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Associations of selenium status with cardiometabolic risk factors: An 8-year follow-up analysis of the Olivetti Heart Study

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ABSTRACT

Objective: High selenium status has been associated with adverse cardiometabolic outcomes in selenium-replete populations such as the US. In populations with lower selenium status such as in Italy, there is little epidemiological evidence about the association of selenium with cardiometabolic risk factors. We therefore examined cross-sectional and prospective relationships of serum selenium concentrations with cardiometabolic risk factors including blood pressure, diabetes and blood lipids in the Olivetti Heart Study.
Methods: The study population consisted of 445 adult male individuals for whom baseline serum selenium measurement and cardiometabolic risk factors at baseline (1994–1995) and follow-up examination (2002–2004: average follow-up = 8 years) were available. Serum selenium was measured by atomic absorption spectrophotometry.
Results: Average serum selenium concentration at baseline was 77.5 ± 18.4 μg/L. In cross-sectional analyses, serum selenium levels were positively associated with serum total cholesterol (p for trend <0.0001) and prevalent diabetes (p for trend <0.05). In prospective analysis, serum selenium at baseline was likewise a strong predictor of serum total cholesterol ($p = 0.002$) and LDL-cholesterol ($p = 0.001$) at follow-up, after adjustment for age, BMI, cigarette smoking, physical activity, and lipid-lowering medication. These associations, however, were no longer significant after additional adjustment for baseline blood lipids. Selenium at baseline did not predict changes in total cholesterol levels between the baseline and follow-up examinations [β-coefficient ($\pm$SE) = 0.09 ± 0.12 ($p = 0.46$)].
Conclusion: These findings corroborate previous cross-sectional associations of high selenium status with adverse blood lipid profile and diabetes. However, prospective analyses do not support the causality of these relations. Randomized and experimental evidence is necessary to clarify the mechanisms underlying the observed cross-sectional associations.

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1. Introduction

Selenium is a key component of a number of selenoproteins involved in essential enzymatic functions such as redox homeostasis, thyroid hormone metabolism, immunity and reproduction [1,2]. Because of the potential of these selenoproteins to protect against oxidative stress, significant expectations were raised for the prevention of several chronic diseases including cancer, cardiovascular disease (CVD) and type 2 diabetes [3–5], conditions commonly associated with oxidative stress. Indeed, a number of observational studies have examined the association between selenium status and risk of CVD across different populations [6–12]. Inverse associations have been found particularly in populations with relatively low selenium intake or status [6–10]. However, results from a few randomized trials of selenium supplementation do not support a role for selenium in cardiovascular disease prevention at the present time [10,13–15].

Furthermore, recent findings from observational studies and randomized clinical trials have raised concern that high selenium exposure may lead to adverse cardiometabolic effects, particularly in selenium-replete populations such as that of the US [16–23]. Specifically, several unrelated studies suggest that high selenium

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Table 1
Baseline characteristics of participants by selenium tertiles. The Olivetti Heart Study.

N	Total (445)	Selenium tertiles		
		I (134)	II (159)	III (152)
Selenium (μg/L) [range]	77.5 ± 18.4 [17.9–200.1]	58.0 ± 11.1 [17.9–69.6]	76.7 ± 3.7 [69.7–82.6]	95.4 ± 14.4* [82.8–200.1]
Age (years)	50.9 ± 6.9	51.0 ± 5.8	50.3 ± 7.1	51.5 ± 7.4
BMI (kg/m^2)	26.8 ± 2.9	26.7 ± 3.0	26.9 ± 2.9	26.7 ± 2.8
SBP (mmHg)	128.5 ± 16.5	128.6 ± 17.3	126.9 ± 16.5	130.0 ± 15.9
DBP (mmHg)	83.2 ± 9.4	82.2 ± 9.4	83.1 ± 9.6	84.2 ± 9.1
Total cholesterol (mg/dL)	221.4 ± 39.1	210.5 ± 40.0	222.6 ± 41.3	229.9 ± 33.4*
Smoking (%)	42.0	49.0	44.0	34.0**
Hypertension (%)	37.0	33.0	36.0	41.0
Diabetes (%)	3.0	3.0	1.0	7.0**
Physical activity (%)	84.0	87.0	85.0	82.0
Lipid-lowering medication (%)	10.0	13.0	6.0	10.0

Data are expressed as means ± SD, or as percentages.
* *p* for trend <0.0001.
** *p* for trend <0.05.

status or selenium supplementation may be associated with an increased risk of diabetes [16–19]. In addition, cross-sectional studies in the UK and the US have shown a more atherogenic lipid profile and higher prevalence of hypertension associated with higher selenium status [20–23]. As cross-sectional studies cannot establish a temporal relationship, longitudinal evidence is needed.

We therefore examined the relationship of serum selenium concentrations with cardiometabolic risk factors in an 8-year follow-up analysis of the Olivetti Heart Study, an ongoing epidemiological investigation of the metabolic, nutritional and genetic precursors of CVD in an unselected male population from southern Italy [24–26].

2. Materials and methods

2.1. Study population

The Olivetti Heart Study population is based on the male workforce of the Olivetti factories in Pozzuoli (Naples) and Marcianise (Caserta), Southern Italy. The study was launched in 1975 to investigate the interplay between metabolic, nutritional and genetic factors in the development of atherosclerosis-related disease in a population with low rates of cardiovascular morbidity and mortality at that time [24]. The general characteristics of the study and its methodological procedures have been previously described [25,26]. The local ethics committee approved the study protocol, and participants provided their informed consent to participate. A total of 1085 individuals aged 25–74 years (mean ± SD = 51.5 ± 7.2 years) were examined in 1994–1995; of these, 907 (83.6%) were seen again in 2002–2004 and were considered eligible for the present analysis. The relevant characteristics of the subjects lost to follow-up were not significantly different from those of the rest of the population (data not shown). In the present analysis, we included 445 individuals for whom baseline serum selenium measurement and cardio-metabolic risk factors at baseline (1994–1995) and follow-up examination (2002–2004: average follow-up = 8 years) were available.

2.2. Study protocol

At both baseline and follow-up, physical examinations were performed between 0800 and 1100 h, in a quiet and comfortable room within the medical centers of the Olivetti factories, with the participants having fasted for at least 13 h. The participants were allowed to pursue their normal activities but were discouraged from engaging in vigorous exercise and were asked to abstain from smoking and from drinking alcohol, coffee, tea and other beverages containing caffeine during the morning of the study. The study included a physical examination and anthropometric measurements, a resting 12-lead electrocardiogram, a blood test, a fasting timed urine collection and the administration of a questionnaire including information on medical history, working and leisure time physical activity, dietary and smoking habits.

Body weight and height were measured on a standard beam balance scale with an attached ruler. Body weight was measured to the nearest 0.1 kg, and body height was measured to the nearest 1.0 cm, with subjects wearing light indoor clothing without shoes. Body mass index (BMI) was calculated as weight (kg) divided by the height (m^2). Smoking habits, alcohol consumption, and degree of habitual physical activity were investigated by a standardized questionnaire.

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) (phase V) were taken three times 2 min apart with a random zero sphygmomanometer (Gelman Hawksley Ltd., Sussex, UK) after the subject had been sitting for at least 10 min. The average of the second and third reading was recorded. Hypertension was defined as systolic BP ≥ 140 and/or diastolic BP ≥ 90 mmHg or current antihypertensive drug treatment [26].

A fasting venous blood sample was taken in the seated position between 0800 and 1000 h, after the BP measurements, for determination of serum insulin, lipids, and glucose. The blood specimens were immediately centrifuged and stored at −70 °C until analyzed. At both baseline and follow-up examination, serum total cholesterol and glucose levels were measured with automated methods (Cobas-Mira, Roche, Italy). Serum LDL-cholesterol was only measured at the follow-up examination using the Friedewald formula [27], because HDL-cholesterol was not available at the baseline, thus precluding LDL-cholesterol estimation. Type 2 diabetes was defined as a fasting blood glucose level ≥126 mg/dL or anti-diabetic therapy.

2.3. Selenium measurements

Baseline serum selenium was measured by atomic absorption spectrophotometry. Briefly, serum (1 mL) of each individual was treated with 65% HNO_3 (20% final concentration) for 16 h and centrifuged for 30 min at 18,000 × *g*. Supernatants were collected and analyzed for selenium (Se) content. Baseline serum selenium content was determined by graphite furnace atomic absorption spectrophotometry (Analyst 800, Perkin-Elmer, Norwalk, CT) using the following parameters: pretreatment temperature, 1300 °C; atomization temperature, 1900 °C; with 0.015 mg of palladium (Pd) plus 0.01 mg of $Mg(NO_3)_2$ as matrix modifier. The measurements were performed using a graphite furnace equipped with Zeeman-effect background correction system. Pyrolytic graphite-

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Table 2
Cross-sectional associations of total cholesterol levels. The Olivetti Heart Study.

Independent variables	Dependent variable – baseline total cholesterol (mg/dL)	
	$\beta \pm$ SE	p
Age (years)	0.08 ± 0.27	0.77
BMI (kg/m^2)	−0.41 ± 0.63	0.52
Physical activity (yes)	−1.67 ± 5.06	0.74
Smoking (yes)	−0.65 ± 3.70	0.86
Selenium (rank)	0.06 ± 0.01	0.0001

Adjusted for lipid-lowering medication; $R^2 = 0.05$.

coated THGA tube (Perkin-Elmer) with an integrated Lvov-type platform was used for the metal determination. A Se standard in 2.5% HNO_3 (Spectrascan) was used as a stock solution for the construction of the 3-point calibration curve. Each measurement was carried out in triplicate. The intra-assay and inter-assay coefficients of variation were less than 3 and 4.8%, respectively.

2.4. Statistical methods

Descriptive data are expressed as means and standard deviation, or as percentages. For descriptive analyses of baseline characteristics, participants were divided by tertiles of baseline serum selenium concentrations. Analysis of variance (ANOVA) was used to assess differences between group means, and chi-square (χ^2) test for differences between categorical variables. Since the distribution of original and log-transformed selenium levels was not normal (Kolmogorov–Smirnov test; $p = 0.01$), we considered for the analyses the rank values of selenium (Kolmogorov–Smirnov test; $p = 0.09$). Bivariate relationships between main features were evaluated by Pearson correlation analysis. Multivariate linear regression analyses were carried out to estimate the cross-sectional and prospective associations of baseline selenium with blood lipids, as well as the predictive role of selenium and other selected variables with respect to changes in total cholesterol levels between the baseline and follow-up examinations. Covariates comprised the following: baseline age, BMI, cigarette smoking, physical activity, use of lipid-lowering medication (model 1), as well as the baseline value of total cholesterol (model 2) in prospective analyses. Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS-PC, version 15; SPSS, Inc., Chicago, IL). Statistical significance was inferred at a two-tailed $p < 0.05$.

3. Results

Table 1 shows the baseline characteristics of the study population by tertiles of baseline serum selenium concentrations. In the total cohort of 445 participants, mean (±SD) serum selenium concentration at baseline was 77.5 (±18.4) μg/L, which is in line with previous estimates of selenium status in Italian samples [28–30]. Age, BMI, and blood pressure values, for continuous variables, as well as hypertension, physical activity, and use of lipid-lowering medication, for categorical variables, did not significantly differ across selenium tertiles. Smoking was inversely related to selenium status, as consistently reported in several previous studies [11,12,16,18–23]. Increased serum selenium levels were significantly associated with increased serum total cholesterol (p for trend <0.0001) and with a higher prevalence of diabetes (p for trend <0.05). Baseline serum selenium and baseline serum total cholesterol were significantly correlated ($r_s = 0.20$, $p < 0.001$).

The cross-sectional association of serum selenium with serum total cholesterol was further corroborated in multivariate regression analyses, after adjustment for baseline age, BMI, cigarette smoking, physical activity, and lipid-lowering medication (Table 2).

Table 3
Multivariate regression analysis of predictors of LDL-cholesterol after 8 years. The Olivetti Heart Study.

	Dependent variable – LDL cholesterol 2002–2004 (mg/dL)	
	$\beta \pm$ SE	p
Model 1		
Age (years)	0.53 ± 0.25	0.03
BMI (kg/m^2)	−0.98 ± 0.58	0.09
Physical activity (yes)	−1.44 ± 4.66	0.76
Smoking (yes)	4.95 ± 3.40	0.15
Selenium (rank)	0.04 ± 0.01	0.001
$R^2 = 0.07$		
Model 2		
Age (years)	0.55 ± 0.20	0.006
BMI (kg/m^2)	−0.88 ± 0.47	0.06
Physical activity (yes)	−1.20 ± 3.79	0.75
Smoking (yes)	4.80 ± 2.77	0.08
Selenium (rank)	0.01 ± 0.01	0.37
Total cholesterol 1994–1995 (mg/dL)	0.55 ± 0.04	0.001
$R^2 = 0.38$		

All variables adjusted for lipid-lowering medication.

The β-coefficient (±SE) for total cholesterol associated with selenium was 0.06 ± 0.01 ($p = 0.0001$). The multivariate adjusted mean values (±SE) of baseline serum total cholesterol, across selenium tertiles, were as follows: 210.0 ± 3.3 (I tertile); 223.5 ± 3.0 (II tertile); 229.5 ± 3.1 (III tertile) (data not shown).

In prospective analysis, baseline serum selenium was a strong predictor of serum total cholesterol ($p = 0.002$) and LDL-cholesterol ($p = 0.001$) at follow-up examination, after adjustment for baseline age, BMI, cigarette smoking, physical activity, and lipid-lowering medication (model 1). These associations, however, were no longer significant after additional adjustment for baseline serum total cholesterol (model 2). Results were very similar for both LDL-cholesterol (Table 3) and total cholesterol (data not shown).

Likewise, baseline selenium did not predict changes in total cholesterol levels [β-coefficient (±SE) = 0.09 ± 0.12 ($p = 0.46$)] between the baseline and follow-up examinations (Table 4).

Additional analyses were performed to examine the association of baseline serum selenium with incident hypertension among normotensive individuals at baseline ($n = 281$), and with incident diabetes among non-diabetic individuals at baseline ($n = 430$). In these analyses, baseline selenium status was not prospec-

Table 4
Multivariate regression analysis of predictors of changes in total cholesterol between baseline and follow-up examinations. The Olivetti Heart Study.

	Dependent variable – changes in total cholesterol (mg/dL)	
	$\beta \pm$ SE	p
Model 1		
Age (year)	0.64 ± 0.24	0.008
BMI (kg/m^2)	−0.92 ± 0.57	0.11
Smoking (yes)	5.63 ± 3.35	0.09
Physical activity (yes)	0.69 ± 4.58	0.88
Selenium (rank)	−0.01 ± 0.13	0.29
$R^2 = 0.19$		
Model 2		
Age (year)	0.63 ± 0.22	0.005
BMI (kg/m^2)	−1.01 ± 0.52	0.05
Smoking (yes)	5.60 ± 3.07	0.07
Physical activity (yes)	0.51 ± 4.20	0.90
Selenium (rank)	0.09 ± 0.12	0.46
Total cholesterol 1994–1995 (mg/dL)	−0.37 ± 0.04	0.0001
$R^2 = 0.32$		

All variables adjusted for lipid-lowering medication at baseline and at follow-up.

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tively associated with incident hypertension or diabetes (data not shown). However, the cumulative incidence of type 2 diabetes was extremely low in our sample (1.4%), thus constraining the statistical power of these analyses.

4. Discussion

In this study, we examined cross-sectional and prospective relationships of serum selenium concentrations with cardiometabolic risk factors in an 8-year follow-up analysis of the Olivetti Heart Study. In agreement with recent reports [20–22], we found positive cross-sectional associations between selenium status and serum total cholesterol in our data. However, in prospective analyses baseline serum selenium was not a predictor of changes in cholesterol levels between the baseline and follow-up examinations, which does not support the causality of the cross-sectional relations.

Cross-sectional studies have consistently identified strong, graded, positive associations between selenium status and blood lipids in different populations and across a wide range of selenium concentrations worldwide [20–22,29,31–35]. Prospective findings from the present study do not support a lipid-raising effect of selenium. To our knowledge, this is the first longitudinal evidence examining the association of selenium status with blood lipids.

Only three relatively small randomized trials have examined the effect of selenium supplementation alone on blood lipids, and their results are conflicting [36–38]. Specifically, two of these trials, conducted in Finland and China, found no significant differences between treatment groups [36,37]. In the UK, the PRECISE Pilot trial randomized 501 elderly volunteers [mean (±SD) plasma selenium 88.8 (±19.2) μg/L] to a six-month treatment with 100, 200 or 300 μg selenium/day as high-selenium yeast or placebo yeast [38]. Supplementation at 100 and 200 μg selenium/day lowered serum total cholesterol and non-HDL cholesterol; the 300 μg/day dose had no significant effect on total or non-HDL cholesterol, but raised HDL-cholesterol significantly.

In the present study, we also found a positive cross-sectional association of higher selenium status with diabetes prevalence. Unfortunately, longitudinal analyses were limited by the very low incidence of type 2 diabetes in our sample (1.4%). Our cross-sectional findings are in agreement with two previous analyses from the US National Health and Nutrition Examination Survey (NHANES) showing positive associations between serum selenium concentrations and the prevalence of type 2 diabetes [16,18], and with a recently published cross-sectional study from Taipei reporting positive associations between serum selenium and serum fasting glucose concentrations [35]. These cross-sectional findings, however, do not allow us to determine whether high selenium is a cause or a consequence of the disease process. A *post hoc* analysis of the Nutritional Prevention of Cancer (NPC) trial in the Eastern US showed that supplementation with selenium (200 μg/day as high-selenium yeast) compared to placebo increased the risk of type 2 diabetes, mainly in men and in participants with high baseline plasma selenium [17]. Based on this evidence, the effect of selenium on diabetes risk warrants further investigation.

In our study, the association of selenium status with blood pressure levels and hypertension was not significant in either cross-sectional or longitudinal analyses. Previous studies from populations with variable selenium status have reported inconsistent results [23,29,31,39–41]. For example, in the Flemish Study on Environment Genes and Health Outcomes (FLEMENGHO), higher blood selenium concentrations were associated with lower systolic and diastolic blood pressure levels at baseline and with a lower risk of hypertension over 5.2 years of follow-up in men, but not among women [41]. Conversely, in a recent cross-sectional analysis of serum selenium and hypertension in the US NHANES 2003–2004, higher selenium concentrations were associated with a higher prevalence of hypertension in both men and women [23]. Unfortunately, no data are available on the effect of selenium supplementation on blood pressure endpoints in randomized controlled trials using single selenium supplements.

Mechanistic evidence to explain the potential associations of selenium with lipids and diabetes is limited at the present time. However, a number of sources provide evidence of a clear connection between lipoproteins, insulin resistance and selenium metabolism [42–46]. In general, selenium is known to be a trace mineral with a narrow therapeutic window and considerable inter-individual variability in terms of metabolic sensitivity and optimal selenium intake [47]. Current recommendations on dietary selenium intake (55–75 μg/day) are based on optimizing the activity of plasma glutathione peroxidase [48], which requires a plasma selenium concentration of 92 μg/L [49]. From a mechanistic point of view, selenium intakes above the level recommended for optimal activities of selenoproteins will simply result in the non-specific incorporation of selenomethionine in place of methionine in albumin and other proteins [1]. Health benefits above these intakes have not been proven as yet.

There are some limitations with the present study. *First*, the study population was limited to white male participants from an occupational setting, which may restrict the generalizability of these findings. However, the consistency of the observed cross-sectional associations between selenium status and blood lipids and diabetes with several previous reports [16,18,20–22,29,31–35] strengthens the external validity of our findings. *Second*, we cannot rule out the potential for residual confounding by unmeasured or unknown factors that may have contributed to our findings. The cross-sectional associations of selenium status with blood lipids and diabetes could be driven by a common dietary factor or by general over-nutrition. *Third*, selection bias related to follow-up may represent a further potential limitation of this study. However, a comparison of baseline selected characteristics between the overall Olivetti sample ($N = 1085$) and included participants ($N = 455$) was not suggestive of major selection bias in our study population (data not shown). *Finally*, we had limited statistical power to address the prospective association of selenium status with incident diabetes. Given the voluntary nature of the study population, we cannot rule out the potential for a "healthy volunteer" bias, which may have contributed to a low incidence of type 2 diabetes in this study. Major strengths of the present study are its prospective nature, high standardization of data collection, and length of follow-up.

In conclusion, findings from the present study are reassuring as regards potential adverse effect of high selenium status on blood lipids, for concentrations of selenium within the physiological range for optimal selenoprotein activities, such as in Italy and most European countries [50]. Potential differences in the effects, either beneficial or detrimental, of selenium on cardiometabolic outcomes might be explained by the variability of selenium status and selenium dietary intakes across different countries and population subgroups [51–55]. Further prospective and randomized studies should be conducted to investigate the link between selenium and cardiometabolic outcomes, especially diabetes, across different ranges of selenium concentration.

Conflict of interest

The authors do not have potential conflicts of interest regarding this manuscript.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.atherosclerosis.2011.03.027.

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