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## The Association between Selenium and Lipid Levels: a Longitudinal Study in Rural Elderly Chinese

Chen Chen<sup>5</sup>, Yinlong Jin<sup>5</sup>, Frederick W. Unverzagt<sup>2</sup>, Yibin Cheng<sup>5</sup>, Ann M. Hake<sup>3,4</sup>, Chaoke Liang<sup>5</sup>, Feng Ma<sup>5</sup>, Liqin Su<sup>5</sup>, Jingyi Liu<sup>5</sup>, Jianchao Bian<sup>6</sup>, Ping Li<sup>7</sup>, and Sujuan Gao<sup>1</sup>

<sup>1</sup>Department of Biostatistics, Indiana University School of Medicine, Indianapolis, Indiana

<sup>2</sup>Department of Psychiatry, Indiana University School of Medicine, Indianapolis, Indiana

<sup>3</sup>Department of Neurology, Indiana University School of Medicine, Indianapolis, Indiana

<sup>4</sup>Eli Lilly and Company, Indianapolis, Indiana

<sup>5</sup>Institute for Environmental Health and Related Product Safety, Chinese Center for Disease Control and Prevention, Beijing, China.

<sup>6</sup>Shandong Institute for Prevention and Treatment of Endemic Disease in China, Jinan, China

<sup>7</sup>Sichuan Provincial Center for Disease Control and Prevention in China, Chengdu, China

### Abstract

A protective effect of selenium on lipid levels has been reported in populations with relatively low selenium status. However, recent studies found that high selenium exposure may lead to adverse cardiometabolic effects, particularly in selenium-replete populations. We examined the associations of selenium status with changes in lipid levels in a 7-year follow up of an elderly Chinese cohort including participants from selenium-deplete areas. Study population consisted of 140 elderly Chinese aged 65 or older with nail selenium levels measured at baseline (2003-2005). Lipid concentrations were measured in fasting blood samples collected at baseline and the 7-year follow-up (2010-2012). Analysis of covariance (ANCOVA) models was used to determine the association between baseline selenium status and changes in lipid levels from baseline to follow-up adjusting for other covariates. Mean ( $\pm$ standard deviation) baseline selenium concentration was  $0.41 \pm 0.2$  mg/kg. In prospective analysis, we found that individuals in the highest selenium quartile group showed 1.11 SD decrease on total-cholesterol ( $p < 0.001$ ), 0.41 SD increase on HDL-cholesterol ( $p < 0.001$ ) and 0.52 SD decrease on triglyceride after 7 years than those in the lowest selenium quartile group. The similar trends were seen with significant lipids changes in the 2th

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Address correspondence to: Sujuan Gao, Ph.D., Department of Biostatistics, Indiana University School of Medicine, 410 West 10<sup>th</sup> Street, #3000, Indianapolis, IN 46202-2872; Phone: U.S. (317) 274-0820; Fax: (317)274-2678; sgao@iupui.edu.

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and 3th quartile groups. Selenium has modestly beneficial effects on blood lipid levels in a population with relatively low selenium status. Our result suggests adequate dietary selenium intake as a potential prevention strategy for lowering lipid levels in selenium deplete populations.

## Keywords

selenium; lipids; elderly Chinese

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## Introduction

Selenium is an essential micronutrient with a narrow safety margin. Adequate selenium intake is needed to maximize antioxidant activities of glutathione peroxidases and other selenoproteins [1, 2]. In animal experiments, selenium supplementation decreased plasma total and low-density lipoprotein cholesterol levels and increased HDL cholesterol levels, whereas selenium deficiency had the opposite effect [3-5]. However, the relationship between selenium status and cardiovascular disease risk in human studies remains inconsistent [6-9].

Several cross-sectional studies have examined the association between selenium levels and lipids profile [10-15], or between selenium levels and the risk of cardiovascular diseases (CVD) [6-9, 16-21] in different populations. An association between higher selenium level and lower lipids has been reported particularly in populations with relatively low selenium status [6, 17-19]. However, in contrast to the putative benefits of selenium, recent observational studies have raised concern that high selenium exposure may lead to adverse cardiometabolic effects, particularly in selenium replete populations such as that of the US [10-11, 22-23]. Furthermore, a few randomized trials found no effect of selenium supplementation on serum cholesterol level [24] and cardiovascular disease prevention [7]. Nonetheless, most of these studies are cross-sectional, which cannot establish a causality relationship, and there is little longitudinal data on the relationship between selenium status and lipids profiles of the elderly.

Data from our populations where selenium supplementation is rare may be able to offer insight on the relationship between selenium and lipid levels. In this article, we report results from a longitudinal study of rural elderly Chinese cohort and examine the association between baseline selenium status and changes in lipid levels.

## METHODS

### Study Population

Participants for the current study were from the Selenium and Cognitive Decline study, a longitudinal epidemiologic project funded by the National Institute of Health examining the long-term impact of selenium on cognitive decline in rural elderly Chinese. Two thousand Chinese aged 65 and older from four counties in China were enrolled at baseline between December 2003 and May 2005. Details of the study and its methodological procedures have been previously described [25-26]. At baseline, venous blood samples were collected after the subjects had fasted for at least 12 hours from 10% of participants from each county

(n=199); of these, 140 subjects were seen again in 2010-2012 and a second fasting blood sample was collected. Approximately 23.6% were lost among the two thousand participants between baseline and the seven years follow-up, but the characteristics of those lost were not significantly different from subjects with followed-up (data not shown). The Indiana University institutional review board and the Institute for Environmental Health and Related Product Safety, Chinese Center for Disease Control and Prevention approved the study.

### **Selenium Measures**

At baseline, nail samples from all study subjects were collected at the time of interview and stored in clean plastic bags labeled with subject identification numbers. Fluorometric determination of trace amount of selenium with 2,3-diaminonaphthalene, described in details elsewhere[27], was used to determine trace amounts of selenium in nail samples. Quality control measures in the laboratory were described previously [25].

### **Lipids measurements**

At both baseline and follow-up examination, serum total cholesterol, high-density lipoprotein (HDL) and triglyceride were tested by Roche Diagnostic kits (enzymic colorimetric method), using Hitachi 7180 automatic biochemistry analyzer. In addition to quality control samples, duplicate samples were used in the lab analysis. If the relative deviation of parallel samples was greater than 10%, we repeated measurement. The average of the two measurements was used in all analyses. The intra- and inter-assay coefficients of variation were less than 1.2% for total cholesterol, 0.9% for HDL cholesterol and 1.4% for triglyceride levels.

### **Other Information**

Other information collected during the baseline interview included age, gender, years of education, body mass index (BMI), whether a participant is a life-long resident of the village since birth, history of alcohol and smoking, and self-reported history of stroke, hypertension, and heart attack. BMI (defined as body weight in kilograms divided by height in meters squared) was derived from height and weight measurements.

### **Statistical analysis**

Descriptive data are expressed as means and standard deviation, or as percentages. Paired t-tests were used to detect significant change in cholesterol, HDL and triglyceride levels from baseline to 7-year follow-up. To detect potential non-linear relationship between selenium and lipid levels, participants were divided into quartile groups according to baseline selenium concentrations. Analysis of variance (ANOVA) was used to compare differences among group means, and chi-squared tests were used for differences in proportions between categorical variables.

For each participant with follow-up evaluation, changes in lipid levels were derived as the difference between follow-up and baseline measures. Analysis of covariance (ANCOVA) models was used to determine the association between baseline selenium quartile groups and changes in lipid level while adjusting for covariates. Separate ANCOVA models were used for cholesterol, HDL and triglyceride, respectively.

## Results

Table 1 shows the baseline characteristics of the study population by quartiles of baseline nail selenium concentrations. In the 140 participants, mean (SD) nail selenium concentrations were 0.41(0.2) mg/kg, and mean (SD) cholesterol, HDL and triglyceride concentrations were 4.00(0.8), 1.15(0.3), and 1.11(0.3) (mmol/L), respectively. Higher selenium concentrations were associated with higher BMI, and higher systolic blood pressure measures. Age, sex, life-long residency, history of smoking and drinking alcohol, and other self-reported diseases history did not differ significantly across the selenium quartile groups. Among the baseline participants, selenium concentrations were inversely correlated with HDL ( $r=-0.21$ ,  $P=0.02$ ).

For the 140 participants who had 7-years follow-up evaluations, triglyceride level had decreased significantly at follow-up ( $p=0.003$ ). The Pearson correlation coefficients between baseline and follow-up levels were 0.267, 0.395, and 0.456 for cholesterol, HDL, and triglyceride respectively ( $p<0.001$  for all). (See in Table 2)

Results from separate ANCOVA models are presented in Table 3 showed that baseline selenium level was a strong predictor of the changes of serum total cholesterol ( $p<0.001$ ), HDL-cholesterol ( $p<0.001$ ) and triglyceride ( $p=0.015$ ) between follow-up and baseline measures, after adjustment for BMI, systolic blood pressure and other covariates. Participants in the bottom selenium quartile group were used as the reference group in all models. Individuals in the highest selenium quartile group showed 1.11 SD decrease on total-cholesterol ( $p<0.001$ ), 0.41 SD increase on HDL-cholesterol ( $p<0.001$ ) and 0.52 SD decrease on triglyceride after 7 years than those in the lowest selenium quartile group. The same trends were seen with significant changes in lipids in the 2<sup>th</sup> and 3<sup>th</sup> quartile groups compared to the lowest quartile group. Predicted mean lipids changes by baseline selenium quartile groups are presented in Figure 1 and non-linear trends can be seen in all three plots.

All models in table 3 were repeated with the additional adjustment for baseline lipid levels. Conclusions from all models were unchanged.

## Discussion

In this study, we examined the associations between baseline selenium levels and changes in lipid levels in a 7-year follow up of elderly Chinese in the Selenium and Cognitive Decline study. We found that participants with the higher selenium levels had greater decrease in total cholesterol and greater increase in HDL from baseline to follow-up examination compared to those with lowest selenium levels. To our knowledge, this is the first longitudinal study examining the association of selenium status with changes in lipids in a Chinese population.

Cross-sectional studies examining the relationship between selenium status and lipids profiles have not been consistent [10-15]. Some studies found positive association between selenium and lipid levels, i.e. higher selenium was associated with higher lipid levels [10-11, 14-15], while others found no significant relationship [12-13]. Baseline selenium concentrations in our sample (mean  $0.41\pm 0.2$ mg/kg) indicate that our cohort population had

relatively low dietary selenium intake. The selenium level in our samples was similar to the Finland urban men aged 55-69 y (mean toenail selenium concentration, 0.47 mg/kg) [28] and the Netherland subcohort populations which randomly drawn from the Netherland total Cohort study on diet and cancer (mean toenail selenium concentration, 0.553 mg/kg) [29]. It is noteworthy that the mean population selenium concentration in our sample was lower than toenail selenium levels in the American men (0.84mg/kg), American women (0.77mg/kg) [30], and young adults (0.86±0.15 mg/kg)[31], and also lower than the Northern Italy healthy controls (median level is 0.65 mg/kg) [32].

There had two previous longitudinal studies examining the relationship between selenium level and changes in lipids and both reported no association [33, 34]. In the adult male cohort of the Olivetti Heart Study, baseline serum selenium was a strong predictor of serum cholesterol ( $p=0.002$ ) and LDL ( $p=0.001$ ) at follow-up examination after adjusting for covariates. These associations, however, were no longer significant after additional adjustment for baseline lipids. Selenium at baseline did not predict changes in total cholesterol levels between the baseline and follow-up examinations [ $\beta$ -coefficient ( $\pm$ SE) =  $0.09\pm 0.12$  ( $p=0.46$ )] [33]. However, non-linear trend was not explored in this study. Another cohort assessed cholesterol, HDL and LDL levels 5 times from 1980 to 2007 in Finland where selenium levels were the lowest in the world in the 1980s before a nationwide selenium fertilization program. This study found that selenium measured in 1986 was not associated with lipids assessed in 2001 and 2007 ( $p>0.05$ ) [34]. Interestingly, cross-sectional analysis of both studies found that high selenium associated with adverse lipids profile, but failed to find baseline selenium associated with changes in lipid levels in prospective analyses.

There are several potential explanations for the difference in results between our study and the two previous ones. Firstly, our population had relatively low mean selenium levels compared with the Olivetti and Finland cohorts [33-34]. Like the findings from Rayman and her colleagues [35], we hypothesize that the association between selenium levels with lipids changes or antioxidant outcomes will probably be influenced by the baseline selenium status of the population studied. Besides, Cross-sectional study from the Third National Health and Nutrition Examination Survey showed an inverse association between serum selenium levels and cardiovascular mortality at low selenium levels ( $< 130$  ng/ml) but a modest increase in mortality at high selenium levels ( $> 150$  ng/ml) [20]. This supports our hypothesis from a biological mechanism view that selenium has narrow safety margin with large inter-individual variability in metabolic sensitivity [36-37]. It is plausible that a U-shaped relationship may exist between selenium level and lipid profiles in that both low and high selenium levels would lead to adverse effects on blood lipids [38, 39-40]. Neither of the two previous studies included results investigating a potential non-linear relationship.

A second explanation for the difference between our study and the two previous studies may be in the stability of the baseline selenium measures. In the Finland study, large scale selenium fertilization program was implemented after baseline selenium measures, thus it is possible that the baseline selenium measures may no longer represent participants' selenium levels during follow-up. In contrast, the majority of our study participants were lifelong residents of the same villages where they were interviewed, and the participants were known

not to take vitamin supplements; hence, the ascertained selenium levels can be inferred as lifelong exposure without the influence of supplements.

Our findings corroborated the antioxidant benefits of selenium on health outcomes [6, 17-19]. Our result was consistent with a randomized trial where 501 elderly volunteers in the UK received 100, 200 or 300µg selenium per day as high-selenium yeast or a yeast-based placebo for 6 months [35]. Compared with the placebo group, participants in the 100µg or 200µg selenium/day groups lowered serum total cholesterol by 0.22mmol/L(p=0.02) or 0.25mmol/L(p=0.008) after 6 months, respectively; Although HDL increased significantly at the 300µg/day group, there had no significant effect on total or non-HDL cholesterol at this dose. This proved that selenium has modestly beneficial effects on blood lipids in persons with relatively low selenium status. But it still should not be used to justify the use of selenium supplementation as additional or alternative therapy for dyslipidemia, particularly in higher selenium regions.

Our study has a number of strength. First, participants in the cohort were mostly life-long residents of the rural villages, thus their baseline selenium levels reflect dietary intake without the influence of selenium supplementation. Second, the availability of repeated blood samples provides the opportunity to examine changes in lipid levels.

This study also had important limitations. First, the sample size was relatively small, mostly due to the small number of participants with blood samples from baseline. Thus our results would need to be confirmed in other studies with larger sample sizes. Second, we cannot rule out the potential for confounding by unmeasured factors, such as the use of lipid lowering medications. Recent findings from the EVA study suggested that long-term use of fibrates (but not statins) increased plasma selenium concentrations in dyslipidemic aged patients [41]. However, such medication use cannot explain the significantly higher increase in selenium levels found in the lowest selenium quartile group. Third, GSHPx activity was not measured in this study and we are unable to determine the extent of GSHPx activity has in the relationship between selenium and lipids levels.

In conclusion, in this rural elderly Chinese cohort we found that participants with the higher selenium levels had greater decrease in total cholesterol and greater increase in HDL from baseline to follow-up examination compared to those with the lowest selenium levels. Our result, if confirmed in other studies, suggests adequate dietary selenium intake as a potential prevention strategy for lowering lipid levels in selenium deplete populations.

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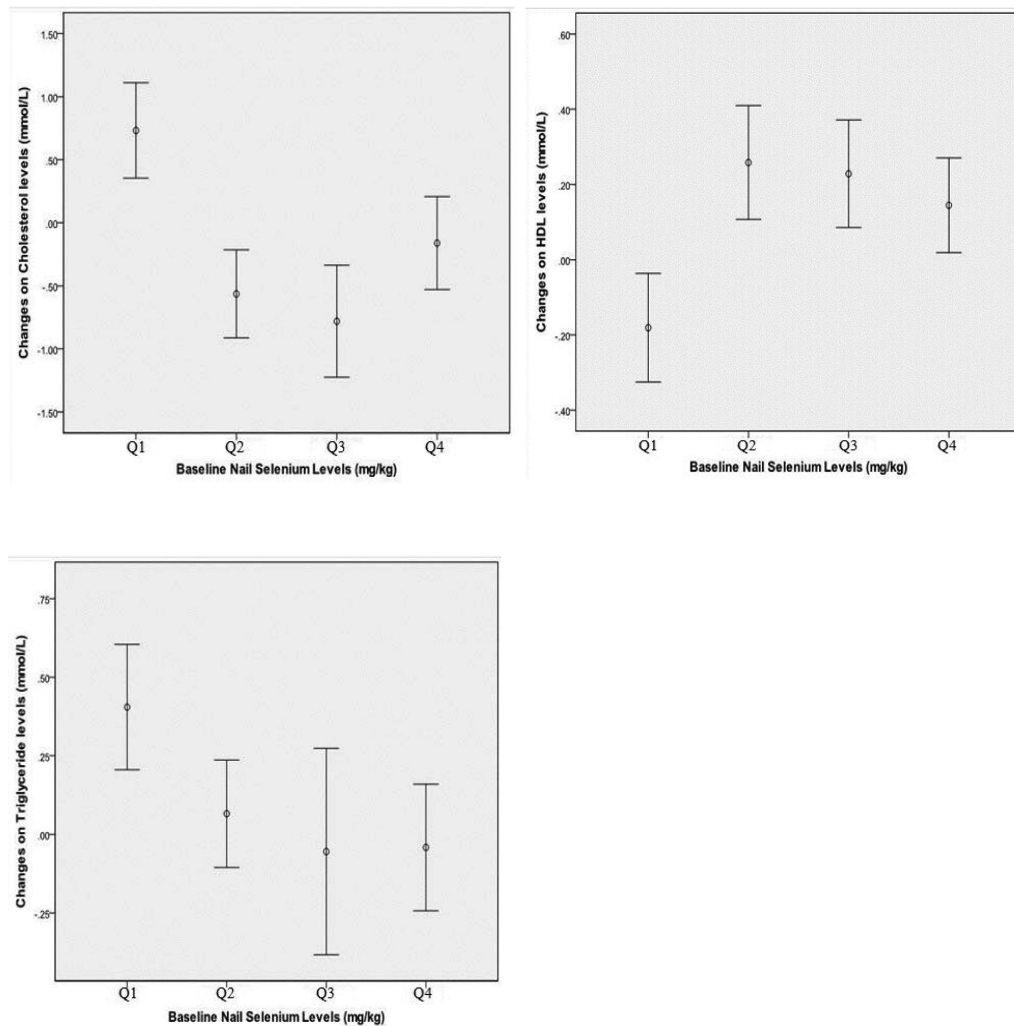
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### Highlights

We examined the associations of selenium status with changes in lipid levels in a 7-year follow up of an elderly Chinese cohort including participants from selenium-deplete areas. In prospective analysis, we found that participants with the higher selenium levels had greater decrease in total cholesterol and greater increase in HDL from baseline to follow-up examination compared to those with lowest selenium levels, which suggested that adequate dietary selenium intake as a potential prevention strategy for lowering lipid levels in selenium deplete populations.



**Figure 1.** Relationship between baseline selenium and changes on Cholesterol, HDL and triglyceride levels after 7-year follow-up adjusted for age, gender, body mass index, smoking history, alcohol history, and self-reported history of stroke, hypertension, and angina. The horizontal axis represents baseline nail selenium quartile groups. The vertical axis represents the means and 95% confidence intervals of changes in the two lipids measurements, derived as the difference between follow-up and baseline lipids measures. Higher values on the vertical axis indicate greater lipid increase.

**Table 1**

Participants' Baseline Characteristics According to Baseline Selenium Levels Measured in Nail Samples.

Baseline Characteristics	Total n=140	Means (SD) by Selenium Quartile Groups*				P-value
		Q1(low) n=35	Q2 n=35	Q3 n=35	Q4(high) n=35	
Selenium level, mg/kg	0.41(0.2)	0.19(0.03)	0.34(0.04)	0.45(0.03)	0.67(0.1)	<0.001
Age	69.35(4.1)	68.70(3.3)	69.68(4.9)	69.08(3.6)	69.96(4.1)	0.409
Male, %	49.2	54.0	56.0	50.0	36.7	0.21
Body Mass Index, kg/m <sup>2</sup>	22.94(3.6)	22.04(2.7)	21.92(3.2)	23.38(3.5)	24.44(4.5)	0.001
Systolic blood pressure, mmHg	143.21(24.2)	133.21(19.7)	141.54(20.6)	148.3(27.3)	149.9(24.1)	0.002
Diastolic blood pressure, mmHg	83.03(12.34)	79.98(10.84)	83.48(12.49)	84.56(13.79)	84.12(11.89)	0.236
life-long residency, %	55.3	60.0	50.0	52.0	59.2	0.674
Alcohol, %	46.2	60.0	42.0	46.0	36.7	0.179
Smoking, %	50.8	23.8	25.7	28.7	21.8	0.592
Self-reported history of, %						
Diabetes	4.0	4.0	4.0	6.0	2.0	0.800
Hypertension	15.6	10.0	8.0	20.0	24.5	0.07
Stroke	1.0	0	0	0	4.1	0.103
Heart Attack	3.5	6.0	2.0	4.0	2.0	0.66
Cholesterol, mmol/L	4.00(0.8)	3.99(.7)	3.68(.6)	3.87(.7)	4.24(.7)	0.004
HDL, mmol/L	1.15(0.3)	1.30(.3)	1.13(.2)	1.08(.2)	1.13(.3)	0.02
Triglyceride, mmol/L	1.11(0.3)	1.2(.7)	.96(.3)	1.11(.8)	1.09(.6)	0.356

\* Range of baseline selenium levels is lower than 0.245 mg/kg in the lowest quartile (Q1), from 0.246 to 0.407 mg/kg in Q2, from 0.408 to 0.523 in Q3, and higher than 0.523 mg/kg in the highest quartile (Q4).

**Table 2**

Changes in serum lipids levels between Baseline and 7-year Follow-up evaluations

	Cholesterol, mmol/L	HDL, mmol/L	Triglyceride, mmol/L
Means(SD) at baseline	4.00 (0.8)	1.15 (0.3)	1.11 (0.3)
Means(SD) at 7-year	4.19 (0.8)	1.26 (0.3)	1.01 (0.3)
Change from baseline to 7-year	0.19	0.11	-0.1 *
Pearson correlation coefficients between baseline and follow-up	0.267 **	0.395 **	0.456 **

\* P&lt;0.05

\*\* P&lt;0.001

**Table 3**

Separate analysis of covariance (ANCOVA) models on changes in Cholesterol, HDL and triglyceride levels between baseline and 7-year follow-up examinations.

Outcome Variable	Selenium Quartile groups, mg/kg	Parameter Estimate	Standard Error Estimate	p-value
<b>Cholesterol</b>	Q1	Reference	--	--
	Q2	-1.222	0.27	<0.001
	Q3	-1.637	0.28	<0.001
	Q4	-1.109	0.29	<0.001
<b>HDL</b>	Q1	Reference	--	--
	Q2	0.409	0.09	<0.001
	Q3	0.459	0.10	<0.001
	Q4	0.411	0.11	<0.001
<b>Triglyceride</b>	Q1	Reference	--	--
	Q2	-0.282	0.17	0.091
	Q3	-0.478	0.17	0.005
	Q4	-0.524	0.18	0.004

All models adjusted for age, gender, body mass index, smoking history, alcohol history, and self-reported history of stroke, hypertension, and angina.