Original Article

Influence of serum selenium concentrations on hypertension: the Lipid Analytic Cologne cross-sectional study

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Aims: Selenium is an antioxidant micronutrient with potential associations with hypertension. Few studies have investigated the association of serum selenium concentrations with blood pressure and hypertension in countries with low dietary selenium intake such as Germany, with inconsistent findings.

Methods: We undertook a cross-sectional analysis of participants in the Lipid Analytic Cologne (LIANCO) cohort. To reduce potential confounding, we restricted the analysis to 792 participants who were never smokers, who did not use antihypertensive medications, and who did not have diabetes or known atherosclerotic disease. Hypertension was defined as blood pressure at least 140 and/or at least 90 mmHg. About half of the cohort was diagnosed as hypertensive. Selenium was measured by inductively coupled plasma-dynamic reaction cell-mass spectrometry (ICP-DRC-MS).

Results: Mean ± standard deviation (SD) serum selenium concentration was 68 ± 32 μg/l. The multivariable adjusted differences (95% confidence intervals) in blood pressure levels comparing the highest (>91.9 μg/l) to the lowest (≤42.8 μg/l) quartile of serum selenium were 5.2 (1.4 to 8.9), 2.8 (0.7 to 4.8), and 2.4 (−0.4 to 5.2) mmHg for systolic, diastolic, and pulse pressure, respectively (*P* for trend for all <0.003). The corresponding multivariable adjusted odds ratio for the presence of hypertension was 1.52 (0.98 to 2.36; *P* trend = 0.004).

Conclusions: The data suggest that even in a population with very low serum selenium concentrations higher serum selenium concentrations are associated with higher blood pressure levels and a higher prevalence of hypertension. These findings call for careful evaluation of the effects of selenium on blood pressure endpoints in randomized clinical trials.

Keywords: blood pressure, hypertension, selenium, trace elements

Abbreviations: ICP-DRC-MS, inductively coupled plasma-dynamic reaction cell-mass spectrometry; LIANCO, Lipid Analytic Cologne

INTRODUCTION

Selenium is an essential trace element with antioxidant properties mediated through glutathione peroxidases and other selenoenzymes [1]. Because oxidative stress is involved in hypertension development [2], it has been suggested that selenium may play a role in blood pressure control and hypertension prevention [3–5]. However, recent findings from observational studies and randomized clinical trials have raised concerns that high selenium exposure may lead to adverse cardiometabolic effects, including hypertension, hypercholesterolemia and type 2 diabetes, at least in selenium-replete populations [6,7]. The few studies that have evaluated the association between selenium and blood pressure have been inconsistent, reporting inverse [5,8], null [9,10], or positive [11] associations.

There are significant differences in selenium concentrations between world regions and countries depending on nutritional selenium intake and/or supplement use. In the USA, selenium intake ranges between 80 and 165 μg/day [7]. As a consequence, 99% of the adult population has serum selenium concentrations above 95 μg/l and 50% of the population has concentrations above 124 μg/l [12]. Most countries in Europe, including Germany, are selenium-depleted regions [13]. The daily selenium intake in Germany is about 35 μg [14], well below the recommended dietary allowance of 55 μg/day [4]. Serum selenium concentrations in a German population

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are approximately 70 μg/l on average [15]. Data on the association of selenium with cardiometabolic factors from populations with low dietary selenium intake such as European countries are relatively sparse. The aim of the present study, then, was to explore the relationship between serum selenium concentrations and blood pressure levels and with the prevalence of hypertension in a selenium-depleted population.

METHODS

Study population

The Lipid Analytic Cologne (LIANCO) study [16,17] was a cohort study designed to assess the relationships between genetic mutations, serum lipoproteins, other biochemical parameters, and clinical data on hypertension, diabetes and atherosclerotic disease. Between spring 1999 and March 2002, a total of about 5000 patients were recruited in the Cologne (Germany) area by hospitals and office-based physicians. Since our objective for the present analysis was to evaluate the association of selenium with blood pressure levels unconfounded by other cardiovascular risk factors, we restricted the study sample to participants who were never-smokers, who were free of atherosclerotic cardiovascular disease and diabetes. Moreover, they should not be using antihypertensive medications. Selenium measurements were available in 792 eligible participants. Approval of the study protocol was obtained from the Ethics Committee of the University of Cologne. All participants gave written informed consent.

Selenium determination

Serum samples were stored at −20°C and were shipped frozen to the analytical laboratory in Neuherberg (Germany). We determined ^{80}Se in serum samples using an ELAN (Perkin Elmer, Rodgau-Jügesheim, Germany) inductively coupled plasma-dynamic reaction cell-mass spectrometer (ICP-DRC-MS) in DRC-mode. In short, ^{103}Rh at a concentration of 1 μg/l was added to each 1 : 10-diluted sample as internal standard. Sample introduction was carried out using a peristaltic pump equipped with an 'antipulse-head' (SPETEC, Erding, Germany), connected to a Meinhard nebulizer with a cyclon spray chamber. The radio frequency power was set to 1250 W, the plasma gas was 15 l Ar per minute, and the nebulizer gas was approximately 0.9 l Ar per minute after daily optimization. For DRC, the reaction gas was methane at a flow rate of 0.6 ml/min, the rejection parameter q was 0.6, and the rejection parameter a was 0. Each sample was measured in triplicate and typical coefficients of variation ranged between 3 and 5%.

For quality control, we determined serum selenium in a subset of the samples using a reference method based on graphite furnace atomic absorption spectrometry (Model 4100 ZL with Zeeman correction, Perkin-Elmer) according to methods previously described [18]. In short, the samples were measured with $Mg(NO_3)_2 + Pd(NO_3)_2$ (each 0.2%) as matrix modifier. The assay also contained 0.3% HCl and 0.4% Triton X 100. A final dilution of the samples of 1 : 10 was obtained by appropriate addition of Milli-Q H_2O. Quantification was performed with the standard addition method. The atomization program consisted of seven steps:

Temperature (°C)	Ramp (s)	Hold (s)	Internal gas flow (ml/min)
100	20	15	250
130	20	20	250
530	15	25	250
1200	20	20	250
1900	0	5	0
2450	1	3	250
30	0	10	250

For analytical quality control, we measured selenium concentrations in reference control materials of human serum, ClinCheck (Recipe, Munich, Germany) and Seronorm (Sero, Billingstad, Norway) using ICP-DRC-MS. The manufacturers' target mean values were 62 μg/l (ClinCheck) and 81 μg/l (Seronorm). The quality control measurements ($n = 6$) revealed a recovery of 99 ± 3.5% (ClinCheck) and 101 ± 4.1% (Seronorm).

Blood pressure and hypertension

Blood pressure readings were obtained by trained health professionals under standard practice conditions using a mercury sphygmomanometer with an appropriate size cuff placed on the bare arm after study participants had been sitting quietly for at least 5 min. SBP and DBP were obtained at the appearance and disappearance of Korotkoff sounds, respectively. Pulse pressure was calculated as the difference between SBP and DBP. Hypertension was defined as having a SBP of at least 140 mmHg and/or a DBP of at least 90 mmHg. In the current study we did not include patients taking antihypertensive medications.

Statistical analysis

Descriptive statistics are presented as means [standard deviation (SD)] or percentages unless otherwise indicated. Study participants were divided into quartiles of serum selenium concentrations based on the overall study population. Adjusted mean differences in blood pressure levels and odds ratios for hypertension comparing each quartile of serum selenium to the lowest quartile were calculated using multivariable linear and logistic regression analysis, respectively. The models were adjusted for sex, age (continuous), BMI (continuous) and hormone replacement status (yes, no). Tests for linear trend were calculated by including serum selenium as a continuous variable in the models. We also estimated average differences in blood pressure levels and odds ratios for hypertension comparing the 75th to the 25th percentiles of the serum selenium distribution in the overall population (corresponding to 92.0 and 42.8 μg/l of selenium, respectively) assuming a linear relationship between serum selenium and blood pressure.

To further explore the shape of the relationship between serum selenium and blood pressure measurements and hypertension, we used restricted quadratic splines [19] with knots at the 5th, 50th, and 95th percentiles of the serum selenium distribution in the fully adjusted model.

We also evaluated the interactions of selenium (modeled as a linear term) with sex, age (<50 and ≥50 years), and BMI (<25 and ≥25 kg/m^2) by fitting interaction terms between selenium and the variables of interest and adjusting for the other variables in the model. Since we identified a strong interaction between selenium and sex, we present post-hoc analyses separately for men and women. Statistical analyses were performed using Stata version 11 (StataCorp LP, College Station, Texas, USA).

RESULTS

Of the 792 participants included, 362 (45.7%) were men and 380 (48.0%) were hypertensive (Table 1). The average (SD) SBP and DBP and pulse pressure levels were 133.8 (19.5), 81.9 (10.5), and 51.8 (14.5) mmHg, respectively. Compared to nonhypertensive participants, those with hypertension were significantly older (56.5 vs. 50.2 years; $P < 0.0001$) and had a significantly higher BMI (27.2 vs. 25.5 kg/m^2; $P < 0.0001$), but both groups had a similar sex distribution (44.7 vs. 46.8% of men in nonhypertensives and hypertensives, respectively; $P = 0.57$).

The average serum selenium concentration in the study population was 68.2 μg/l (SD 31.5 μg/l; range 1.2 to 167.0 μg/l). Serum selenium levels were significantly higher in women compared to men (74.8 vs. 60.4 μg/l; $P < 0.001$). Serum selenium concentrations were significantly positively associated with age in both men and women, whereas there was no association with BMI (Table 2).

Participants with hypertension had significantly higher serum selenium concentrations than those without hypertension (72.8 vs. 64.0 μg/l; $P < 0.001$). The average difference in serum selenium concentrations between hypertensive and nonhypertensive individuals was 8.8 μg/l [95% confidence interval (CI) 4.4 to 13.1 μg/l]. In multivariable adjusted models (Table 3), the average differences (95% CIs) comparing the highest (>91.9 μg/l) to the lowest (≤42.8 μg/l) selenium quartiles were 5.2 (1.4 to 8.9), 2.8 (0.7 to 4.8), and 2.4 (−0.4 to 5.2) mmHg for SBP, DBP, and pulse pressure, respectively. The multivariable adjusted odds ratio (95% CI) for the presence of hypertension comparing the highest to the lowest selenium quartile was 1.52 (0.98 to 2.36; P trend = 0.004; Table 4). When serum selenium was used as a continuous parameter in the multivariable model, an increase from the 25th to the 75th percentiles in the serum selenium distribution was associated with a 43% increase in the odds of hypertension (95% CI 12 to 83%).

In spline regression models, the prevalence of hypertension increased with increasing selenium concentrations throughout the whole range of measured selenium concentrations (Fig. 1). Furthermore, the nonlinear spline terms were not statistically significant, indicating that the relation between serum selenium concentrations and blood pressure could be represented by a linear term.

In subgroup analyses, we identified a strong interaction between selenium and sex on blood pressure levels and hypertension risk (Fig. 2). In women, an increase from the 25th to the 75th percentiles of the serum selenium distribution was associated with statistically significant increases of 6.7, 3.0, and 3.7 mmHg in SBP and DBP and pulse pressure, respectively, whereas the association in men was small and not statistically significant (Table 3).

TABLE 1. Characteristics of study population by hypertension status

Characteristic	All participants	No hypertension	Hypertension	*P* value*
n	792	412	380	
Male sex	362 (45.7)	184 (44.7)	178 (46.8)	0.57
Age (years)				
All	53.2 (13.5)	50.2 (13.6)	56.5 (12.6)	<0.001
Male	51.0 (12.5)	50.0 (13.0)	52.0 (11.9)	0.13
Female	55.1 (14.0)	50.4 (14.1)	60.5 (11.8)	<0.001
BMI (kg/m^2)				
All	26.3 (4.1)	25.5 (4.0)	27.2 (3.9)	<0.001
Male	26.9 (3.5)	26.1 (3.4)	27.6 (3.4)	<0.001
Female	25.9 (4.4)	25.0 (4.4)	26.8 (4.3)	<0.001
Serum selenium (μg/l)†				
All	68.2 (31.5)	64.0 (29.9)	72.8 (32.5)	<0.001
Male	60.4 (28.7)	60.1 (25.7)	60.7 (31.5)	0.85
Female	74.8 (32.3)	67.2 (32.7)	83.4 (29.6)	<0.001
SBP (mmHg)				
All	133.8 (19.5)	119.7 (9.9)	148.9 (15.6)	–
Male	133.3 (16.3)	121.9 (8.7)	145.2 (13.5)	–
Female	134.1 (21.9)	118.0 (10.4)	152.2 (16.6)	–
DBP (mmHg)				
All	81.9 (10.5)	75.5 (7.1)	88.9 (9.0)	–
Male	83.2 (9.7)	77.4 (6.5)	89.3 (8.8)	–
Female	80.8 (10.9)	74.0 (7.3)	88.6 (9.1)	–
Pulse pressure (mmHg)				
All	51.8 (14.5)	44.2 (8.7)	60.0 (15.1)	–
Male	50.1 (12.7)	44.5 (8.5)	55.9 (13.6)	–
Female	53.3 (15.7)	44.0 (8.8)	63.7 (15.3)	–

Values are means (SD) for continuous or *n* (%) for categorical variables, respectively.
BP, blood pressure.
*Comparisons of hypertensive vs. nonhypertensive participants were made using *t*-tests or Fisher's exact tests, when appropriate.
†To convert μg/l of selenium to μmol/l divide by 79.

TABLE 2. Characteristics of study population by serum selenium quartile

Characteristic	Quartile of serum selenium				
	First	Second	Third	Fourth	*P* trend*
n	198	198	198	198	–
Serum selenium (μg/l)					
Range	1.2–42.8	>42.8–65.0	>65.0–91.9	>91.9–167.0	–
Mean	31.2	52.3	79.4	110.0	–
Sex, % male	61.6	53.0	39.9	28.3	<0.001
Age (years)					
All	48.9	51.6	55.3	57.1	<0.001
Male	48.5	49.7	53.4	55.3	<0.001
Female	49.4	53.7	56.6	57.9	<0.001
BMI (kg/m^2)					
All	26.2	26.4	26.6	26.0	0.92
Male	26.9	26.6	27.3	26.7	0.73
Female	25.1	26.3	26.1	25.8	0.54
SBP (mmHg)					
All	130.8	131.2	134.5	138.6	<0.001
Male	132.8	131.6	134.8	135.7	0.16
Female	127.5	130.7	134.3	139.7	<0.001
DBP (mmHg)					
All	80.4	81.5	82.8	83.1	0.001
Male	82.4	83.7	83.4	83.8	0.49
Female	77.2	78.9	82.4	82.8	<0.001
Pulse pressure (mmHg)					
All	50.4	49.7	51.7	55.5	<0.001
Male	50.4	47.9	51.3	51.9	0.20
Female	50.3	51.8	51.9	56.9	<0.001
Hypertension (%)					
All	46.0	39.4	47.0	59.6	<0.001
Male	55.7	39.1	44.3	60.7	0.85
Female	30.3	39.8	48.7	59.2	<0.001

Values are means for continuous data or % for categorical data, unless otherwise indicated.
BP, blood pressure.
**P* values for trend are derived from linear or logistic regression models in which serum selenium concentrations are introduced as continuous linear terms.

Similarly, an increase from the 25th to the 75th percentiles of the serum selenium distribution was associated with a 2.06 odds ratio for hypertension in women but was not associated with an increased risk of hypertension in men (Table 4). Finally, the association of serum selenium with blood pressure or hypertension was similar in subgroups defined by age or BMI (Fig. 2).

DISCUSSION

In these selected individuals from a cross-sectional study of a German population with low selenium levels, we found a significant association of serum selenium concentrations with blood pressure levels and with the prevalence of hypertension. Compared to the lowest quartile, participants

TABLE 3. Adjusted average differences (95% CIs) in blood pressure levels by serum selenium status

	Quartile of serum selenium					75th vs. 25th percentiles‡ of serum selenium
	First	Second	Third	Fourth	*P* trend	
SBP (mmHg)						
All*	0.0 (reference)	−0.8 (−4.4–2.7)	0.9 (−2.7–4.5)	5.2 (1.4–8.9)	<0.001	4.2 (2.2–6.3)
Male†	0.0 (reference)	−1.2 (−5.9–3.5)	−0.3 (−5.4–4.8)	0.6 (−5.1–6.3)	0.73	0.6 (−2.6–3.7)
Female†	0.0 (reference)	0.2 (−5.3–5.7)	2.7 (−2.5–8.0)	8.3 (3.2–13.4)	<0.001	6.7 (4.1–9.3)
DBP (mmHg)						
All*	0.0 (reference)	0.9 (−1.1–2.8)	2.0 (0.0–4.0)	2.8 (0.7–4.8)	0.001	1.8 (0.7–3.0)
Male†	0.0 (reference)	1.4 (−1.2–4.0)	0.2 (−2.6–3.0)	0.7 (−2.4–3.9)	0.92	0.1 (−1.7–1.8)
Female†	0.0 (reference)	0.5 (−2.5–3.5)	3.6 (0.8–6.5)	4.2 (1.4–7.0)	<0.001	3.0 (1.6–4.5)
Pulse pressure (mmHg)						
All*	0.0 (reference)	−1.7 (−4.4–1.1)	−1.1 (−3.8–1.7)	2.4 (−0.4–5.2)	0.003	2.4 (0.8–3.9)
Male†	0.0 (reference)	−2.6 (−6.2–1.0)	−0.5 (−4.4–3.4)	−0.1 (−4.5–4.3)	0.71	0.5 (−2.0–2.9)
Female†	0.0 (reference)	−0.3 (−4.5–3.9)	−0.9 (−4.9–3.1)	4.1 (0.2–8.0)	<0.001	3.7 (1.6–5.7)

BP, blood pressure.
*Linear regression models adjusted for sex, age, BMI, and hormone use.
†Linear regression models including interaction terms for selenium and sex, adjusted for age, BMI, and hormone use.
‡Average difference in blood pressure between the 75th and 25th percentiles of the serum selenium distribution in the overall population (corresponding to 92.0 and 42.8 μg/l of serum selenium, respectively), assuming a linear relationship between serum selenium and blood pressure.

TABLE 4. Adjusted odds ratios (95% CIs) for hypertension by serum selenium status

	Quartile of serum selenium					75th vs. 25th percentiles[‡] of serum selenium
	First	Second	Third	Fourth	*P* trend	
Male[†]	1.00 (reference)	0.48 (0.28–0.84)	0.49 (0.27–0.90)	0.99 (0.51–1.94)	0.58	0.90 (0.62–1.30)
Female[†]	1.00 (reference)	1.26 (0.64–2.49)	1.72 (0.90–3.30)	2.74 (1.45–5.15)	<0.001	2.06 (1.47–2.88)

BP, blood pressure.
[*]Logistic regression models adjusted for sex, age, BMI, and hormone use.
[†]Logistic regression models including interaction terms for selenium and sex, adjusted for age, BMI, and hormone use.
[‡]Odds ratios for hypertension comparing the 75th and 25th percentiles of the serum selenium distribution in the overall population (corresponding to 92.0 and 42.8 μg/l of serum selenium, respectively), assuming a linear relationship between serum selenium and blood pressure.

in the highest selenium quartile had increased SBP, DBP and pulse pressure by 5.1, 2.7 and 2.4 mmHg, respectively. These differences are clinically highly relevant since even 1–2 mmHg decreases in SBP and/or DBP have been associated with decreased cardiovascular risk in population studies [10,20]. Mean selenium concentrations in our study (68 ± 31 μg/l) were similar to those reported previously for German participants [14,15] and below levels required for full activation of plasma glutathione peroxidase (70–90 μg/l) [20].

Our results are in agreement to and expand those of Laclaustra *et al.* [4] who showed an association with selenium concentrations with higher prevalence of hypertension in the USA, a population with high serum selenium concentrations (mean concentration 137 μg/l). We show that this association is present also in individuals with much

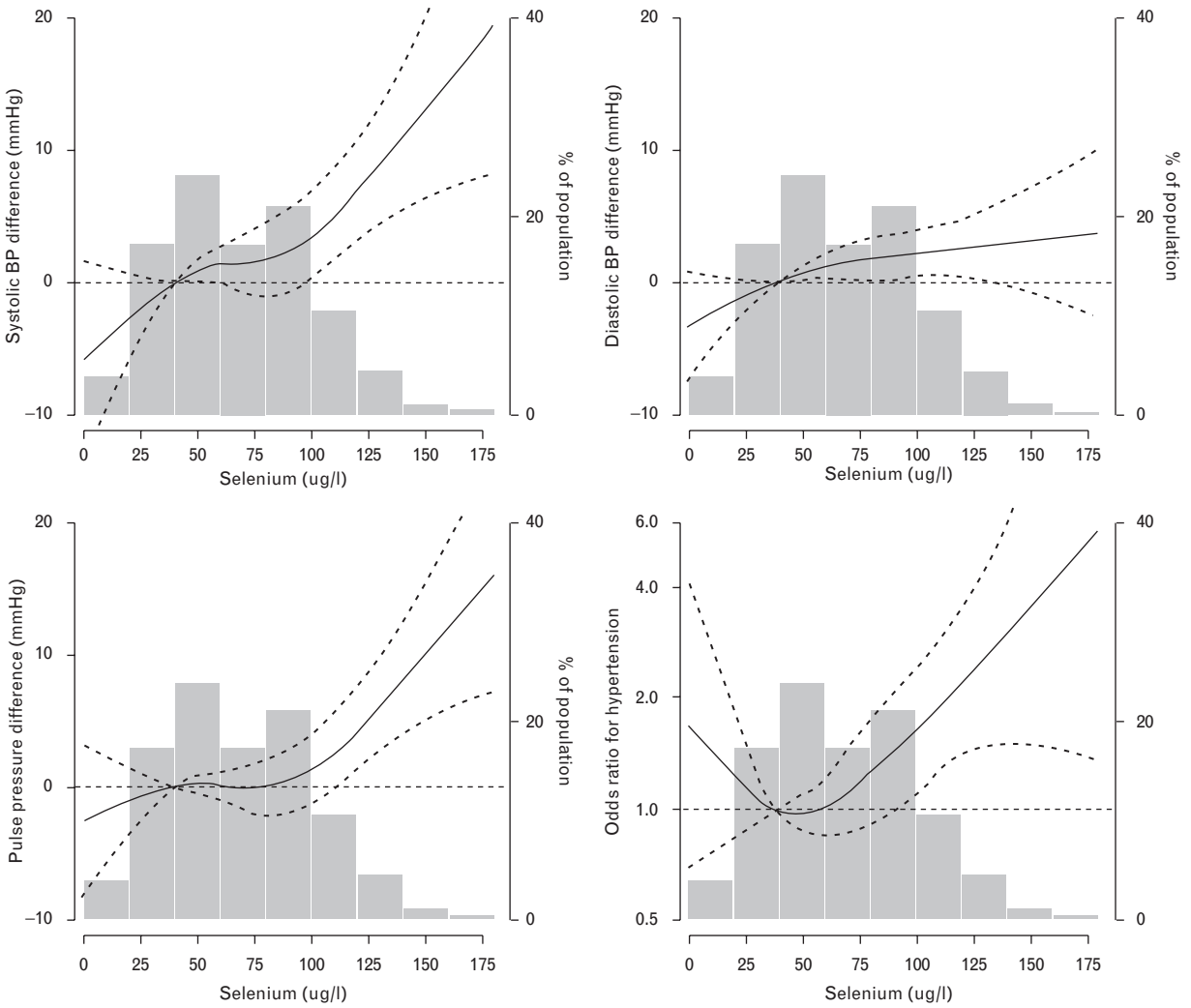

FIGURE 1 Adjusted differences in blood pressure levels and odds ratios for hypertension by serum selenium concentrations. Serum selenium was modeled as restricted quadratic splines with nodes at the 5th, 50th, and 95th percentiles. Multivariable linear regression models (for SBP and DBP and pulse pressure levels) and logistic regression models (for hypertension) were adjusted for sex, age (continuous), BMI (continuous), and hormone replacement status (yes, no). Blood pressure levels at the 20th percentile (39.1 μg/l) of the serum selenium distribution were used as reference. The dashed lines represent the 95% confidence intervals. The histograms show the distribution of selenium concentrations in the study population.

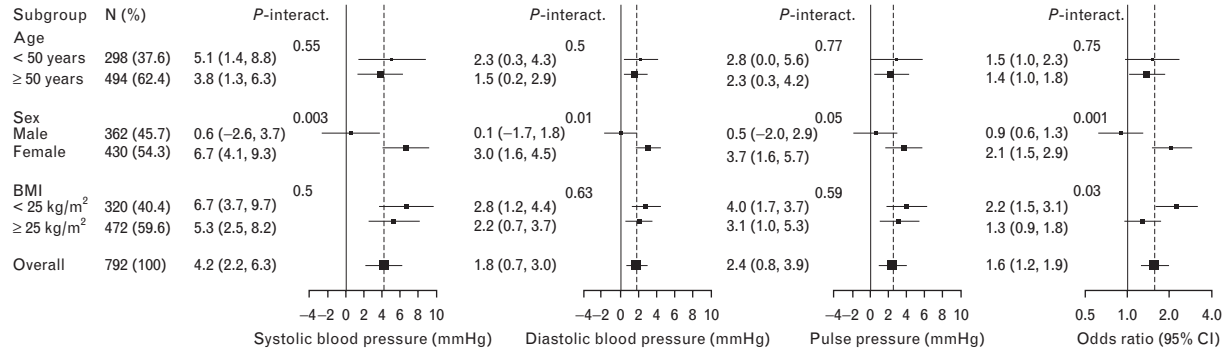

FIGURE 2 Adjusted differences in blood pressure levels and odds ratios for hypertension comparing the 75th to the 25th percentiles of the serum selenium distribution (corresponding to 92.0 and 42.8 μg/l of selenium, respectively) in selected population subgroups. Odds ratios were adjusted for other variables in the Figure. The squares are centered at the point estimates and their surface represents the inverse of the variance of the point estimates. The horizontal lines represent the 95% confidence intervals.

lower baseline selenium. Previous studies in European countries, all with mean selenium concentrations of less than 100 μg/l, have produced conflicting results. Salonen *et al.* [8] found an inverse association between serum selenium and SBP in 722 men participating in the Kuopio Ischemic Heart Disease Risk Factor Study. In the Flemish Study on Environment Genes and Health Outcomes (FLEMENGHO), higher blood selenium concentrations were associated with lower SBP and DBP at baseline and with a lower risk of hypertension over 5.2 years of follow-up among men, but not among women [5]. However, no relationship was found between serum selenium concentrations and blood pressure levels in another study conducted in Finland in 1100 elderly men [9], in a cross-sectional analysis of the Olivetti Heart Study among 364 southern Italian men [10], or in a French population [11]. Possible reasons for the inconsistent findings are differences in study designs (e.g. cross-sectional vs. longitudinal), potential variations in the intake of other antioxidants (e.g. vitamins C and E), diabetes and smoking status, medication use, different age and sex distribution, and differences in the population selection. For example, the population in a study that found no association between selenium levels and blood pressure [9] consisted of survivors of a cohort sampled 15 years earlier and was thus no longer representative of the population.

No data are available on the effect of selenium supplementation on blood pressure endpoints in randomized controlled trials using single selenium supplements. A mixed antioxidant supplement (selenium 50 μg/day, vitamin E 60 mg/day and β-carotene 15 mg/day) was associated with isolated diastolic hypertension in a randomized study of 29 584 Chinese participants [21]. In the HDL-Atherosclerosis Treatment Study, selenium 100 μg/day given along with vitamin C 1000 mg/day, vitamin E 800 IU/day and β-carotene 25 mg/day had no effect on blood pressure levels during 3 years of follow-up [22].

Our findings are in line with a number of studies that have found associations between high selenium concentrations and elevated lipid levels [10,23] and diabetes [24], at least in countries with moderate (10–50%) or low (<10%) prevalence of low selenium status. Furthermore, selenium supplementation increased the risk of incident diabetes in the Nutritional Prevention of Cancer trial [25], and the Selenium and vitamin E Cancer Prevention Trial was stopped prematurely because of lack of benefit and safety issues including a nonsignificant increase in type 2 diabetes in the group receiving selenium-only supplements [26]. On the contrary, the Prevention of Cancer by Intervention with Selenium pilot study, a randomized clinical trial conducted in the UK, found that selenium supplementation had a small beneficial effect on lipid levels after 6 months of follow-up [27]. Additional evidence from observational studies and randomized clinical trials is needed to establish the effects of selenium supplementation on cardiovascular and metabolic risk factors across populations with different levels of selenium status.

Sex differences in selenium-associated health effects have been previously reported. Arnaud *et al.* [28] found that selenium concentrations were positively associated with higher odds of the metabolic syndrome in women but not in men. Moreover, Combs *et al.* [29] found that selenium supplementation increased triiodothyronine (T3) concentrations in men but not in women. Several factors may contribute to the selenium–sex interaction, such as dyslipidemia, impaired fasting glucose [30], alcohol consumption [31], obesity [32], and sex hormones [32]. In post-hoc analyses of the present study we found a highly significant interaction between sex and serum selenium concentrations on blood pressure endpoints. We also found higher selenium concentrations in women compared to men, a phenomenon that has been observed in some [33,34], but not in most studies investigating sex differences in selenium concentrations [11,30,35–39]. Since our interaction analyses were performed *post hoc*, they have an increased risk of type I error and need to be interpreted with caution. In addition, biosynthesis of selenoenzymes and selenoprotein displays sex-specific differences in a dose-dependent manner [5]. Moreover, it has been reported that a variation in the selenoprotein S 1 gene locus contributes to cardiovascular risk only in women [40]. In general, the sexual dimorphism of various selenium effects has been widely documented [41]. Although the exact molecular mechanisms for the sexual dimorphic nature of the association of selenium status and blood pressure remains to be elucidated, sex-specific differences in selenoprotein biosynthesis may play an important role [41]. Future analyses of selenium and cardiovascular risk factors should carefully evaluate sex differences to confirm the interactions that we observed in the present study.

The mechanisms through which selenium may be associated with hypertension or other cardiovascular risk factors remain unclear. Selenium is incorporated into various selenoproteins such as glutathione proxidase, thioredoxin reductase, iodothyronine deiodinase and selenoprotein P, and through those it is involved in many biological functions, such as protection against oxidative stress and immune and thyroid functions [7]. One possible mechanism may be involving the generation of reactive oxygen species (ROS), since some selenium compounds can act as a pro-oxidant [42] and since ROS have been associated with the pathogenesis of hypertension [43]. More than 25 selenoproteins have been identified so far in humans, many of them of unknown function. We can speculate that since some selenium compounds, such as the inorganic selenite, induce oxidative stress, they may thus potentially increase blood pressure levels starting even at low (total) selenium levels. Both inorganic and organic forms of selenium are utilized as nutritional and supplemental selenium sources, and in multivitamin preparations and weight-loss products sodium selenite is predominantly used. The main nutritional form of selenium, selenomethionine, whereas not an oxidizing agent, can produce metabolites with strong oxidant potential, therefore causing a graded relationship with increasing blood pressure even in populations with overall low selenium levels. In our study we did not have information on the activity of glutathione peroxidase or other selenoproteins. Future studies will need to assess not only total selenium but also selenoprotein activity to better understand the association between selenium and risk factors.

Other limitations of our study include the cross-sectional design, the lack of data on vitamin/mineral supplement use, and on dietary sources of selenium that could confound the observed associations. An additional limitation was the use of office-based one-point blood pressure measurements that may limit the accuracy of the blood pressure phenotype. However, one single blood pressure measurement has been clearly shown to predict cardiovascular risk [44], and this type of measurement error likely resulted in an underestimation of the association between selenium and blood pressure in our data.

Our study also had several strengths, including the use of a uniquely homogenous population since we excluded participants with conditions that influence serum selenium, such as smoking or diabetes. Moreover, we further excluded participants using antihypertensive medications, as well as those with known atherosclerotic disease, since atherosclerotic disease is an inflammatory state that may induce an acute-phase response proportional to its severity with corresponding decreases in selenium concentrations [3]. The applicability of the results on the population level is, however, limited by this approach.

The role of selenium on the development or prevention of cardiovascular risk factors and clinical cardiovascular disease remains controversial [45–47]. In our study, serum selenium concentrations were associated with higher prevalence of hypertension in a selenium-depleted population. The differences of more than 5 mmHg between the highest and lowest quartiles for SBP may be associated with an increased number of cardiovascular events. Our results complement previous studies which showed an association of selenium concentrations with blood pressure levels and hypertension in a selenium-replete population [4]. Considering the widespread supplement use and the potential effects of selenium on blood pressure, lipids and glycemia, randomized trials of selenium supplementation are needed to establish the effect of selenium intake on cardiometabolic risk factors.

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Conflicts of interest

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Reviewer's Summary Evaluation

Referee 1

Strengths: Well conducted and well analyzed study showing that even in population with very low selenium levels there was a graded increase in blood pressure with increasing levels of selenium, consistent with reports in other population with much higher levels.

Weaknesses: The participants were not truly representative of the German population since a more homogeneous subgroup from the LIANCO survey were selected for this "physiological" study.

A more robust relationship between selenium levels and blood pressure levels in important subgroups (e.g. men) could not be demonstrated, likely due to the relatively small sample size for this type of study.