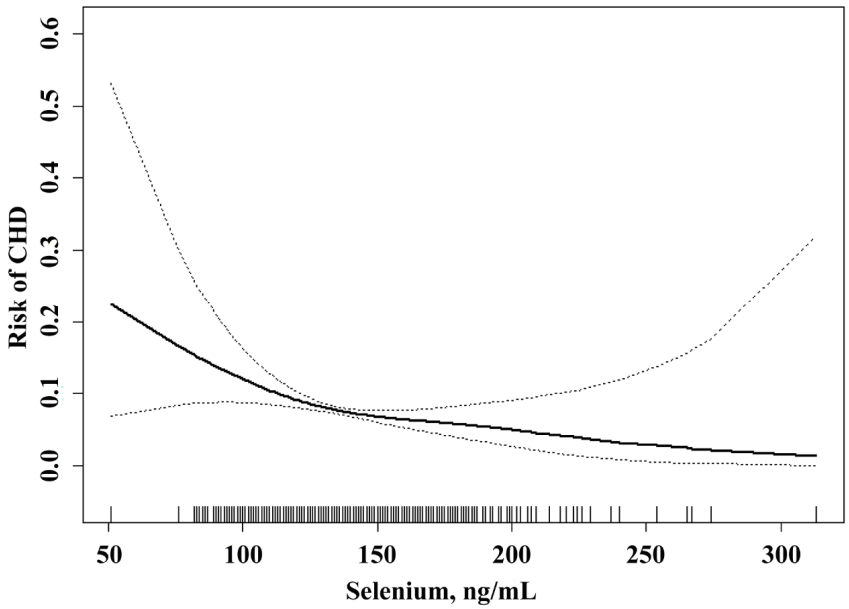

Figure 3. Multivariate adjusted smoothing spline plots of CHD by serum selenium concentration. Adjusted for age (continuous), sex, race (non-Hispanic white, black, Mexican American, other Hispanic, other race/ethnicity, or missing), education (less than high school, high school, more than high school, or missing), body mass index (<18.5, 18.5-24.9, 25-29.9, >30, or missing), current cigarette smoker (yes, no, or missing), alcohol use (yes, no, or missing), intake energy (continuous), total fat (continuous) and dietary fiber (continuous), and hypertension (yes, no, or missing).

Table 4. Associations of dietary intake of selenium and serum selenium concentration with CHD by subgroup analysis

Subgroups	Dietary selenium		Serum selenium	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age				
<44	1.004 (0.999, 1.009)	0.131	0.987 (0.894, 1.090)	0.796
45-65	1.002 (0.998, 1.006)	0.423	0.984 (0.961, 1.007)	0.172
≥65	1.000 (0.998, 1.003)	0.896	0.990 (0.982, 0.998)	0.020*
Sex				
Female	0.995 (0.990, 1.000)	0.047*	0.986 (0.972, 1.000)	0.044*
Male	1.003 (1.001, 1.005)	0.008**	0.991 (0.981, 1.001)	0.065
Body mass index				
<18.5	0.979 (0.950, 1.009)	0.166	0.812 (0.465, 1.418)	0.463
18.5-24.9	0.998 (0.993, 1.003)	0.474	0.984 (0.968, 1.000)	0.052
25-29.9	1.002 (1.000, 1.005)	0.106	0.994 (0.982, 1.006)	0.354
≥30	1.002 (0.998, 1.005)	0.296	0.983 (0.968, 0.999)	0.036*
Current alcohol use				
No	1.000 (0.998, 1.003)	0.808	0.986 (0.977, 0.996)	0.004**
Yes	1.004 (1.000, 1.007)	0.047*	0.995 (0.980, 1.011)	0.553
Current cigarette smoker				
No	1.002 (0.999, 1.004)	0.178	0.987 (0.976, 0.998)	0.019*
Yes	1.003 (0.998, 1.007)	0.209	1.002 (0.986, 1.019)	0.800
Diabetes				
No	1.001 (0.998, 1.003)	0.491	0.990 (0.981, 0.999)	0.037*
Yes	1.001 (0.997, 1.005)	0.721	0.979 (0.963, 0.995)	0.010*
Hypertension				
No	1.000 (0.997, 1.004)	0.867	0.986 (0.972, 1.001)	0.072
Yes	1.002 (1.000, 1.005)	0.108	0.990 (0.981, 1.000)	0.040*

†Adjusted for age (continuous), sex, race (non-Hispanic white, black, Mexican American, other Hispanic, other race/ethnicity, or missing), education (less than high school, high school, more than high school, or missing), body mass index (<18.5, 18.5-24.9, 25-29.9, >30, or missing), current cigarette smoker (yes, no, or missing), alcohol use (yes, no, or missing), intake energy (continuous), total fat (continuous) and dietary fiber (continuous), and hypertension (yes, no, or missing).
*p<0.05, **p<0.01.

all-cause mortality are shown in Table 5. In unadjusted models, compared with the lowest quartile, participants with higher dietary intake of selenium was inversely associated with risk of death (Hazard ratio [HR]: 0.462, 95% CI: 0.379, 0.564, p<0.001). In multivariate adjusted models, compared with the lowest quartile. The second quartile of dietary intake of selenium was inversely associated with all-cause mortality (HR: 0.802, 95% CI: 0.658, 0.977,

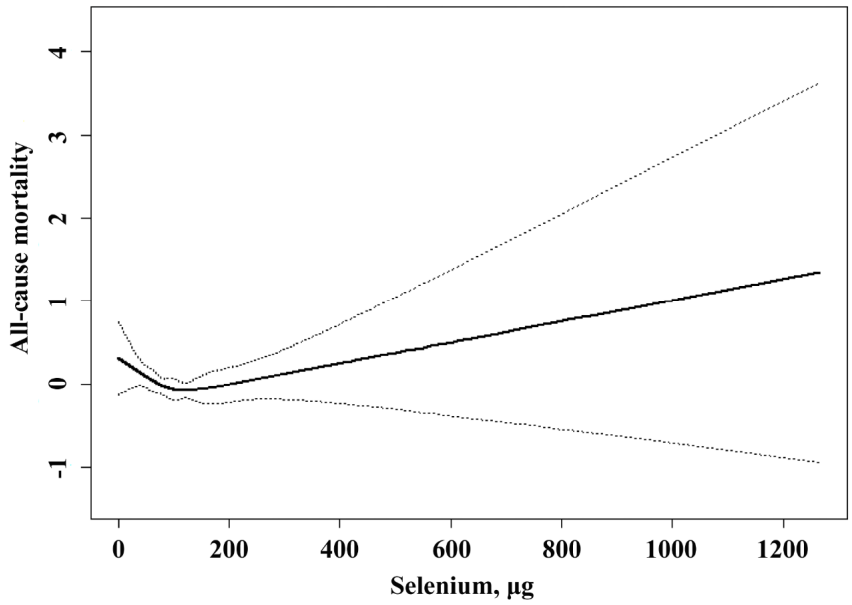

Figure 4. Multivariate adjusted smoothing spline plots of and all-cause mortality by dietary intake of selenium. Adjusted for age (continuous), sex, race (non-Hispanic white, black, Mexican American, other Hispanic, other race/ethnicity, or missing), education (less than high school, high school, more than high school, or missing), body mass index (<18.5, 18.5-24.9, 25-29.9, >30, or missing), current cigarette smoker (yes, no, or missing), alcohol use (yes, no, or missing), intake energy (continuous), total fat (continuous) and dietary fiber (continuous), and hypertension (yes, no, or missing).

p=0.029). The smoothing curve showed that the relationship between dietary intake of selenium and all-cause mortality was non-linear (Figure 4). All-cause mortality decreased with dietary intake of selenium concentration up to the turning point and thereafter increased with increasing dietary selenium intake. In addition, to better explain the associations, comparison results and trend differences between dietary selenium intake and serum selenium are shown in Table 6.

DISCUSSION

In this large-sample study in United States, we first analyzed the associations of dietary intake of selenium and serum selenium concentration with CHD prevalence. A multivariable regression model revealed that serum selenium concentration was negatively associated with CHD prevalence. Compared with participants in the lowest quartile for serum selenium concentration (≤114 ng/mL), those in the higher quartile had a statistically significant decrease in CHD prevalence. Univariable analysis revealed that dietary intake of selenium was negatively associated with CHD. However, the relationship was not significant after full adjustment for confounding factors. Notably, the GAM with a spline-smoothing function revealed a nonlinear relationship between serum selenium concentration and CHD prevalence, with the increase in serum selenium concentration corresponding to a slow decrease in CHD prevalence. In addition, the relationship between dietary intake of selenium and all-cause mortality was non-linear, and a U-shaped curve was observed.

Although the potential role of selenium in the development and progress of CHD has been studied for decades, the results of research on dietary selenium intake or circulating selenium concentration remain inconclusive. In this paper, at first, we reviewed the current studies in different countries and regions to discussion on the role of selenium for CHD. Previous studies in China have investigated the relationships between selenium and incidence and mortality of CHD. Of these, a nested case-control study demonstrated that plasma selenium concentration was associated with decreased incidence of CHD.[31] In contrast, a larger prospective study showed that no significant association was observed between selenium concentration and heart disease mortality.[24] Similar finding was also observed case-control study in United States, which investigated the association between toenail selenium concentration and risk of CHD.[23] In addition, several studies in other countries have shown that low-selenium concentrations are associated with increased risk CHD risk or mortality.[10,25,29] According to the literature review results, most studies of the association between selenium concentration and CHD have been conducted in European countries or China, which have lower selenium concentration compared with that in the United States. To our knowledge, in addition to differences in background selenium concentration, reasons for differences in research results between include socioeconomic conditions or other determinants of selenium concentration. Circulating selenium concentration depends not only on dietary exposure but also on the form of selenium intake, selenium metabolism, and the pathophysiological response to conditions related to increased oxidative stress or inflammation. Moreover, the selenium content of food varies geographically because of differences in concentrations in soil and water and the use of selenium-containing fertilizers.[32]

In this paper, the results suggested that a higher serum selenium concentration is associated with decreased risk of CHD. The underlying mechanisms have several possible explanations. First, selenium is a component of GSH-Px, which plays a key role in the mechanism of antioxidation,[33] and animal experiments have demonstrated that glutathione peroxidase-1 deficiency accelerates the process of atherosclerosis.[34,35] Selenoprotein can protect endothelial cells from oxidative damage by restoring GSH-Px express

Table 5. Associations of dietary intake of selenium with all-cause mortality

	Non-adjusted	*p*-value	Adjusted for age and sex	*p*-value	Multivariate adjusted model[†]	*p*-value
Selenium	0.995 (0.994, 0.997)	<0.001***	0.999 (0.997, 1.000)	0.1221	1.000 (0.998, 1.002)	0.915
Selenium (μg)						
Q1	Reference		Reference		Reference	
Q2	0.707 (0.584, 0.855)	<0.001***	0.748 (0.618, 0.905)	0.003**	0.802 (0.658, 0.977)	0.029*
Q3	0.615 (0.506, 0.746)	<0.001***	0.753 (0.618, 0.917)	0.005**	0.846 (0.681, 1.052)	0.132
Q4	0.462 (0.379, 0.564)	<0.001***	0.732 (0.594, 0.901)	0.003**	0.840 (0.649, 1.088)	0.187
p for trend	<0.0001		0.003		0.201	

[†]Adjusted for age (continuous), sex, race (non-Hispanic white, black, Mexican American, other Hispanic, other race/ethnicity, or missing), education (less than high school, high school, more than high school, or missing), body mass index (<18.5, 18.5-24.9, 25-29.9, >30, or missing), current cigarette smoker (yes, no, or missing), alcohol use (yes, no, or missing), intake energy (continuous), total fat (continuous) and dietary fiber (continuous), and hypertension (yes, no, or missing).
*p<0.05, **p<0.01, ***p<0.001.

Table 6. The comparison results and trend differences between dietary selenium intake and serum selenium

Exposure details	Study population	No. of subjects	Mean age, years	Selenium concentration		Outcomes	
				Case subjects	Noncase subjects	Risk of CHD	All-cause mortality
Dietary intake of selenium	NHANES 1999-2006	17867	49.24±18.98	106.48±59.47 μg	95.75±47.96 μg	There was no evidence of association between dietary selenium intake and risk of CHD	NA
Serum selenium	NHANES 2003-2004	2883	61.87±13.73	136.80±19.62 ng/mL	134.34±19.98 ng/mL	Serum selenium concentration was negatively associated with risk of CHD. Compared with the lowest quartile, participants with highest serum selenium concentration had a decreased risk of CHD	NA
Dietary intake of selenium	NHANES 1999-2002	10014	46.25±20.15	NA	NA	NA	Compared with the lowest quartile, the second quartile of dietary intake of selenium was inversely associated with all-cause mortality

sion and enzyme activity.[36] Second, low selenium concentrations might increase platelet aggregation and vasoconstriction by shifting prostaglandin synthesis from prostaglandins to thromboxane.[37] Third, studies have demonstrated that selenium can prevent metal-induced oxidative damage or the formation of inactive complexes with metals and that toxic metals, such as mercury, cadmium, and arsenic, might be related to atherogenesis.[32,38] Finally, selenium can reduce the production of inflammatory prostaglandins and leukotrienes by neutralizing peroxide intermediates 3. Furthermore, our study is the first to report a nonlinear relationship between serum selenium concentration and risk of CHD, with the risk of CHD tending to remain stable with the increase in serum selenium concentration. This finding indicates that increased circulating selenium concentration might not always be beneficial for preventing CHD. Similarly, a cross-sectional study reported a U-shaped relationship between serum selenium concentration and the prevalence of peripheral arterial disease. The prevalence of peripheral arterial disease was reported to decrease with the increase in serum selenium concentration and increase with the increase in selenium concentration at concentrations of 150–160 ng/mL.[39] In addition, a cross-sectional study on US participants in the NHANES showed that higher circulating selenium concentration corresponded to an increased risk of dyslipidemia and suggested a dose–reaction relation.[16] Similar results were also reported in several cross-sectional studies.[40-43] However, high-TC and high-LDLC dyslipidemia is related to CHD, stroke, and peripheral artery disease.[44]

At present, evidence of an association between dietary intake of selenium and CHD prevalence is lacking. Our study revealed no significant association between dietary selenium intake and risk of CHD. Interestingly, our study also explored the association between dietary intake of selenium and all-cause mortality and revealed a U-shaped relationship between them. Compared with the lowest quartile, only the second quartile of dietary intake of selenium was inversely associated with all-cause mortality. The all-cause mortality of participants decreased with dietary intake of selenium concentration up to the turning point and thereafter increased with increasing dietary selenium intake. Similar findings were also found in other studies. In a similar study based on NHANES in 1988-1994, an inverse association was observed between serum selenium concentrations and all-cause and cancer mortality at low selenium concentration (<130 ng/mL) and a modest increase in mortality at high selenium concentration (>150 ng/mL).[45] By considering the initial selenium supplement dose, a study of selenium-rich individuals concluded that additional selenium supplementation had no benefit for adults when the circulating selenium concentration

The aforementioned findings suggest that the health relationship of selenium nutrition is complicated. Selenium is an essential element with a narrow safety margin. Due to the narrow physiological range of selenium, the population is vulnerable to geographical deficiency and toxicity.[45] Selenium could reduce oxidative stress through antioxidant selenoproteins such as glutathione peroxidase, selenoprotein P. With the possible exception of selenoprotein P, the concentration and activity of selenoproteins are maximized at plasma selenium concentrations of 70 to 90 ng/mL, and additional selenium intake above these concentrations did not result in increased glutathione activity.[46] In addition, previous study has demonstrated that several nutrients or individual food intakes is unlikely to be responsible for general nutritionally-related health (NRH) status or mortality.[47] Examining the relationships between dietary patterns, dietary diversity and dietary quality and health outcomes would be preferable. Thus, the health effects of selenium deficiency or excess in current may be mitigated by dietary pattern. Future research should focus on solving this problem.

The strengths of the current study include the use of a large sample size based on a nationally representative sample of the United States population. Additionally, few other studies have comprehensively examined the association between dietary intake of selenium concentration and CHD prevalence. We also identified a nonlinear relationship between serum selenium concentration and CHD. However, this study also has some limitations. First, a cross-sectional design was adopted, making it difficult to identify a causal relationship of dietary intake of selenium and serum selenium concentration with CHD prevalence. Second, the dietary intake data used in this study were collected through 24-hour dietary recall interviews. The dietary assessment method might have led to recall bias of actual intake. Third, due to the limited data available, the mortality data from NHANES in the 1999-2002 were followed, and serum selenium concentrations were not measured in these subjects. Therefore, we only evaluated the association between dietary intake of selenium and all-cause mortality. Finally, our findings may have been influenced by residual confounding factors, such as use of medications.

Conclusion

In conclusion, the results of this cross-sectional analysis reveal a negative and nonlinear association between serum selenium concentration and CHD prevalence. Furthermore, our findings indicate that no significant association exists between dietary selenium intake and risk of CHD. However, a U-shaped association between dietary intake of selenium and all-cause mortality was found. Future high-quality prospective studies should be conducted to verify our conclusions.

AUTHOR DISCLOSURES

The authors declare no conflict of interest.

REFERENCES

1. Rayman MP. Selenium and human health. Lancet. 2012; 379(9822):1256-68. doi: 10.1016/S0140-6736(11)61452-9.
2. Burk RF. Selenium, an antioxidant nutrient. Nutr Clin Care. 2002;5:75-9. doi: 10.1046/j.1523-5408.2002.00006.x.
3. Rayman MP. The importance of selenium to human health. Lancet. 2000;356(9225):233-41. doi: 10.1016/S0140-673 6(00)02490-9.
4. Xiang S, Dai Z, Man C, Fan Y. Circulating selenium and cardiovascular or all-cause mortality in the general population: a meta-analysis. Biol Trace Elem Res. 2019;195: 55-62. doi: 10.1007/s12011-019-01847-8.
5. Fairweather-Tait SJ, Bao Y, Broadley MR, Collings R, Ford D, Hesketh JE, Hurst R. Selenium in human health and disease. Antioxid Redox Signal. 2011;14:1337-83. doi: 10. 1089/ars.2010.3275.

6. Ju W, Ji M, Li X, Li Z, Wu G, Fu X, Yang X, Gao X. Relationship between higher serum selenium level and adverse blood lipid profile. Clin Nutr. 2018;37:1512-7. doi: 10.1016/j.clnu.2017.08.025.
7. Chen J. An original discovery: selenium deficiency and Keshan disease (an endemic heart disease). Asia Pac J Clin Nutr. 2012;21:320-6. doi: 10.6133/apjcn.2012.21.3.01
8. Becker DJ, Reul B, Ozcelikay AT, Buchet JP, Henquin JC, Brichard SM. Oral selenate improves glucose homeostasis and partly reverses abnormal expression of liver glycolytic and gluconeogenic enzymes in diabetic rats. Diabetologia. 1996;39:3-11. doi: 10.1007/bf00400407.
9. Mueller AS, Pallauf J. Compendium of the antidiabetic effects of supranutritional selenate doses. In vivo and in vitro investigations with type II diabetic db/db mice. J Nutr Biochem. 2006;17:548-60. doi: 10.1016/j.jnutbio.2005.10.006.
10. Lubos E, Sinning CR, Schnabel RB, Wild PS, Zeller T, Rupprecht HJ et al. Serum selenium and prognosis in cardiovascular disease: results from the AtheroGene study. Atherosclerosis. 2010;209:271-7. doi: 10.1016/j.atherosclerosis.2009.09.008.
11. Eaton CB, Abdul Baki AR, Waring ME, Roberts MB, Lu B. The association of low selenium and renal insufficiency with coronary heart disease and all-cause mortality: NHANES III follow-up study. Atherosclerosis. 2010;212:689-94. doi: 10.1016/j.atherosclerosis.2010.07.008.
12. Lee KH, Jeong D. Bimodal actions of selenium essential for antioxidant and toxic pro-oxidant activities: the selenium paradox (Review). Mol Med Rep. 2012;5:299-304. doi: 10.3892/mmr.2011.651.
13. Brozmanova J, Manikova D, Vlckova V, Chovanec M. Selenium: a double-edged sword for defense and offence in cancer. Arch Toxicol. 2010;84:919-38. doi: 10.1007/ s00204-010-0595-8.
14. Vinceti M, Filippini T, Wise LA. Environmental selenium and human health: an update. Curr Environ Health Rep. 2018;5:464-85. doi: 10.1007/s40572-018-0213-0.
15. Wang Y, Lin M, Gao X, Pedram P, Du J, Vikram C, Gulliver W, Zhang H, Sun G. High dietary selenium intake is associated with less insulin resistance in the Newfoundland population. PLoS One. 2017;12:e0174149. doi: 10.1371/journal.pone.0174149.
16. Huang YQ, Shen G, Lo K, Huang JY, Liu L, Chen CL et al. Association of circulating selenium concentration with dyslipidemia: Results from the NHANES. J Trace Elem Med Biol. 2020;58:126438. doi: 10.1016/j.jtemb.2019. 126438.
17. Manav M, Su J, Hughes K, Lee HP, Ong CN. Omega-3 fatty acids and selenium as coronary heart disease risk modifying factors in Asian Indian and Chinese males. Nutrition. 2004; 20:967-73. doi: 10.1016/j.nut.2004.08.003.
18. Patel CJ, Pho N, McDuffie M, Easton-Marks J, Kothari C, Kohane IS, Avillach P. A database of human exposomes and phenomes from the US National Health and Nutrition Examination Survey. Sci Data. 2016;3:160096. doi: 10.1038/sdata.2016.96.
19. Kilander L, Berglund L, Boberg M, Vessby B, Lithell H. Education, lifestyle factors and mortality from cardiovascular disease and cancer. A 25-year follow-up of Swedish 50-year-old men. Int J Epidemiol. 2001;30:1119-26. doi: 10.1093/ije/30.5.1119.
20. Kok FJ, De Bruijn AM, Hofman A, Valkenburg HA. Selenium status and chronic disease mortality: Dutch epidemiological findings. Int J Epidemiol. 1987;16:329-32. doi: 10.1093/ije/16.2.329.
21. Ringstad J, Jacobsen BK, Thomassen Y, Thelle DS. The Tromso Heart Study: serum selenium and risk of myocardial infarction a nested case-control study. J Epidemiol Community Health. 1987;41:329-32. doi: 10.1136/jech.41.4.329.
22. Akbaraly NT, Arnaud J, Hininger-Favier I, Gourlet V, Roussel AM, Berr C. Selenium and mortality in the elderly: results from the EVA study. Clin Chem. 2005;51:2117-23. doi: 10.1373/clinchem.2005.055301.
23. Yoshizawa K, Ascherio A, Morris JS, Stampfer MJ, Giovannucci E, Baskett CK, Willett WC, Rimm EB. Prospective study of selenium levels in toenails and risk of coronary heart disease in men. Am J Epidemiol. 2003; 158:852-60. doi: 10.1093/aje/kwg052.
24. Wei WQ, Abnet CC, Qiao YL, Dawsey SM, Dong ZW, Sun XD et al. Prospective study of serum selenium concentrations and esophageal and gastric cardia cancer, heart disease, stroke, and total death. Am J Clin Nutr. 2004; 79:80-5. doi: 10.1093/ajcn/79.1.80.
25. Salonen JT, Alfthan G, Huttunen JK, Pikkarainen J, Puska P. Association between cardiovascular death and myocardial infarction and serum selenium in a matched-pair longitudinal study. Lancet. 1982;2(8291):175-9. doi: 10. 1016/s0140-6736(82)91028-5.
26. Oster O, Drexler M, Schenk J, Meinertz T, Kasper W, Schuster CJ, Prellwitz W. The serum selenium concentration of patients with acute myocardial infarction. Ann Clin Res. 1986;18:36-42. doi: 10.1097/00000441-198601000-00011.
27. Kardinaal AF, Kok FJ, Kohlmeier L, Martin-Moreno JM, Ringstad J, Gomez-Aracena J et al. Association between toenail selenium and risk of acute myocardial infarction in European men. The EURAMIC Study. European Antioxidant Myocardial Infarction and Breast Cancer. Am J Epidemiol. 1997;145:373-9. doi: 10.1093/oxfordjournals. aje.a009115.
28. Bor MV, Cevik C, Uslu I, Guneral F, Duzgun E. Selenium levels and glutathione peroxidase activities in patients with acute myocardial infarction. Acta Cardiol. 1999;54:271-6. doi: 10.1016/S0002-9149(99)00479-8.
29. Beaglehole R, Jackson R, Watkinson J, Scragg R, Yee RL. Decreased blood selenium and risk of myocardial infarction. Int J Epidemiol. 1990;19:918-22. doi: 10.1093/ije/19.4.918.
30. Zachara BA, Ukleja-Adamowicz M, Nartowicz E, Lecka J. Increased plasma glutathione peroxidase activity in patients with acute myocardial infarction. Med Sci Monit. 2001;7: 415-20. doi: 10.1007/0-306-47466-2_186.
31. Yuan Y, Xiao Y, Feng W, Liu Y, Yu Y, Zhou L et al. Plasma metal concentrations and incident coronary heart disease in Chinese adults: the Dongfeng-Tongji cohort. Environ Health Perspect. 2017;125:107007. doi: 10.1289/ EHP1521.
32. Flores-Mateo G, Navas-Acien A, Pastor-Barriuso R, Guallar E. Selenium and coronary heart disease: a meta-analysis. Am J Clin Nutr. 2006;84:762-73. doi: 10.1093/ajcn/84.4.762.
33. Hassanzadeh M, Faridhosseini R, Mahini M, Faridhosseini F, Ranjbar A. Serum levels of TNF-, IL-6, and selenium in patients with acute and chronic coronary artery disease. Iran J Immunol. 2006;3:142-5. doi: IJIv3i3A7.
34. Lewis P, Stefanovic N, Pete J, Calkin AC, Giunti S, Thallas-Bonke V et al. Lack of the antioxidant enzyme glutathione peroxidase-1 accelerates atherosclerosis in diabetic apolipoprotein E-deficient mice. Circulation. 2007;115: 2178-87. doi: 10.1161/CIRCULATIONAHA.106.664250.
35. Torzewski M, Ochsenhirt V, Kleschyov AL, Oelze M, Daiber A, Li H et al. Deficiency of glutathione peroxidase-1 accelerates the progression of atherosclerosis in apolipoprotein E-deficient mice. Arterioscler Thromb Vasc Biol. 2007;27:850-7. doi: 10.1161/01.ATV.0000258809.47285.07.
36. Steinbrenner H, Bilgic E, Alili L, Sies H, Brenneisen P. Selenoprotein P protects endothelial cells from oxidative

damage by stimulation of glutathione peroxidase expression and activity. Free Radic Res. 2006;40:936-43. doi: 10.1080/10715760600806248.
37. Huang K, Liu H, Chen Z, Xu H. Role of selenium in cytoprotection against cholesterol oxide-induced vascular damage in rats. Atherosclerosis. 2002;162:137-44. doi: 10.1016/s0021-9150(01)00707-9.
38. Feroci G, Badiello R, Fini A. Interactions between different selenium compounds and zinc, cadmium and mercury. J Trace Elem Med Biol. 2005;18:227-34. doi: 10.1016/j.jtemb.2004.09.005.
39. Bleys J, Navas-Acien A, Laclaustra M, Pastor-Barriuso R, Menke A, Ordovas J, Stranges S, Guallar E. Serum selenium and peripheral arterial disease: results from the national health and nutrition examination survey, 2003-2004. Am J Epidemiol. 2009;169:996-1003. doi: 10.1093/aje/kwn414.
40. Bleys J, Navas-Acien A, Stranges S, Menke A, Miller ER, 3rd, Guallar E. Serum selenium and serum lipids in US adults. Am J Clin Nutr. 2008;88:416-23. doi: 10.1093/ajcn/ 88.2.416.
41. Coudray C, Roussel AM, Mainard F, Arnaud J, Favier A. Lipid peroxidation level and antioxidant micronutrient status in a pre-aging population; correlation with chronic disease prevalence in a French epidemiological study (Nantes, France). J Am Coll Nutr. 1997;16:584-91.
42. Stranges S, Laclaustra M, Ji C, Cappuccio FP, Navas-Acien A, Ordovas JM, Rayman M, Guallar E. Higher selenium status is associated with adverse blood lipid profile in British adults. J Nutr. 2010;140:81-7. doi: 10.3945/jn.109. 111252.
43. Su L, Gao S, Unverzagt FW, Cheng Y, Hake AM, Xin P et al. Selenium level and dyslipidemia in rural elderly Chinese. PLoS One. 2015;10:e0136706. doi: 10.1371/journal.pone.0136706.
44. Dandapat S, Robinson JG. Guidelines for management of hyperlipidemia: Implications for treatment of patients with stroke secondary to atherosclerotic disease. Curr Neurol Neurosci Rep. 2016;16:24. doi: 10.1007/s11910-016-0621-1.
45. Bleys J, Navas-Acien A, Guallar E. Serum selenium levels and all-cause, cancer, and cardiovascular mortality among US adults. Arch Intern Med. 2008;168:404-10. doi: 10.1001/archinternmed.2007.74.
46. Xia Y, Hill KE, Byrne DW, Xu J, Burk RF. Effectiveness of selenium supplements in a low-selenium area of China. Am J Clin Nutr. 2005;81:829-34. doi: 10.1093/ajcn/81.4.829.
47. Lee MS, Huang YC, Su HH, Lee MZ, Wahlqvist ML. A simple food quality index predicts mortality in elderly Taiwanese. J Nutr Health Aging. 2011;15:815-21. doi: 10.1007/s12603-011-0081-x.