

Prospective study of serum selenium concentrations and esophageal and gastric cardia cancer, heart disease, stroke, and total death¹⁻³

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ABSTRACT

Background: We previously reported an inverse association between prediagnostic serum selenium concentrations and the risk of esophageal squamous cell carcinoma (ESCC) and gastric cardia cancer (GCC) but not gastric noncardia cancer (GNCC) in a nested study from the Nutrition Intervention Trial in Linxian, China.

Objective: We examined the relation between baseline serum selenium and the subsequent risk of death from ESCC, GCC, GNCC, heart disease (HD), stroke, and total death over 15 y of follow-up (1986–2001).

Design: We measured baseline serum selenium concentrations in 1103 subjects randomly selected from a larger trial cohort. We identified 516 deaths during the 15-y follow up, including 75 from ESCC, 36 from GCC, 116 from HD, and 167 from stroke. Relative risks (RRs) and 95% CIs were estimated by using Cox proportional hazards regression models. Reported RRs estimated the change in risk conferred by a 25% increase in serum selenium relative to the population distribution. All estimates were adjusted for sex, age, smoking, drinking, and serum cholesterol.

Results: We found significant inverse associations between baseline serum selenium and death from ESCC (RR: 0.83; 95% CI: 0.71, 0.98) and GCC (0.75; 0.59, 0.95). Trends toward inverse associations were noted for death from HD (0.89; 0.78, 1.01; $P = 0.07$), but no association was noted for total death (0.96; 0.90, 1.02) or stroke (0.99; 0.88, 1.11).

Conclusion: Population-wide selenium supplementation in the region of China with low serum selenium and high incidences of ESCC and GCC merits serious consideration. *Am J Clin Nutr* 2004;79:80–5.

KEY WORDS Selenium, esophageal squamous cell carcinoma, gastric cardia cancer, stroke, heart disease, cohort

INTRODUCTION

Recently, several prospective cohort studies and randomized intervention trials have reported an association between serum selenium concentrations and human chronic disease. These studies suggest that selenium, an essential trace element for humans and a normal constituent of the diet, is anticarcinogenic and can prevent cardiovascular disease. The positive results of clinical cancer trials (1–5) support this conclusion, especially when considered in light of converging evidence from epidemiologic and mechanistic studies (6–11).

The Nutrition Intervention Trials were 2 randomized, placebo-controlled, clinical trials conducted by our group (12) in Linxian, China, where there is poor nutrition and high rates of esophageal squamous cell carcinoma (ESCC) and gastric cardia cancer (GCC) (13). In the larger General Population Trial, 29 584 Linxian residents were tested with 4 different combinations of nutrient supplements or placebo for 5.25 y. The group supplemented with selenium, β -carotene, and α -tocopherol had statistically significant reductions in all-cause mortality (9%) and in total cancer mortality (13%). The mortality rates for ESCC, GCC, and gastric noncardia cancer (GNCC) showed trends toward reductions in mortality of 4%, 18%, and 28%, respectively, but these reductions were not statistically significant (1). A previous prospective study in this cohort indicated a significant inverse relation between baseline serum selenium concentrations and risk of ESCC and GCC over 5.25 y of follow-up, with relative risks (RRs) of 44% and 53%, respectively, in a comparison between the highest and lowest quartiles (14).

The Nutritional Prevention of Cancer (NPC) Trial, carried out by Clark et al (3) in the United States, involved 1312 subjects and tested whether selenium supplementation (200 μ g/d with high-selenium brewer's yeast) could reduce the recurrence of nonmelanoma skin cancer. Although selenium supplementation showed no protective effect against skin cancer, it was associated with a statistically significant decrease in several secondary endpoints: total cancer mortality (52%), total cancer incidence (39%), and incidences of lung (44%), colorectal (61%), and prostate (65%) cancers (3, 4). Recent updates

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of data from this trial showed that subjects with a baseline serum selenium concentration in the lowest tertile ($<1.33 \mu\text{mol/L}$, or $<105 \mu\text{g/L}$) had the greatest reduction in total cancer incidence.

Few clinical trials have studied selenium and the risk of heart disease (HD) or stroke as the primary endpoint. Prospective observational studies have found that selenium may also protect against cardiovascular disease, but this association remains controversial (15). The primary objective of this study was to evaluate the relation between baseline serum selenium concentrations and the subsequent risk of death from ESCC, GCC, GNCC, HD, stroke, and total death over 15 y of follow-up (1986–2001) in a random subsample of the Nutrition Intervention Trials General Population Trial cohort.

SUBJECTS AND METHODS

Cohort population

The subjects in this study were selected from the cohort of all participants in the General Population Trial of Linxian, China. Elsewhere, we described in detail the design, choice of intervention agents, methods of conduct, and primary endpoint analyses of the trial (1, 12, 14). In brief, the participants were 29 584 healthy adults aged 40–69 y from 4 Linxian communes. In the spring of 1985, 1 y before the intervention started, each participant was interviewed, was given a brief physical examination, and had 10 mL blood drawn. The intervention began in March 1986 and continued through May 1991 (5.25 y). In accord with a fractional factorial design, the participants were randomly assigned to receive either a vitamin-mineral combination or a placebo. One-eighth of all participants received the placebo only. In total, 4 different vitamin-mineral combinations were tested: factor A (10 000 IU vitamin A and 45 mg zinc oxide), factor B (52 mg riboflavin and 40 mg niacin), factor C (180 mg ascorbic acid and 30 μg Mo), and factor D (50 μg yeast Se, 15 mg β -carotene, and 30 mg α -tocopherol). We obtained written informed consent from each participant before trial enrollment. Throughout the study, human subjects protection procedures were followed in accord with those prescribed by the US National Institutes of Health and the Chinese Academy of Medical Sciences.

Village doctors ascertained mortality among trial participants through monthly follow-up. Diagnoses of cancer were made at commune and county hospitals and by an additional study team that provided clinical and diagnostic services, including endoscopy, for patients with symptoms suggestive of esophageal or stomach cancer. For anatomic localization of the gastric adenocarcinomas, cancers were defined as GCC if they were in the most proximal 3 cm of the stomach and as GNCC if they originated outside this region. Ninety-five percent of the esophageal and gastric cancers had anatomic localization made by endoscopy, surgery, X-rays, or a combination thereof. Diagnoses of HD and stroke were made by local physicians and reviewed by experienced senior Chinese clinicians involved in this study.

Deaths in this cohort were attributed to 1 of 36 different causes. Because most (66%) of the cancer deaths were from ESCC and GCC, and because we previously detected an association between serum selenium and cancer at these sites (14), we treated these 2 sites as separate categories. We also exam-

ined GNCC separately and then combined all other cancer deaths. HD includes coronary, ischemic, hypertensive, and other types of HD. The stroke endpoint includes both hemorrhagic and thrombotic strokes. These 2 diagnoses cannot be separated because few diagnoses are based on computed tomography or magnetic resonance imaging in this population. The category “other death” includes many causes of death, such as accidents ($n = 6$), liver cirrhosis ($n = 8$), chronic bronchitis ($n = 7$), and other causes with <5 occurrences.

Follow-up time was calculated as the number of days from the start of intervention, May 1986, until the day of death or through May 2001. Only 1.54% of the cohort was lost to follow-up, and those persons were censored at the last time their vital status was known.

Selection of study participants on the basis of serum selenium concentrations

We measured selenium in an age- and sex-stratified subcohort of 1103 persons selected from the 29 584 participants in the General Population Trial as previously described (14). The 1103 subjects of this study were originally selected for a case-cohort study that matched an age- and sex-stratified random sample of the entire cohort at baseline to 1079 case subjects over the first 5.25 y of follow-up. Treatment group assignment was not considered in this subject draw because of the multiple analytes to be measured in this and other studies, because the partial factorial design limits the number of people who received placebo alone to one-eighth of the participants, and because treatment group could be examined as a potential confounder and controlled for in the analyses. Selenium was assayed at the National Health and Nutrition Examination Survey (NHANES) Laboratory, Centers for Disease Control and Prevention, Atlanta. Elsewhere, we described in detail the selenium assays and quality-control procedures (14).

Statistical analysis

We compared categorical variables between groups with the use of chi-square tests and compared continuous variables between groups with the use of t tests. We estimated RRs and 95% CIs by using Cox proportional hazards models. We adjusted for smoking, drinking, body mass index (BMI; in kg/m^2), and serum cholesterol in all of our models. Models for HD and stroke were also adjusted for diastolic and systolic blood pressure at baseline. All estimates came from models stratified on 6 sex-age sampling strata. The 6 strata were defined by sex and the following 3 age categories at the start of the intervention: 1) ≤ 50 y, 2) >50 –60 y, and 3) >60 y. Additional stratum-specific continuous age terms were used to adjust for variation within each age stratum. Addition of variables to these models representing either serum α -tocopherol concentration or assignment to treatment with the selenium-containing factor D during the trial period showed no evidence of confounding; therefore, these variables were not included (data not shown).

For all endpoints, we examined 3 different metrics for selenium exposure. First, selenium was used as a continuous variable standardized to the average size of the 2 central quartiles (the standardized unit was $0.15 \mu\text{mol/L}$, or $11.5 \mu\text{g/L}$). Second, we classified subjects into quartiles and estimated RRs separately within each quartile. Third, we used the quartile score as

TABLE 1Number of subjects and subject characteristics by case status at baseline for a nested cohort from the General Population Trial in Linxian, China¹

	Total cohort	Survivors	Total deaths	Deaths						
				ESCC	GCC	GNCC	Other cancer	HD	Stroke	Other death
Total										
<i>n</i>	1103	587	516	75	36	24	32	116	167	66
Age (y)	56.6 ± 8.0 ²	53.3 ± 7.8	60.2 ± 6.5 ³	58.5	59.2	59.4	58.7	61.3	60.2	61.7
Smokers (%)	38.3	31.5	45.9 ³	45.3	52.8	50.0	53.1	53.5	34.1	54.5
Drinkers (%)	20.7	20.6	20.7 ³	21.3	33.3	41.7	21.7	19.8	16.8	16.7
BMI (kg/m ²)	21.9 ± 2.6	22.1 ± 2.6	21.7 ± 2.5 ³	21.8	21.6	21.4	21.5	21.1	22.2	21.6
Women⁴										
<i>n</i>	495	311	184	26	14	4	10	38	74	18
Age (y)	55.2 ± 8.4	52.7 ± 7.9	59.3 ± 7.6	56.0	61.9	53.0	53.9	60.2	59.9	61.5
Smokers (%)	0.4	0.00	1.1	0.0	0.0	0.0	0.0	2.6	1.4	0.0
Drinkers (%)	6.1	7.40	3.8	0.0	14.3	0.0	10.0	2.6	4.1	0.0
BMI (kg/m ²)	22.2 ± 3.0	22.3 ± 2.9	22.1 ± 3.1	21.7	22.4	21.2	22.1	21.7	22.5	21.4
Men										
<i>n</i>	608	276	332	49	22	20	22	78	93	48
Age (y)	57.7 ± 7.4	54.0 ± 7.6	60.8 ± 5.7	59.9	57.6	60.7	60.8	61.8	50.5	62.2
Smokers (%)	68.1	67.0	70.8	69.4	86.4	60.0	77.3	78.2	60.2	75.0
Drinkers (%)	32.6	35.5	30.1	32.7	45.5	50.0	27.3	28.2	26.9	22.9
BMI (kg/m ²)	21.6 ± 2.1	21.9 ± 2.0	21.4 ± 2.1	21.6	21.2	21.5	21.3	20.8	21.7	21.6

¹ Smoking was defined as ever smoking ≥6 mo, and drinking was defined as any alcohol consumption in the previous 12 mo. ESCC, esophageal squamous cell carcinoma; GCC, gastric cardia cancer; GNCC, gastric noncardia cancer; HD, heart disease.

² $\bar{x} \pm SD$.

³ Subjects who died were significantly more likely to be male ($P < 0.0001$), to be older ($P < 0.0001$), to have a lower BMI ($P = 0.005$), and to smoke ($P < 0.0001$) than were subjects who survived.

⁴ Significantly different from men for age ($P < 0.0001$), smokers ($P < 0.0001$), drinkers ($P < 0.0001$), and BMI ($P = 0.0004$).

an ordinal variable. On the basis of the quartile classification, we calculated 2 sets of P values. The P for trend test assigns each quartile its ordinal value and tests whether there is a (log) linear change in RR with increasing quartile. The P global (3 df) tests whether the risks in quartile 2, 3, and 4 are greater than the risk in quartile 1 without assuming any linear progression. Deviations from log linearity, sensitivity analysis, adjustment for confounding, interactions, and testing the proportional hazards assumption were conducted as previously reported (14).

RESULTS

Shown in **Table 1** are the numbers of subjects, mean ages, percentages of smokers and drinkers, and mean BMIs for the total cohort, for those who survived until May 2001, and for those who died of various causes during the follow-up period. Results are shown for the total cohort and for women and men separately. There were 516 deaths in the cohort during the follow-up period, including 75 from ESCC, 36 from GCC, 24 from GNCC, 32 from other cancers, 116 from HD, 167 from stroke, and 66 from other causes. Sixty-six percent (111/167) of cancer deaths were from ESCC or GCC. Fifty-nine percent (167/283) of cardiovascular disease deaths were from strokes. For all mortality categories, there were more deaths in men than in women. Overall, persons who died during the follow-up period were significantly more likely to be men ($P < 0.0001$), to be older ($P < 0.0001$), to have lower BMIs ($P = 0.005$), and to smoke ($P < 0.0001$) than were persons who survived. No significant differences in alcohol consumption were observed between those who died and those who survived ($P = 0.96$).

Overall, the characteristics presented in Table 1 were significantly different between the men and the women. Compared

with the men, the women were younger ($P < 0.0001$), were far less likely to smoke ($P < 0.0001$) or drink alcohol ($P < 0.0001$), and had higher BMIs ($P = 0.0004$). The dramatic differences in smoking and drinking behavior reflect the distribution of these habits in the entire cohort. Although tobacco and alcohol use are strong risk factors for ESCC in Western countries, in Linxian smoking confers only a moderate increase in the risk of ESCC, whereas alcohol use is not associated with an increased risk of ESCC (16, 17). The minimal use of alcohol and tobacco by women and their minor importance in the etiology of ESCC in Linxian is reflected in the approximately equal number of ESCC cases in men and women in the underlying cohort (16).

The mean serum selenium concentration in this cohort was 0.93 $\mu\text{mol/L}$ (73 $\mu\text{g/L}$). The quantile values of the overall cohort at the 10th, 25th, 50th, 75th, and 90th percentiles were as follows: 0.66, 0.77, 0.91, 1.06, and 1.19 $\mu\text{mol/L}$. There was no significant difference in the median serum selenium concentration between the women (0.92 $\mu\text{mol/L}$) and the men (0.93 $\mu\text{mol/L}$).

RRs, 95% CIs, and the results of tests of statistical significance relating serum selenium concentrations to subsequent total and specific causes of death are presented in **Table 2**. On a continuous scale, statistically significant inverse associations were observed between baseline serum selenium concentrations and mortality from both ESCC (RR: 0.83; 95% CI: 0.71, 0.98) and from GCC (RR: 0.75; 95% CI: 0.59, 0.95). When the sample was classified by quartile of baseline serum selenium concentration, the global test of decreasing risk of ESCC was significant ($P = 0.015$) and the trend test was nearly significant ($P = 0.07$). Compared with persons in the lowest quartile of

TABLE 2

Relative risk (RR) and 95% CI of mortality endpoints with baseline serum selenium concentration as a continuous variable and as quartiles from the General Population Trial in Linxian, China, 1986–2001¹

Cause of death	No. of cases	Quartiles											
		Continuous ²			I ³	2 (>0.77 μmol/L)		3 (>0.91 μmol/L)		4 (>1.06 μmol/L)		P for trend ⁴	Global P ⁵
		RR	95% CI	P		RR	95% CI	RR	95% CI	RR	95% CI		
All	516	0.96	(0.90, 1.02)	0.16	1.00	1.01	(0.79, 1.30)	0.96	(0.75, 1.23)	0.93	(0.72, 1.19)	0.57	0.80
ESCC	75	0.83	(0.71, 0.98)	0.03	1.00	0.98	(0.53, 1.81)	1.14	(0.63, 2.04)	0.35	(0.16, 0.81)	0.070	0.015
GCC	36	0.75	(0.59, 0.95)	0.02	1.00	0.68	(0.28, 1.61)	0.62	(0.27, 1.43)	0.31	(0.11, 0.87)	0.012	0.067
GNCC	24	0.99 ⁶	(0.75, 1.32)	0.96	1.00	1.22	(0.34, 4.36)	1.19	(0.34, 4.24)	1.64	(0.49, 5.48)	0.46	0.83
Other cancer	32	1.21	(0.95, 1.53)	0.21	1.00	2.22	(0.78, 6.34)	0.89	(0.26, 3.10)	1.95	(0.66, 5.81)	0.29	0.099
HD	116	0.89	(0.78, 1.01)	0.07	1.00	0.47	(0.29, 0.80)	0.66	(0.41, 1.07)	0.66	(0.41, 1.08)	0.17	0.05
Stroke	167	0.99 ⁶	(0.88, 1.11)	0.87	1.00	1.73	(1.08, 2.75)	1.33	(0.83, 2.15)	1.43	(0.89, 2.30)	0.82	0.39

¹ RR, 95% CI, and *P* values come from regression models stratified by sex and age with additional adjustment by separate continuous age variables for each age strata and variables for cholesterol, smoking, drinking, and BMI. Models for heart disease (HD) and stroke were also adjusted for diastolic and systolic blood pressure. Assignment to treatment D during the trial period, which contained selenium, did not influence risk estimates and therefore was not included in these models. ESCC, esophageal squamous cell carcinoma; GCC, gastric cardia cancer; GNCC, gastric noncardia cancer.

² The RR and 95% CI for the continuous measure were standardized to the average size of the 2 central quartiles. Therefore, this is the RR associated with a 25% change in serum concentration relative to the cohort distribution. One standardized selenium unit is equal to 0.15 μmol/L.

³ The lowest quartile served as the reference group in quartile analysis models.

⁴ Derived from the models by assigning each person the ordinal value of the quartile.

⁵ Derived from the 3 df test for the overall quartile model.

⁶ The apparent discrepancy in the direction of risk between the continuous (RR: 0.99) and the quartile (RR > 1) RRs are a function of the categorization of the continuous variable. This discrepancy resolves with slight changes in the selenium value used as the cutoff separating quartile 1 from quartile 2. Neither classification resulted in any evidence of statistical significance.

serum selenium, those in the highest quartiles had a 65% significant reduction in the risk of mortality from ESCC (RR: 0.35). The near significance of the trend test was due to the statistically insignificant elevated point estimate (RR: 1.14; 95% CI: 0.63, 2.04) in quartile 2. For GCC deaths, the decrease in RR with increasing quartile was monotonic (*P* for trend = 0.01, *P* for global test = 0.07). Compared with those in the lowest quartile of serum selenium concentration, those in the highest quartile had a 69% reduction in the risk of death from GCC (RR: 0.31; 95% CI: 0.11, 0.87).

No significant association was observed between baseline serum selenium concentration and mortality from GNCC for any metric used (Table 2). We found a nearly significant protective association between selenium concentration and HD in the continuous scale analysis (RR: 0.89; 95% CI: 0.78, 1.01; *P* = 0.07). In the quartile analysis, the global test indicated significance. Subjects in the second quartile had a 53% significant reduction in the risk of death from HD (RR: 0.47).

No significant association was observed between the baseline serum selenium concentration and stroke in the continuous variable analysis (RR: 0.99; 95% CI: 0.88, 1.11) or in the quartile analysis. Point estimates for all analyses suggested a small protective effect for total mortality, but none of the contrasts was significant. Finally, we found no evidence that age, sex, smoking, or drinking modified the association of baseline serum selenium concentration with any of the endpoints. Assignment to the selenium-containing treatment (factor D) during the trial period did not significantly confound or modify any of the risk estimates presented in this analysis.

DISCUSSION

Linxian is a rural mountainous county in Henan Province in north-central China, where the mortality rates from ESCC and

GCC are ≈100 times those in US whites (1, 13). Because of the geography of Linxian and because of the low socioeconomic status of its population, the diets of Linxian residents were low in fresh fruit, vegetables, meat, and other animal products when the blood samples were drawn in 1985. Blood concentrations of various micronutrients, including retinol, β-carotene, riboflavin, vitamin C, and vitamin E, were all low by US standards (18–21).

It is noteworthy that the mean population selenium concentration in our cohort was low when compared with that in the United States (0.93 compared with 1.58 μmol/L, respectively). Indeed, the 96th percentile (1.19 μmol/L) in our population was lower than the 1st percentile (1.20 μmol/L) in the NHANES III study (22). Selenium deficiency is considered to occur when the serum selenium concentration is below ≈1 μmol/L, a concentration that corresponds to the amount of selenium contained in maximally expressed plasma selenoproteins and to the upper limit of glutathione peroxidase responses to selenium supplements in healthy people (6, 23–26). On the basis of this criterion, 69% of the subjects (766/1103) in this analytic cohort were considered to be selenium deficient.

We found significant inverse associations between baseline serum selenium concentrations and mortality from both ESCC and GCC. No significant association was observed for GNCC or other cancer. We detected a possible threshold effect between serum selenium and HD mortality. Persons in the second quartile or higher were at decreased risk of HD. In our study, there was no convincing association between baseline serum selenium concentrations and mortality from stroke. A protective but insignificant association was noted for total death.

Other studies also showed an inverse relation between baseline serum selenium concentrations and the risk of mortality from ESCC, GCC, and other cancers. A previous nested case-

control study conducted by our group drew similar conclusions for ESCC and GCC over 5.25 y of follow-up in the Linxian population (14). A trial in a population at high risk of liver cancer in China found a 35% reduction in liver cancer incidence in the group supplemented with selenized table salt (5). Data from the NPC study showed that selenium supplementation was effective in reducing the risk of multiple cancers (3, 4, 27). The NPC study also showed that the protective effect was greatest for subjects who entered the trial with baseline serum concentrations in the lowest tertile ($<1.33 \mu\text{mol/L}$, or <105 ; 27, 28). These results suggest that selenium supplementation for chemoprevention of cancer should be targeted at populations with low serum selenium concentrations, such as in Linxian, where 97% of the population has serum selenium concentrations below this cutoff.

Two new trials of the effect of selenium on cancer incidence are underway or being planned. Currently, the Selenium and Vitamin E Cancer Prevention Trial (SELECT) is recruiting 32 400 US men to examine the effect of selenium and vitamin E on prostate cancer incidence over 12 y (29). The Prevention of Cancer by Intervention with Selenium (PRECISE) trial is being planned to examine the effect of selenium on cancer incidence in the United Kingdom, Sweden, and Denmark—3 countries with relatively low serum selenium concentrations (15).

For HD the global test of the effect of selenium was significant, whereas tests using the continuous metric and the ordinal variable were not. These results are consistent with a threshold effect, that is, a serum concentration of selenium above which risk is uniformly decreased. In our study, there was no convincing association between baseline serum selenium concentrations and mortality from stroke.

Two nested case-control studies in the United States and the Netherlands found no clear association (30, 31) between the lower serum selenium concentration and an increased risk of HD; however, a nested case-control study from Finland and a Danish cohort study did report protective associations (32, 33). The Dutch study found no significant association with stroke (31). In the Nutrition Intervention Trials in Linxian, selenium-containing interventions were associated with trends toward reductions in cerebrovascular mortality of 38% and 10% in the Dysplasia Trial and in the General Population Trial, respectively, but the reductions were not statistically significant in either case (1, 2).

Confounding by unmeasured risk factors is always possible in association studies. From related studies in this population, we know that Linxian residents had low serum concentrations of many vitamins in the early 1980s (18–21). Thus, the associations with selenium might have been due to another nutrient that covaries with selenium. However, in our previous nested case-cohort study in Linxian (14), we measured fat-soluble vitamins and selenium and found that the association between selenium and upper gastrointestinal tract cancers in this cohort persisted after adjustment for these other serum vitamins (unpublished observations, 2003). Therefore, we believe that the associations between selenium and diseases in the current study are specific.

Blood samples in the analytic cohort of the current study were collected in 1985. Lifestyle and socioeconomic status in this population have changed since 1985 and may have affected the selenium distribution in this population. However, recent unpublished data from our group show that the distribution of

serum selenium concentrations in this population is still low. On the basis of past (14) and current results, we are currently evaluating the feasibility of population-wide selenium supplementation for the region of China with low selenium concentrations and a high incidence of ESCC and GCC. 

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W-QW and CAA were responsible for data analysis and manuscript preparation. Y-LQ, SMD, Z-WD, PRT, and SDM were responsible for the overall study design, completion, quality control, statistical design, and manuscript preparation. X-DS and J-HF were responsible for cohort continuity and data collection and analysis. EWG was responsible for laboratory analysis and quality control. None of the authors had any financial or personal conflicts of interest.

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