Sex Difference in The Association Between Plasma Selenium and First Stroke: A Community-Based Nested Case-Control Study

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Research

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Abstract

Background: To date, there is no clearly defined association between plasma selenium levels and first stroke. We aimed to investigate the association between baseline plasma selenium and first stroke risk in a community-based, Chinese population.

Methods: Using a nested case-control study design, a total of 1255 first stroke cases and 1255 matched controls were analyzed. Participant plasma selenium concentrations were measured by inductively coupled plasma mass spectrometry (ICP-MS) and the association of plasma selenium with first stroke risk was estimated by conditional logistic regression models.

Results: Overall, a nonlinear negative association between plasma selenium with first total stroke and first ischemic stroke risks was found in males, but not in females. Compared with participants with lower selenium levels (tertile 1-2, <94.1 ng/mL), participants with higher selenium levels (tertile 3, ≥94.1 ng/mL) had significantly lower risks of first total stroke (OR: 0.63; 95% CI: 0.48, 0.83) and first ischemic stroke (OR: 0.61; 95% CI: 0.45, 0.83) in males, but not in females with first total stroke (OR: 0.92; 95% CI: 0.69, 1.22) and first ischemic stroke (OR: 0.89; 95% CI: 0.65, 1.22). Furthermore, a stronger association between plasma selenium and first total stroke was found in males with higher vitamin E levels (≥13.5 μg/mL *vs.* <13.5 μg/mL *P*-interaction=0.007). No significant association was observed between plasma selenium and first hemorrhagic stroke risk in either males or females.

Conclusion: Our study indicated a significant, nonlinear, negative association between plasma selenium and first stroke in males, but not in females.

TRIAL REGISTRATION: ChiCTR1800017274.

Introduction

Stroke is a leading cause of mortality and disability worldwide. Accounting for almost one third of worldwide stroke mortality, China bears the heaviest stroke burden in the world [1,2]. Since control of risk factors for stroke helps decrease stroke burden [3,4], the identification of novel risk factors is urgent to further lower stroke risk. Recently, accumulating evidence has indicated that trace elements might exert effects on stroke [5,6].

Selenium (Se), an essential trace element, acts as the active center of selenoproteins or selenoenzymes (eg, glutathione peroxidases), which have many important biological functions including antioxidant, anti-inflammatory and immunoregulatory roles [7-9]. Insufficient or excessive selenium intake may be associated with many adverse health outcomes [10-12]. Particularly, health problems caused by selenium deficiency need to be given great attention in China, a Se-deficient country where it is estimated that over 105 million people potentially face adverse health impacts due to selenium deficiency [13,14]. Although cross-sectional epidemiologic studies have indicated inverse associations between selenium levels with stroke risk [15-17], previous prospective epidemiologic studies have reported inconsistent findings on the

associations between selenium concentrations with stroke risk [18-21]. Moreover, few studies have thoroughly analyzed the potential modifiers affecting this association. Therefore, the prospective relationship between plasma selenium and risk of first stroke remains inconclusive and deserves further investigation.

To fill the knowledge gap mentioned above, we performed a nested case-control study to investigate the association between baseline plasma selenium levels and risk of first total stroke and stroke subtypes (ischemic stroke and hemorrhagic strokes), and examined any possible effect modifiers using data from a community-based population in China. To the best of our knowledge, this study is the first of its kind to evaluate this relationship in a community-based Chinese population.

Methods

Study population and design

Our present study is a subset of the China H-type Hypertension Registry Study (CHHRS; URL: http://www.chictr.org.cn; Unique identifier: ChiCTR1800017274) which was an ongoing community-based non-intervention, prospective, observational, multicenter, real-world registry study and was mainly conducted in Rongcheng county, Shandong province, and Lianyungang, Jiangsu province, China. It was designed to establish a national registry of patients with hypertension, to investigate the prevalence and treatment of H-type hypertension in China and the related factors affecting its prognosis, and finally to construct a risk prediction model of cardio-cerebral and renal vascular diseases. Eligible participants were men and women aged ≥18 years with essential hypertension, defined as seated systolic blood pressure (SBP) ≥140 mm Hg and/or seated diastolic blood pressure (DBP) ≥90 mm Hg at the screening visit. Participants were excluded if they had psychological or nervous system impairment resulting in an inability to demonstrate informed consent or were unable to be followed-up according to the study protocol. The trial consisted of 2 stages: screening and recruitment and a 3-year observation follow-up period. Participants were scheduled for follow-up every 3 months. At each visit, blood pressure, heart rate, the usage of medications, adverse events, and study outcome events were measured and recorded. The primary outcome was first composite of cardiovascular events consisting of nonfatal stroke, myocardial infarction, and vascular death and all-cause death.

The current nested case-control study utilized data from the CHHRS which had been conducted in Rongcheng, a coastal area of Shandong province, China. This study matched stroke cases with an equal number of controls (patients without stroke) by age ± 1 year, sex, and village. Patients with stroke data from the Chinese Centers for Disease Control and Prevention (CDC, 2016-2018) who had complete records (physical exam, questionnaire, and biological samples) were selected as cases. The initial sample consisted of 1401 incident cases and 1401 matched controls. Next, we excluded participants with missing serum calcium value (n=287) and unpaired individuals (n=5). Based on the inclusion and exclusion criteria, 1255 stroke cases and 1255 matched controls with complete calcium measurements were selected for final data analysis (Supplementary Figure 1).

Ethics

The present study was approved by the Ethics Committee of the Institute of Biomedicine, Anhui Medical University, Hefei, China. All participants signed an approved written consent form after the study protocol was thoroughly explained to them.

Outcomes

The primary outcome of the present study was a first nonfatal or fatal stroke. Secondary outcomes included first ischemic stroke (fatal and nonfatal), and first hemorrhagic stroke (fatal and nonfatal).

Information on incidence of first stroke for all participants was obtained via the Center for Disease Control and Prevention of Rongcheng county, and checked against the national health insurance system with electronic linkage to all hospitalizations, or ascertained through active follow-up. Diseases were coded according to the International Classification of Diseases, 10th Revision (ICD-10). Secondary outcomes included first ischemic stroke (I63) and first hemorrhagic stroke (I60-I61). The primary outcome (first nonfatal or fatal stroke) included first ischemic stroke (I63), first hemorrhagic stroke (I60-I61) and no type stroke (I64).

According to government regulations, local authorities from medical institutions are required to report all new cases of stroke to the local Center for Disease Control and Prevention. A report card which includes information on demographics, diagnostic basis and date of stroke is required to be submitted on the 28th of each month. Quality control, including finding and deleting repeated cases, error checking, and determining any missed cases, is completed by trained officials. Furthermore, the staff from the local Center for Disease Control and Prevention would double check these information and also be responsible for deleting repeated cases and finding logistical errors and missed cases. In addition, 5% of all uploaded cases are randomly chosen for further confirmation by phone or door-to-door interviews.

Laboratory assays

Baseline serum total homocysteine (tHcy), fasting glucose levels, and lipids were measured using automatic clinical analyzers (Beckman Coulter, AU680) at the Shenzhen Tailored Medical laboratory in Shenzhen, China. Estimated glomerular filtration rates (eGFR) were estimated by the Chronic Kidney Disease Epidemiology Collaboration equation. Baseline plasma vitamin E concentrations were measured using liquid chromatography–tandem quadrupole mass spectrometry (LC-MS/MS) and plasma selenium concentrations were measured by inductively coupled plasma mass spectrometry (ICP-MS) using Thermo Fisher iCAP Q ICP-MS in a commercial laboratory (Beijing DIAN Medical Laboratory, China). In the present study, the intra-assay CV for selenium ranged from 1.02% to 7.93%, while the inter-assay CV for selenium ranged from 2.79% to 3.51%. According to a previous study [22], the reference value (50-120 ng/mL) for plasma selenium levels was used in this study.

Statistical analysis

Baseline characteristics are presented as means ± SDs for continuous variables and as frequency (%) for categorical variables. Differences in baseline characteristics between males and females, and cases and controls, were compared using Chi-square tests for categorical variables and *t*-tests for continuous variables. Differences in population characteristics according to selenium tertiles were compared using ANOVA tests, or Chi-square tests, accordingly.

Variables that are known as traditional or suspected risk factors for stroke [23], and matched variables or variables that showed significant differences between cases and controls were adjusted for in the models. Odds ratios (ORs) and 95% confidence intervals (95% CIs) for first stroke, first ischemic stroke, and first hemorrhagic stroke were calculated by modeling plasma selenium as tertiles using conditional logistic regression, without and with adjustment for matched variables (sex and age), body mass index (BMI), baseline systolic blood pressure (SBP), baseline diastolic blood pressure (DBP), smoking status, alcohol consumption, labor intensity, baseline total homocysteine (tHcy), plasma vitamin E, fasting glucose, estimated glomerular filtration rate (eGFR), antiplatelet drugs, lipoprotein-lowering drugs, glucose-lowering drugs, antihypertensive drugs, self-reported hypertension, self-reported diabetes, self-reported atrial fibrillation, and self-reported hyperlipidemia. A generalized additive model (GAM) and smooth curve fitting (penalized spline method) were evaluated to further characterize the shape of the association between serum selenium and first stroke and its subtypes. As additional exploratory analyses, possible modifications of the association between plasma selenium (tertile 3, ≥94.1 *vs.* tertile 1-2, <94.1 ng/mL) and first total stroke in male and female participants were also assessed for variables including age (<70 *vs.* ≥70 y), BMI (<24 *vs.* ≥24kg/m^2), current smoking (yes *vs.* no), current alcohol drinking (yes *vs.* no), baseline SBP (<140 *vs.* ≥140 mmHg), fasting glucose (<6.1 *vs.* ≥6.1 mmol/L or diabetes), total cholesterol (<5.78 [median] *vs.* ≥5.78 mmol/L), triglycerides (<1.17 [median] *vs.* ≥1.17 mmol/L), estimated glomerular filtration rate (<90 *vs.* ≥90 mL/min/1.73m^2), total homocysteine (<12.5 [median] *vs.* ≥12.5 μmol/L), and vitamin E (<13.5 [median] *vs.* ≥13.5 μmol/L) using multivariate logistic regression models. Diabetes was defined as fasting serum glucose ≥7.0 mmol/L or self-reported use of anti-diabetic medications, or physician diagnosed diabetes. Potential interactions were examined by including the interaction terms into those logistic regression models with the greatest number of confounding variables.

A 2-tailed $P<0.05$ was considered to be statistically significant in all analyses. R software version 3.4.3 (www.R-project.org) and Empower version 2.17.8 (www.empowerstats.com, X&Y Solutions, Inc.) were used for all statistical analyses.

Results

Study participants and baseline characteristics

A total of 1255 first stroke cases (1079 cases of first ischemic stroke, 171 cases of first hemorrhagic stroke, and 5 cases of first uncertain type of stroke) and 1255 matched controls were included in this analysis. The mean age of all participants at baseline was 70.75 years (SD, 8.06), 49.48% of the

participants were male and the mean selenium level was 87.24 ng/mL (SD, 18.57). Baseline characteristics of male and female participants are shown in Table 1. Detailed plasma selenium concentration distribution of subjects is listed in Supplemental Table 1 and 95.1% of the participants were within the normal range of selenium levels as the reference value (50-120 ng/mL) for plasma selenium concentrations. As shown in Table 1, male participants had non-significantly higher selenium levels than females (87.68 ± 18.58 *vs.* 86.80 ± 18.55 ng/mL; *P*=0.230). Males also tended to be older, were more likely to be current smokers and current drinkers, had higher DBP and tHcy levels, as well as lower BMI, SBP, TC, TG, glucose, and vitamin E levels at baseline and a lower frequency of lipid-lowering, glucose-lowering and antihypertensive drug use, and were less likely to be hypertensive patients, or self-reported diabetic and self-reported hyperlipidemia patients compared with female participants.

Baseline characteristics of cases and control participants are shown in Table 2. Stroke cases had non-significantly lower selenium levels than controls (86.63 ± 17.63 *vs.* 87.84 ± 19.45 ng/mL; *P*=0.101). Stroke cases also tended to have higher BMI, baseline BP, TG, fasting glucose, tHcy levels, and a higher frequency of antiplatelet, glucose-lowering and antihypertensive drug use, were more likely to be current smokers, hypertensive and self-reported diabetic patients, as well as have lower high-density lipoprotein-cholesterol levels at baseline compared with controls. In addition, plasma selenium was positively associated with BMI, current smoking, current alcohol drinking, self-reported diabetes, higher frequency of glucose-lowering drug use, TC, high-density lipoprotein-cholesterol, fasting glucose, and vitamin E levels and was inversely associated with labor intensity and tHcy levels at baseline (Supplemental Table 2).

Association between plasma selenium concentration and first stroke in total participants

Overall, there was a nonlinear negative association between plasma selenium levels with the risk of first total stroke and first ischemic stroke (Fig. 1A and Fig. 1B), but not with the risk of first hemorrhagic stroke (Supplemental Fig. 2A) in total participants. Consistently, when plasma selenium was assessed as tertiles, significantly lower risks of first total stroke (Model 2, OR: 0.77; 95%CI: 0.61, 0.97) and first ischemic stroke (Model 2, OR: 0.78; 95%CI: 0.60, 0.99) were found in participants in tertile 3 (≥94.1 ng/mL) than in those in tertile 1 (<79.1 ng/mL) (Table 3). Due to the similar first total stroke and first ischemic stroke prevalence in participants with selenium levels in tertile 1 and tertile 2 (Table 3), we combined these two groups into one group called tertile 1-2. Compared with participants with lower selenium levels in tertile 1-2 (<94.1 ng/mL), significantly lower risks of first total stroke (Model 2, OR: 0.76; 95%CI: 0.63, 0.93) and first ishcemic stroke (Model 2, OR: 0.75; 95%CI: 0.61, 0.93) were found in those with a higher selenium levels in tertile 3 (≥94.1 ng/mL) (Table 3). However, no significant association was found between plasma selenium concentrations and first hemorrhagic stroke (Table 3).

Association between plasma selenium concentrations and first stroke by sex

Given the differences in plasma selenium levels between male and female participants (87.68 ± 18.58 *vs.* 86.80 ± 18.55 ng/mL), we further investigated the possible effect of sex on the selenium-first stroke association. Overall, there was a nonlinear negative association between plasma selenium levels with the risks of first total stroke and first ischemic stroke in males (Fig. 1C and Fig. 1D), but not in females (Fig.

1E and Fig. 1F). Furthermore, there was no significant association between plasma selenium and first hemorrhagic stroke in both sexes (Supplemental Fig. 2B-C). Consistently, when plasma selenium was assessed as tertiles, the highest tertile (T3, ≥94.1 ng/mL) of plasma selenium was associated with a lower first total stroke risk in males (Model 2, OR: 0.67; 95%CI: 0.48, 0.93, *P*=0.017), but not in females (Model 2, OR: 0.85; 95%CI: 0.61, 1.19, *P*=0.353) compared with the lowest tertile (T1, <79.1 ng/mL) of plasma selenium (Table 4). Accordingly, higher selenium levels in tertile 3 (≥94.1 ng/mL) were associated with a lower first total stroke risk in males (Model 2 OR: 0.63; 95%CI: 0.48, 0.83, *P*=0.001), but not in females (Model 2, OR: 0.92; 95%CI: 0.69, 1.22, *P*=0.563) compared with lower selenium levels in tertile 1-2 (<94.1 ng/mL) (Table 4).

Similar effects of sex on the selenium-first ischemic stroke association were also observed and are displayed in Table 4. However, no significant association was found between plasma selenium and first hemorrhagic stroke risk among both males and females (Table 4).

Stratified analysis by potential effect modifiers in male and female participants

Stratified analyses were conducted to explore potential modifiers affecting the association between plasma selenium (tertile 3, ≥94.1 *vs.* tertile 1-2, <94.1 ng/mL) and first total stroke risk among male participants (Table 5). A stronger nonlinear negative association between baseline plasma selenium and first total stroke was found among males with higher vitamin E levels compared to those with lower vitamin E levels (≥13.5 μg/mL; OR, 0.39; 95%CI: 0.25, 0.60; *vs.* <13.5 μg/mL; OR, 0.85; 95%CI: 0.62, 1.17; *P* for interaction=0.007). None of the other variables, including age (<70 *vs.* ≥70 years), BMI (<24 *vs.* ≥24 kg/m^2), current smoking (yes *vs.* no), current alcohol drinking (yes *vs.* no), baseline SBP (<140 *vs.* ≥140 mmHg), fasting glucose (<6.1 *vs.* ≥6.1 mmol/L or diabetes), TC (<5.78 [median] *vs.* ≥5.78 mmol/L), TG (<1.17 [median] *vs.* ≥1.17 mmol/L), eGFR (<90 *vs.* ≥90 mL/min/1.73m^2), and total homocysteine (<12.5 [median] *vs.* ≥12.5 μmol/L) were found to modify the association between plasma selenium (tertile 3, ≥94.1 *vs.* tertile 1-2, <94.1 ng/mL) and the risk of first stroke in males (*P* for all interactions >0.05).

Furthermore, none of the above variables significantly modified the association of plasma selenium and the risk of first total stroke in female participants (*P* for all interactions >0.05) (Supplemental Table 3).

Discussion

This nested case-control study demonstrates that higher baseline plasma selenium is associated with lower risks of first total stroke and first ischemic stroke in males, but not in females. Plasma vitamin E levels significantly modified the association between plasma selenium and first total stroke in males. Furthermore, no significant association was found between plasma selenium and first hemorrhagic stroke risk in either male or female participants.

Conflicting findings of the association between plasma selenium and the risk of stroke have been reported by previous studies. A nested case-control study [20] enrolling 1304 stroke cases found that higher plasma selenium levels were significantly associated with a lower risk of hemorrhagic stroke, but

not ischemic stroke; the odds ratios (ORs) of hemorrhagic and ischemic stroke were 0.68 (95%CI: 0.51, 0.91) and 0.92 (95%CI: 0.82, 1.05) in the higher selenium levels in tertile 3 (compared with tertile 1). One case-control study [17] including 1277 ischemic stroke patients indicated that higher plasma selenium levels were associated with a decreased risk of ischemic stroke, where the OR for those with higher selenium levels in quartile 4 (compared with quartile 1) was 0.10 (95%CI: 0.06, 0.17). Moreover, the Canadian Health Measures Survey (CHMS) and the National Health and Nutrition Examination Study (NHANES) found inverse, cross-sectional associations between whole blood selenium and prevalence of stroke, as well as the Inuit Health Survey (IHS) indicated a reverse relation of whole blood and dietary selenium levels with stroke, but revealed an L-shaped relationship [15,16]. However, the Reasons for Geographic and Racial Differences in Stroke Study (REGARDS) [18] revealed that higher environmental selenium levels were associated with increased stroke risk; the hazard ratio (HR) for those with higher selenium levels in quartile 4 (compared with quartile 1) was 1.33 (95%CI: 1.09, 1.62). It is noteworthy that all of these studies used different sources (plasma, whole blood, diet, and environment) of selenium levels to assess the association between selenium levels and stroke, which might be one reason for the discrepancy of these findings.

Several studies have also explored the association between selenium and stroke mortality, specifically. A cohort study [19] enrolling 23 stroke death cases among 1100 Finnish males found that low serum selenium (<45μg/L) was associated with a higher risk of stroke mortality, reporting an adjusted relative risk of 3.7 (95%CI: 1.0, 13.1). The NHANES III cohort study [24] including 13887 participants found that the association curve for selenium and stroke mortality had a reversed U-shape. However, another cohort study including 1103 Chinese participants found no significant association of plasma selenium levels and stroke mortality [25]. Notably, these studies focused on stroke mortality and these findings might not represent the association of plasma selenium levels and first stroke risk. Similarity, prospective associations between selenium status/intake and cardiovascular outcomes remain inconclusive [26-28]. None of the above research reported a sex difference in the association between plasma selenium and stroke risk, and the results of these studies remain inconclusive. The present study provides an opportunity to explore the possible relation of plasma selenium and first stroke, and to examine the potential effect modifiers in a community-based Chinese population.

Our current study provides three new insights into the field. First, to the best of our knowledge, this is the first study to find a significantly nonlinear, inverse association between plasma selenium with first total stroke and first ischemic stroke risks in males, but not in females. The differences in the primary outcome (first stroke) between sex in our study may be explained by the differences in the way selenium is metabolized between the male and female reproductive systems. The retention rate for selenium is highly efficient in the testes, while it appears that the female reproductive system does not retain significant levels of selenium as efficiently [29-31]. In addition, the testes might compete for selenium utilization with the brain under selenium-compromised conditions [32], suggesting that the brain in males might be more susceptible to selenium deficiency than in females. The interaction of selenium with the thyroid axis may be another reason for the differences. Wang et al. [33] has demonstrated strong sex-specific differences in risk and development for hyperthyroidism in relation to baseline selenium intake, selenium deficiency

might constitute a risk factor for hyperthyroidism in males but no substantial association was found between hyperthyroidism prevalence and selenium status in females. Since hyperthyroidism has been reported to associate with 2- to 3-fold increased risk for ischemic and non-ischemic stroke [34]. Therefore, we speculate that high selenium levels may reduce the adverse effects in males due to the selenium deficiency, which may explain why the nonlinear inverse association between serum selenium and first stroke was mainly found among males. Further prospective studies are needed to verify this differential association by sex.

Second, we observed a sharp decline in the risk of first stroke when plasma selenium was over 94.1 ng/mL, suggesting that this value might serve as a high plasma selenium cut-off point marking a decreased risk of first stroke or a low plasma selenium cut-off point marking an increased risk of first stroke. This cut-off value agrees with a previous study which reported that plasma selenium >90μg/L was sufficient to optimize functions of selenoproteins [35], which are believed to carry out the functions of selenium in the role of selenium compounds. Schomburg Lutz et.al [36] also reported that deficiency of Selenoprotein-P, the main carrier of selenium to target organs and reduces tissue oxidative stress both directly and by delivering selenium to protective selenoproteins, was associated with increased risk of stroke in a North European population without history of cardiovascular disease. However, it should also be noted that this cut-off value is still within the normal range for human plasma selenium (50-120 ng/mL) [22], and our findings were found mainly among a population with normal selenium levels, with a prevalence of plasma selenium <50, 50 to 120, and >120 ng/mL of 1.2%, 95.1%, and 3.7% in this study (Supplemental Table 1). Therefore, the use of the cut-off value for plasma selenium concentration among stroke patients needs careful consideration. Our results, if further confirmed, might have vital clinical and public health implications for community residents in China.

Third, our study is the first to indicate a stronger nonlinear negative relation of plasma selenium and first stroke in male participants with higher plasma vitamin E levels (≥13.5 μg/mL) than those with lower plasma vitamin E levels (<13.5 μg/mL). This finding suggests that higher plasma selenium and higher plasma vitamin E levels may jointly decrease the first stroke risk. A previous meta-analysis demonstrated a significant inverse association between dietary vitamin E intake and stroke risk, where a higher dietary vitamin E intake was associated with a lower risk of stroke [37]. The exact mechanisms underlying a high selenium × high vitamin E interaction remain unclear. One plausible biological explanation for the interaction may be due to that both selenium and vitamin E belong to vital antioxidants and participate in protecting against brain oxidative stress [38], one of the hallmarks of stroke. Accordingly, high plasma vitamin E and selenium levels may share some cellular and molecular mechanisms for the pathogenesis of stroke, which could cause the interaction in the nonlinear negative relation of plasma selenium and first stroke in males. Further studies are warranted to verify this hypothesis.

While the mechanisms underlying the effect of selenium on first stroke remain inconclusive, an association seems reasonable due to several vital biological functions of selenium. Hosnedlova et al. [39] demonstrated that selenium mainly exerts a protective effect against oxidative lipid damage of the brain and modulates neurotoxicity and oxidative stress in the nervous tissue. Furthermore, modulation of

inflammatory and metabolic signaling, as well as preservation of mitochondrial function may also be involved in the protective role of selenium on stroke [40,41]. Selenium deficiency in heart failure patients was independently associated with impaired exercise tolerance and a 50% higher mortality rate, and impaired mitochondrial function in vitro, in human cardiomyocytes [42]. Ishrap et al. [43] reported that pharmacological selenium supplementation might have an unexpected ability to drive adaptive transcription to counter ferroptosis and protect neurons after stroke both in vitro and in vivo in animal models. Further studies are needed to illuminate the mechanisms underlying the association between plasma selenium and stroke.

Several possible limitations in this study should be mentioned. First, the plasma selenium concentrations only represent the baseline selenium levels of all participants; more frequent measurements during the follow-up would have strengthened the accuracy of our results. Second, only plasma selenium concentrations were used as the biomarker of selenium levels in our study; other biomarkers including whole blood and urinary selenium concentrations should also be considered when performing a sensitivity analysis to confirm our findings. Third, this was a nested, case-control study with a relatively small sample size from a community-based population and all stratified analyses were not prespecified, thus, this work was a product of hypothesis generating, and further larger-scale cohort studies are needed to verify the findings. Finally, since selenium is renally eliminated under the influence of diuretics, we adjusted all antihypertensive drugs together and did not analyze the effects of diuretic separately on the association, thus, further analysis is need to clarify this issue.

Perspectives and significance

In summary, we found a significantly nonlinear, inverse association between baseline plasma selenium and the risks of first stroke and first ischemic stroke in males, but not in females. In addition, no significant association between plasma selenium and first hemorrhagic stroke was found among either sex. If further confirmed, our findings may provide useful data for clinical and nutritional guidelines on the primary prevention of first stroke, by taking plasma selenium into account to serve as a potentially modifiable risk factor, and a possible biomarker for purposes of monitoring and intervention.

Abbreviations

CHHRS, China H-type Hypertension Registry Study; CDC, Chinese Centers for Disease Control and Prevention; OR, odds ratio; CI, confidence intervals; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; tHcy, total homocysteine; eGFR, estimated glomerular filtration rate; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein-cholesterol.

Declarations

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Authors' contributions

Concept and design of this study: Dr. Ping Li and Xiping Xu; Manuscript composition: Dr. Huan Hu, and Ping Li; Data acquisition and collation: Lishun Liu; Statistical analysis: Huan Hu, Ping Wang and Ziyi Zhou; Reviewed and revised the manuscript: Ping Li, Xiao Huang, Huihui, Bao, and Xiping Xu. The other authors coordinated this analysis. All authors read and approved the final manuscript.

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Conflict of Interest Disclosures:

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Availability of data and materials

All data are available from the corresponding author upon request.

Ethics approval and consent to participate

The protocol of the present study was approved by the the Ethics Committee of the Institute of Biomedicine, Anhui Medical University, Hefei, China. All participants signed an approved written consent form.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 Baseline Characteristics of male and female participants.[a]

Characteristics	Total	Male	Female	*P* value
N	n=2510	n=1242	n=1268	
Age, y	70.75 ± 8.06	71.42 ± 8.09	70.10 ± 7.98	<0.001
BMI, kg/m^2	26.19 ± 4.10	25.34 ± 3.57	27.02 ± 4.41	<0.001
Current smoking, n (%)	551 (21.95)	547 (44.04)	4 (0.32)	<0.001
Current alcohol drinking, n (%)	612 (24.38)	599 (48.23)	13 (1.03)	<0.001
Baseline SBP, mmHg	153.25 ± 23.09	150.80 ± 22.34	155.66 ± 23.56	<0.001
Baseline DBP, mmHg	85.25 ± 12.30	86.20 ± 12.50	84.33 ± 12.02	<0.001
Self-reported hypertension, n (%)	1312 (52.27)	553 (44.52)	759 (59.86)	<0.001
Self-reported diabetes, n (%)	424 (16.89)	161 (12.96)	263 (20.74)	<0.001
Self-reported hyperlipidemia, n (%)	264 (10.52)	108 (8.70)	156 (12.30)	0.003
Self-reported atrial fibrillation, n (%)	46 (1.83)	26 (2.09)	20 (1.58)	0.335
Hypertension, n (%)[b]	2016 (80.32)	940 (75.68)	1076 (84.86)	<0.001
Labor intensity, n (%)				<0.001
Mild	1885 (75.10)	887 (71.42)	998 (78.71)	
Moderate	488 (19.44)	280 (22.54)	208 (16.40)	
Severe	137 (5.46)	75 (6.04)	62 (4.89)	
Medication use, n (%)				
Antiplatelet drugs	83 (3.31)	47 (3.78)	36 (2.84)	0.186
Lipid-lowering drugs	44 (1.75)	15 (1.21)	29 (2.29)	0.039
Glucose-lowering drugs	301 (11.99)	112 (9.02)	189 (14.91)	<0.001
Antihypertensive drugs	1152 (45.90)	476 (38.33)	676 (53.31)	<0.001
Laboratory results				
TC, mmol/L	5.85 ± 1.20	5.64 ± 1.08	6.05 ± 1.29	<0.001
TG, mmol/L	1.40 ± 0.85	1.21 ± 0.74	1.59 ± 0.91	<0.001
HDL-C, mmol/L	1.63 ± 0.39	1.63 ± 0.42	1.62 ± 0.36	0.558
Glucose, mmol/L	6.26 ± 2.32	6.09 ± 2.09	6.43 ± 2.51	<0.001
tHcy, μmol/L	13.87 ± 7.15	15.26 ± 8.58	12.50 ± 5.03	<0.001
eGFR, mL/min/1.73 m^2	92.49 ± 14.41	92.26 ± 15.06	92.71 ± 13.75	0.428

Vitamin E, μg/mL	14.04 ± 3.98	12.90 ± 3.27	15.16 ± 4.28	<0.001
Selenium, ng/mL	87.24 ± 18.57	87.68 ± 18.58	86.80 ± 18.55	0.230

[a] Variables are presented as mean ± SD or n (%). [b] Hypertension was defined as self-reported history of hypertension, or use of antihypertensive drugs, or SBP ≥140 mm Hg, or DBP ≥90 mm Hg. **Abbreviations:** BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein-cholesterol; tHcy, total homocysteine; and eGFR, estimated glomerular filtration rate.

Table 2 Baseline Characteristics of cases and control participants.[a]

Characteristics	First stroke cases	Non-stroke controls	*P* value
N	n=1255	n=1255	
Age, y	70.75 ± 8.07	70.76 ± 8.06	0.987
Male, n (%)	621 (49.48)	621 (49.48)	1.000
BMI, kg/m^2	26.51 ± 4.42	25.87 ± 3.73	<0.001
Current smoking, n (%)	296 (23.59)	255 (20.32)	0.048
Current alcohol drinking, n (%)	295 (23.51)	317 (25.26)	0.306
Baseline SBP, mmHg	157.17 ± 23.81	149.34 ± 21.66	<0.001
Baseline DBP, mmHg	87.20 ± 12.82	83.31 ± 11.43	<0.001
Self-reported hypertension, n (%)	746 (59.44)	566 (45.10)	<0.001
Self-reported diabetes, n (%)	261 (20.80)	163 (12.99)	<0.001
Self-reported hyperlipidemia, n (%)	129 (10.28)	135 (10.76)	0.696
Self-reported atrial fibrillation, n (%)	29 (2.31)	17 (1.35)	0.074
Hypertension, n (%)[b]	1075 (85.66)	941 (74.98)	<0.001
Labor intensity, n (%)			0.003
Mild	978 (77.93)	907 (72.27)	
Moderate	221 (17.61)	267 (21.27)	
Severe	56 (4.46)	81 (6.45)	
Medication use, n (%)			
Antiplatelet drugs	60 (4.78)	23 (1.83)	<0.001
Lipid-lowering drugs	22 (1.75)	22 (1.75)	1.000
Glucose-lowering drugs	193 (15.38)	108 (8.61)	<0.001
Antihypertensive drugs	664 (52.91)	488 (38.88)	<0.001
Laboratory results			
TC, mmol/L	5.84 ± 1.21	5.85 ± 1.20	0.768
TG, mmol/L	1.49 ± 0.92	1.31 ± 0.77	<0.001
HDL-C, mmol/L	1.59 ± 0.38	1.66 ± 0.40	<0.001
Glucose, mmol/L	6.54 ± 2.53	5.98 ± 2.05	<0.001
tHcy, μmol/L	14.26 ± 7.95	13.47 ± 6.22	0.006

eGFR, mL/min/1.73 m^2	91.69 ± 15.31	93.29 ± 13.40	0.005
Vitamin E, μg/mL	14.13 ± 4.00	13.95 ± 3.95	0.269
Selenium, ng/mL	86.63 ± 17.63	87.84 ± 19.45	0.101

[a] Variables are presented as mean ± SD or n (%). [b] Hypertension was defined as self-reported history of hypertension, or use of antihypertensive drugs, or SBP ≥140 mm Hg, or DBP ≥90 mm Hg. **Abbreviations:** BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein-cholesterol; tHcy, total homocysteine; and eGFR, estimated glomerular filtration rate.

Table 3 Risk of first stroke (total and subtypes) associated with plasma selenium concentrations in total participants.[a]

Selenium, ng/mL	Cases/controls	Model 1		Model 2	
		OR (95% CI)	*P* value	OR (95% CI)	*P* value
First total stroke					
Tertiles					
T1 (<79.1)	420/417	*Ref.*		*Ref.*	
T2 (79.1 to <94.1)	434/402	1.07 (0.88, 1.30)	0.516	1.02 (0.82, 1.26)	0.891
T3 (≥94.1)	401/436	0.90 (0.73, 1.11)	0.317	0.77 (0.61, 0.97)	0.027
Categories					
T1-T2 (<94.1)	854/819	Ref.		Ref.	
T3 (≥94.1)	401/436	0.87 (0.73, 1.04)	0.119	0.76 (0.63, 0.93)	0.007
Ischemic stroke					
Tertiles					
T1 (<79.1)	360/363	*Ref.*		*Ref.*	
T2 (79.1 to <94.1)	372/340	1.10 (0.89, 1.35)	0.376	1.05 (0.83, 1.33)	0.672
T3 (≥94.1)	347/376	0.92 (0.74, 1.14)	0.444	0.78 (0.60, 0.99)	0.045
Categories					
T1-T2 (<94.1)	732/703	*Ref.*		*Ref.*	
T3 (≥94.1)	347/376	0.87 (0.72, 1.06)	0.163	0.75 (0.61, 0.93)	0.009
Hemorrhagic stroke					
Tertiles					
T1 (<79.1)	58/54	*Ref.*		*Ref.*	
T2 (79.1 to <94.1)	60/61	0.88 (0.50, 1.57)	0.673	0.76 (0.38, 1.55)	0.455
T3 (≥94.1)	53/56	0.85 (0.47, 1.54)	0.587	0.72 (0.35, 1.48)	0.371
Categories					
T1-T2 (<94.1)	118/115	*Ref.*		*Ref.*	
T3 (≥94.1)	53/56	0.92 (0.57, 1.47)	0.718	0.85 (0.48, 1.50)	0.577

[a] ORs of first stroke (total), first ischemic and hemorrhagic stroke in relation to plasma selenium (tertiles) were analyzed using conditional logistic regression models. Model 1 is conditioned on the matching factors of age and sex; Model 2 is conditioned on the matching factors of age and sex, as well as

adjusted for BMI, baseline SBP, baseline DBP, smoking status, alcohol consumption, labor intensity, baseline total homocysteine, vitamin E, fasting glucose, estimated glomerular filtration rate (eGFR), antiplatelet drugs, lipoprotein-lowering drugs, glucose-lowering drugs, antihypertensive drugs, self-reported hypertension, self-reported atrial fibrillation, self-reported diabetes, and self-reported hyperlipidemia.

Table 4. The association of plasma selenium with risk of first stroke (total and subtypes) by sex.[a]

	[b]Male participants			Female participants		
	Cases/controls	Model 1	Model 2	Cases/controls	Model 1	Model 2
		OR (95% CI) *P* value	OR (95% CI) *P* value		OR (95% CI) *P* value	OR (95% CI) *P* value
First total stroke						
Selenium Tertiles						
T1 (<79.1 ng/mL)	206/193	*Ref.*	*Ref.*	214/224	*Ref.*	*Ref.*
T2 (79.1 to <94.1)	218/183	1.12 (0.84, 1.49) 0.452	1.11 (0.80, 1.54) 0.519	216/219	1.04 (0.80, 1.36) 0.764	0.88 (0.65, 1.19) 0.408
T3 (≥94.1)	197/245	0.73 (0.55, 0.98) 0.034	0.67 (0.48, 0.93) 0.017	204/191	1.14 (0.85, 1.54) 0.380	0.85 (0.61, 1.19) 0.353
Selenium Categories						
T1-T2 (<94.1)	424/376	*Ref.*	*Ref.*	430/443	*Ref.*	*Ref.*
T3 (≥94.1)	197/245	0.69 (0.54, 0.89) 0.003	0.63 (0.48, 0.83) 0.001	204/191	1.12 (0.86, 1.44) 0.399	0.92 (0.69, 1.22) 0.563
First ischemic stroke						
Selenium Tertiles						
T1 (<79.1 ng/mL)	179/171	*Ref.*	*Ref.*	181/192	*Ref.*	*Ref.*
T2 (79.1 to <94.1)	191/157	1.16 (0.85, 1.57) 0.343	1.17 (0.82, 1.66) 0.387	181/183	1.05 (0.79, 1.40) 0.716	0.90 (0.64, 1.25) 0.514
T3 (≥94.1)	168/210	0.74 (0.55, 1.01) 0.058	0.67 (0.47, 0.95) 0.027	179/166	1.17 (0.85, 1.60) 0.330	0.84 (0.58, 1.21) 0.347
Selenium Categories						
T1-T2 (<94.1)	370/328	*Ref.*	*Ref.*	362/375	*Ref.*	*Ref.*
T3	168/210	0.69 (0.53,	0.61 (0.45,	179/166	1.14	0.89

(≥94.1)		0.90) 0.006	0.83) 0.001		(0.86, 1.50) 0.362	(0.65, 1.22) 0.479
First hemorrhagic stroke						
Selenium Tertiles						
T1 (<79.1 ng/mL)	26/22	*Ref.*	*Ref.*	32/32	*Ref.*	*Ref.*
T2 (79.1 to <94.1)	26/26	0.81 (0.33, 2.00) 0.646	0.88 (0.25, 3.04) 0.840	34/35	0.98 (0.46, 2.12) 0.962	0.48 (0.17, 1.37) 0.172
T3 (≥94.1)	29/33	0.72 (0.32, 1.60) 0.420	0.80 (0.25, 2.58) 0.714	24/23	1.05 (0.43, 2.57) 0.919	0.58 (0.17, 1.92) 0.368
Selenium Categories						
T1-T2 (<94.1)	52/48	*Ref.*	*Ref.*	66/67	*Ref.*	*Ref.*
T3 (≥94.1)	29/33	0.80 (0.41, 1.54) 0.506	0.86 (0.33, 2.26) 0.761	24/23	1.06 (0.54, 2.10) 0.862	0.95 (0.36, 2.46) 0.910

[a]Model 1 is conditioned on the matching factors of age and sex; Model 2 is conditioned on the matching factors of age and sex, as well as adjusted for BMI, baseline SBP, baseline DBP, smoking status, alcohol consumption, labor intensity, baseline total homocysteine, vitamin E, fasting glucose, estimated glomerular filtration rate (eGFR), antiplatelet drugs, lipoprotein-lowering drugs, glucose-lowering drugs, antihypertensive drugs, self-reported hypertension, self-reported diabetes, self-reported atrial fibrillation, and self-reported hyperlipidemia. [b] Adjusted *P*-interaction between sex and plasma selenium (T3, ≥94.1 ng/mL *vs.* T1-2, <94.1 ng/mL) on first total stroke=0.029. **Abbreviations:** T, tertile; OR,odds ratio; CI, confidence interval.

Table 5 Stratified analysis of the association between plasma selenium concentrations (T3, ≥94.1 ng/mL *vs.* T1-2, <94.1 ng/mL) and incident risk of first total stroke in males.

Subgroups	No. of cases / No. of controls		[a]Adjusted Model	*P* for interaction
	Selenium≥94.1 ng/mL	Selenium<94.1 ng/mL	OR (95% CI)	
Age, y				0.288
<70	98/110	173/161	0.73 (0.50, 1.08)	
≥70	99/135	251/215	0.54 (0.38, 0.76)	
Body mass index, kg/m^2				0.067
<24	44/89	151/152	0.39 (0.24, 0.63)	
≥24	153/156	273/224	0.75 (0.55, 1.02)	
Current smoking				0.739
No	95/136	233/231	0.72 (0.51, 1.01)	
Yes	102/109	191/145	0.54 (0.36, 0.80)	
Current alcohol drinking				0.230
No	98/106	232/207	0.74 (0.51, 1.06)	
Yes	99/139	192/169	0.53 (0.37, 0.77)	
SBP, mmHg				0.759
<140	46/92	124/156	0.60 (0.38, 0.96)	
≥140	151/153	300/220	0.64 (0.47, 0.88)	
Glucose, mmol/L				0.898
<6.1	108/168	274/284	0.66 (0.48, 0.90)	
≥6.1 or diabetes[b]	89/77	150/92	0.66 (0.42, 1.02)	
TC, mmol/L				0.402

<5.78	95/107	262/236	0.77 (0.54, 1.10)	
≥5.78	102/138	162/140	0.53 (0.36, 0.78)	
TG, mmol/L				0.611
<1.17	115/160	246/255	0.71 (0.52, 0.98)	
≥1.17	82/85	178/121	0.55 (0.36, 0.84)	
eGFR, mL/min/1.73m^2				0.753
<90	64/68	173/141	0.71 (0.45, 1.10)	
≥90	133/177	251/235	0.61 (0.45, 0.83)	
tHcy, μmol/L				0.117
<12.5	89/105	129/142	0.81 (0.54, 1.22)	
≥12.5	108/140	293/234	0.55 (0.39, 0.76)	
Vitamin E, μg/mL				0.007
<13.5	117/132	270/277	0.85 (0.62, 1.17)	
≥13.5	80/113	154/99	0.39 (0.25, 0.60)	

[a] ORs of first total stroke in relation to serum selenium levels were calculated using multivariate logistic regression models. Each subgroup analysis adjusted, if not stratified, for age, BMI, baseline SBP, baseline DBP, smoking status, alcohol consumption, labor intensity, baseline total homocysteine, vitamin E, fasting glucose, estimated glomerular filtration rate (eGFR), antiplatelet drugs, lipoprotein-lowering drugs, glucose-lowering drugs, antihypertensive drugs, self-reported hypertension, self-reported diabetes, self-reported atrial fibrillation, and self-reported hyperlipidemia. [b] Diabetes was defined as self-reported history of diabetes mellitus, or use of anti-diabetic medications, or fasting glucose ≥7.0 mmol/L. **Abbreviations:** TC, total cholesterol; T, tertile; OR, odds ratio; CI, confidence interval.

Figures

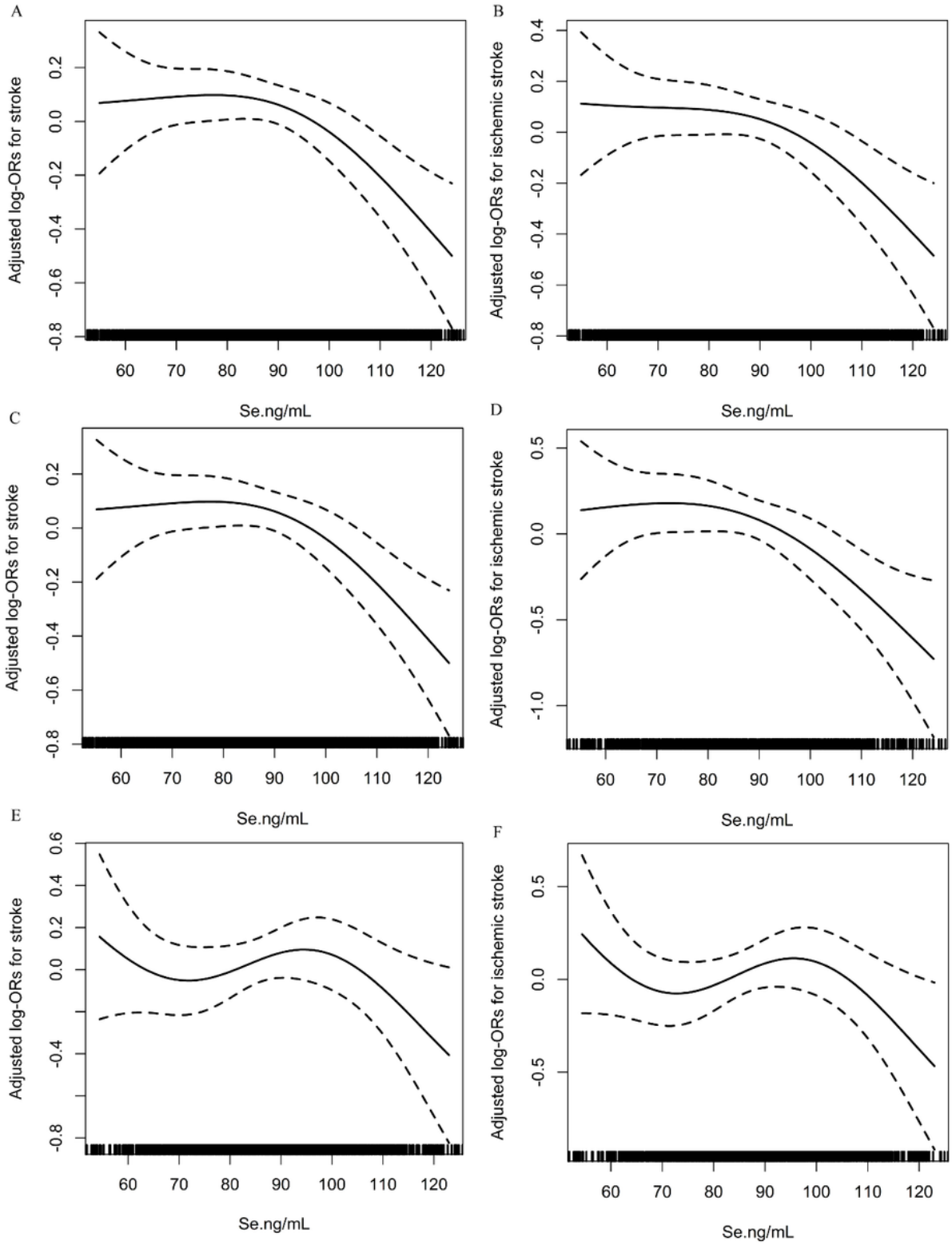

Figure 1

The association between baseline plasma selenium with the risk of first total stroke and first ischemic stroke. Odds ratios for first total stroke (A) total population, (C) males, (E) females, and for first ischemic stroke (B) total population, (D) males, (F) females by plasma selenium levels. In addition to the matching factors (age and sex), the splines also adjusted for BMI, baseline SBP, baseline DBP, smoking status, alcohol consumption, labor intensity, baseline total homocysteine, vitamin E, fasting glucose, estimated

glomerular filtration rate (eGFR), antiplatelet drugs, lipoprotein-lowering drugs, glucose-lowering drugs, antihypertensive drugs, self-reported hypertension, self-reported diabetes, self-reported atrial fibrillation, and self-reported hyperlipidemia.

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