Title: Blood pressure levels and hypertension prevalence in a high selenium environment: results from a cross-sectional study

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Abstract:

Background and Aims. Recent human and laboratory studies have suggested the possibility that selenium overexposure may increase blood pressure. We sought to ascertain whether adults living in a seleniferous area exhibit an association between selenium exposure and both blood pressure levels as well as prevalence of hypertension.

Methods and Results. We measured selenium levels in blood (serum), hair and nail samples obtained from 680 adult volunteers (267 men and 413 women), living in seven Punjabi villages in a seleniferous area and related them to health outcomes, including systolic and diastolic blood pressure and presence of hypertension. In a multivariable restricted cubic spline regression model, adjusted for age, sex and history of hypertension, we found a positive association between systolic blood pressure and both serum (P=0.004) and hair (P=0.058) selenium levels, but not with nail selenium content. Little association emerged between the three selenium biomarkers and diastolic blood pressure. Hypertension prevalence was positively associated with the three exposure indicators (P<0.001). The associations we found were generally stronger in women than in men.

Conclusions. Overall, these findings suggest that chronic overexposure to environmental selenium may increase blood pressure, though there were inconsistencies for this association according to the choice of exposure indicator, the study endpoint and the sex.

Keywords: selenium; environment; cross-sectional study; prevalence; blood pressure; hypertension

Introduction

Selenium is a naturally occurring non-metal element that is both extremely toxic and nutritionally essential in very small quantities [1, 2]. The possibility that the intake of this element may influence human health has attracted considerable attention during the last years [2, 3]. However, despite a large number of experimental and nonexperimental human studies, uncertainties exist regarding the level of selenium intake that is safe for humans [2, 3]. In particular, the upper level of safety for selenium exposure is poorly defined, since in-depth assessments by regulatory authorities preceded recent publication of results from randomized trials [2-4]. The latter have shed light on the safe upper limit of selenium intake and provided results that are consistent with findings in most recent observational studies [2, 3, 5]. In addition to randomized trials [5, 6], investigations carried out in seleniferous areas have been an important source of evidence for assessment of selenium toxicity [2]. Most of the latter studies have been conducted in areas where the selenium content in soil is high. Less commonly, they have focused on persons with a high consumption of selenium from fish or drinking water [2, 3].

The situation is further complicated by the fact that the exposure thresholds as well as the diseases which may be due to selenium toxicity and selenium deficiency are only partially understood [2, 4]. Diseases related to selenium overexposure may include diabetes mellitus [7], other endocrine diseases [8], neurological disease [9-12], and hypertension [13]. In addition, the biomarkers more suitable for selenium exposure monitoring are also not entirely defined, as they may differ in terms of their ability to reflect dietary intake, long-term exposure and the elemental content in specific body parts [14-18]. Nail and hair selenium levels are generally considered to reflect longer-term exposure compared with serum selenium, but their validity has been challenged since their levels may be influenced by intake of other substances such as methionine, and by the relative content of inorganic and organic selenium forms [6, 14, 17, 19, 20].

Here we report the health of a population exposed to high levels selenium in a rural area of Punjab, India, where the soil and general environment have been shown to contain an unusually high content of selenium [21-23]. Our study was focused on the recently raised hypothesis that overexposure to selenium, even at relatively low levels, may increase levels of blood pressure (BP) in humans [24-28].

Methods

Study population

This study was based on a population survey conducted in a seleniferous area of the Punjab where unusually high soil selenium content and the possible occurrence of selenosis had been reported [22]. The soil in approximately 1000 hectares of land in two districts (Hoshiarpur and Nawanshahar) has an unusually high content of selenium, with the two districts designated as being 'highly toxic' or 'moderately toxic' [29]. The project was approved by the institutional ethical committee of Christian Medical College & Hospital, Ludhiana. The survey was focused on the inhabitants of seven villages. Eligible study participants were recruited by means of public announcements and personal contact by village heads. Reasons for refusal were shyness, work-engagement and absence of an incentive. Those who agreed to participate completed a life-style and clinical information questionnaire administered by a project social worker. Blood, hair and nail samples were obtained by a physician, with the latter two being stored in a ziplock bag. Systolic and diastolic blood pressure (SBP and DBP) were measured in the sitting position by one physician for the entire study population, using a mercury sphygmomanometer. The first blood pressure reading was discarded and an average of the second and third readings was used to represent the participant's average BP.

Analytical selenium determination

Selenium content of the blood (serum), hair and nail samples was determined by atomic absorption spectrometry (AAS) after their digestion [22]. AAS equipment was a Hitachi model Z-6100 flame machine equipped with a hydride generator and an electrically heated quartz tube, which served as the selenium-specific detector. Selenium was determined under the following operating conditions: wavelength 196 nm, current of hollow cathode lamp 12 mA, slit 1.3 nm, fill time 10 seconds, inject time 15 seconds, reductant 0.3 % $NaBH_4$ in 0.05% NaOH, HCl 1 mol/L, temperature of quartz tube 900° C, sample loop 500 µL, flow rate of argon 120 mL/min, flow rate of reductant 5.3 mL/min, flow rate of HCl solution 7.3 mL/min, flow rate of waste 15 mL/min. Limits of detection were 0.03 µg/L for serum selenium content, and 0.03 µg/g for hair and nail selenium levels.

Outcome classification

We assessed SBP and DBP as continuous variables and hypertension as a dichotomous endpoint. Hypertension was defined as an average SBP ≥ 140 mmHg, and/or DBP ≥ 90 mmHg, or a participant report of a prior diagnosis of hypertension (defined as 'history of hypertension'), with or without treatment with antihypertensive medication. An alternative study outcome ("newly-diagnosed hypertension") was based on a diagnosis of hypertension made at the study visit, and therefore this subgroup did not include participants with history of hypertension.

Data analysis

We analyzed the distribution of selenium content in participant blood, hair and toenail samples. We calculated a linear regression coefficient and corresponding 95% confidence interval (CI) for relationships between selenium levels in the participant's blood, hair and toenail samples and BP, in the overall study population and in selected subgroups, using both an unadjusted and age-adjusted model. In crude and multivariable logistic regression models, we estimated the prevalence odds ratio (OR) of hypertension according to selenium exposure, using both a one standard deviation higher level of exposure or a dichotomous indicator, i.e. being above or below a specified level of selenium.

We then employed restricted cubic spline regression models to assess the relationship between increasingly higher levels of the selenium biomarkers and both SBP, DBP as well as hypertension prevalence. We used the Stata-15 software (Stata Corp. 2017, College Station, TX, USA) and specifically the 'mkspline' and the 'xblc' routines [30], that employ two postestimation commands which allow generation of a flexible model linking quantitative covariates and response variables, based on restricted cubic splines. We conducted a dose-response analysis for the two continuous variables (mean SBP and DBP) and for the dichotomous hypertension outcome, using as referent point 120 μg/L of serum selenium (in the whole population and in females) and 160 μg/L of serum selenium (in males), and 0.8 μg/g of hair selenium, and 6 μg/g of nail selenium. These referent points were selected as they were the lowest ones allowing to fit the model. Spline regression analyses for SBP and DBP were also adjusted for potential confounders or effect modifiers such as age, sex, history of hypertension, socioeconomic status and village of residence, in various multivariable models.

Results

Overall, 680 residents, 267 men and 413 women, aged >18 years volunteered to participate in the study, representing about 10% of the total eligible population. Demographic characteristics for the study participants are reported in Table 1. For most of the variables recorded, the profile for men and women was similar. The participants' overall mean age was 43 years, with <10% above 60 years. A history of hypertension was reported in 14.7%. The overall median level of serum selenium was 171.3 μg/L, with a wide interquartile range, and in all but one above 100 μg/L (Table 2). Hair and nail selenium levels had an overall median of 1.25 and 5.69 μg/g respectively. No sample was below the detection limit for either serum or hair or nail selenium content. All these biomarkers of exposure, i.e. serum, hair and nail selenium levels, were highly correlated, with corresponding Spearman correlation coefficients of 0.800 (95% CI 0.737, 0.849) for the serum-hair correlation, 0.743 (95% CI 0.663, 0.806) for the serum-nail correlation, and 0.468 (95% CI 0.401, 0.530) for the hair-nail correlation. The overall mean (± standard deviation) levels of SBP and DBP were 120.0±23.3 and 78.0±12.0 mmHg, while median levels were 118 and 80 mmHg (120 in men and 112 women for SBP, 80 in both sexes for DBP - Table 3). A total of 33.5% of the participants (34.1% among men and 33.2% among women) met the diagnosis of hypertension (current or past history).

In the entire study population and in both the crude analysis and in those adjusted for different variables, there was a slight association between levels of hair selenium and blood pressure levels, particularly SBP, while little evidence for such correlations emerged for nail and particularly serum selenium (Tables 4-5). Estimates were statistically imprecise for both hair and nail selenium. The aforementioned associations were substantially confirmed when we limited the analysis to participants without a history of hypertension. In sex-specific analyses, the associations found in the overall population were considerably stronger in women, compared with men, particularly for SBP (Tables 4-5).

We then assessed the prevalence OR of hypertension associated with 1-standard deviation increase in selenium biomarkers levels (Table 6). We observed a positive association between serum selenium and hypertension prevalence with higher ORs in women compared with men, and when newly-diagnosed hypertension was the outcome of interest (OR 1.35, 95% CI 1.00-1.83, P=0.049). Hair selenium levels also directly correlated with hypertension risk (OR for newly diagnosed hypertension=1.31, 95% CI 1.06-1.61, P=0.011), though for this

indicator of exposure the ORs show little evidence of sex-related differences, and did not substantially vary according to the outcome (hypertension versus newly-diagnosed hypertension). On the converse, little evidence of any relationship between nail selenium levels and hypertension prevalence emerged (OR for newly-diagnosed hypertension 1.09, 95% CI 0.88-1.36, P=0.416), independently of the sex and the specific outcome investigated.

When we explored the association between selenium exposure and BP using a multivariable restricted natural cubic spline regression model (Figure 1) adjusting for age, sex, and history of hypertension, a positive association between differences in mean SBP and the corresponding levels of serum and hair selenium was observed (P=0.004 and P=0.058, respectively). No such association was noted for nail selenium concentrations (P=0.230). Adding socioeconomic status score to these multivariable analyses had little effect on the estimates (Supplemental Figure S1). When DBP was the endpoint of interest, little evidence for an association with hair selenium (P=0.088) and, in particular, serum (P=0.522) and nail (P=0.520) selenium levels emerged.

The ORs for prevalence of hypertension were strongly and positively associated with all the three selenium biomarkers over almost the entire range of exposure detected in the study population (Figure 1). Similar results were noted in an unadjusted spline regression model or after adjustment only for sex and age (data not shown), and in the most adjusted model which included sex, age, and socioeconomic status (Supplemental Figure S1).

At levels lower than the referent values we chose, roughly corresponding to the 50-100 µg/L of serum selenium, the relationship between selenium biomarkers and BP or hypertension prevalence was reversed showing evidence of a J-shape curve and possibly – taking into account the lowest exposure levels – of a U-shaped curve (Figure 1). However, the range of selenium exposure showing an inverse association with blood pressure was much narrower than that showing a positive association.

In sex-specific multivariable analyses (Supplemental Figures S2-S5) adjusting for different potential confounders and effect modifiers, an association with SBP was evident only in women compared to men when serum levels of the element were chosen as the exposure biomarker, while DBP showed little association with this indicator in both sexes. A limited association between hair selenium content and BP emerged only in males. Nail selenium levels showed little association with BP levels in either sex. An increase in prevalence OR for hypertension in more exposed individuals emerged in both sexes and for all the three

biomarkers. Further adjustment for village of residence in the multivariable model did not substantially modify the aforementioned trends (data not shown).

Discussion

The possibility that selenium exposure may modify the risk of cardiovascular disease and more generally chronic disease is of considerable interest but the data are conflicting. Several nonexperimental and experimental studies conducted in Western countries have identified little evidence of an association with cardiovascular disease [31] or cancer [6], while a direct relationship has been noted for diabetes mellitus [7]. However, such association have not been systematically investigated in seleniferous environments, and this is also true for the association between selenium and BP [3], despite some evidence of a positive relationship in humans [13]. In addition, no dose-response meta-analysis on this issue exist, neither randomized controlled trials on selenium have reported on BP or hypertension [3, 5].

Epidemiologic studies with cross-sectional and cohort design have reported very conflicting results about the relation of selenium with blood pressure levels and hypertension, i.e. both positive and null and negative associations [24-27, 32, 33]. Concerning laboratory studies, some biological plausibility for a positive association between selenium and BP has been provided, possibly due to the toxic properties of both selenium and even some selenoproteins [4, 34-36]. In particular, administration of selenium in its inorganic tetravalent form (selenite) has been shown to increase BP in rats [34]. The effect was seen at relatively low levels of exposure, and only after long-term administration, thus mirroring the exposure pattern for humans living in seleniferous areas (apart from the uncertainties about the similarity of the chemical forms of selenium in the two settings), and consistently with findings from a case-control study [37]. Selenium might increase BP through its pro-oxidant effects [4, 38-40], being free-radical damage potentially involved in hypertension etiology [41], in paradoxical contrast with the antioxidant properties of selenoproteins.

The present study, which has identified a rather high prevalence of hypertension compared to what expected in a relatively young rural cohort, according to recent reports finding average prevalence in India from 15 to 35% [42-44], suggests a direct relationship between selenium exposure and BP in a high selenium environment. These results appear to confirm previous findings from cross-sectional and cohort studies, which were however

carried out in populations with much lower selenium exposure than was the case for those living in our study area [24-26, 45]. However, compared with the previous studies some difference in the shape of the association between selenium and blood pressure emerged. We were unable to replicate the observation of Laclaustra et al., who in a cross-sectional study in US adults reported a positive association between serum selenium and BP which flattened above 160 μg/L [45]. In our population, the positive association between selenium exposure and both BP levels as well as prevalence of hypertension was monotonic up to the highest levels assessed, i.e. over 1000 μg/L.

Consistent with the findings in other observational studies [46], our results suggest there may be a narrow range of exposure at the lower end of the exposure distribution (up to around 100 μg/L) for which the association between selenium and BP may be null or even inverse. However, lack of statistical precision at the lowest exposure levels did not permit exact identification of a possible U-shaped relationship between selenium and BP levels or hypertension in our study. Some evidence of a U-shaped association between selenium intake and cardiovascular disease risk has emerged from a meta-analysis based on non-experimental prospective studies [47]. In contrast, experimental human studies, i.e. randomized controlled trial, have not provided evidence of a beneficial effect of selenium supplementation, though the specific effect on blood pressure levels and hypertension risk was not tested in those studies [47].

We observed a stronger and more statistically stable association between selenium exposure and BP levels in women compared to men, although some evidence for such associations also emerged in the latter group. However, this could at least in part have been due to the larger sample size for women, which made more precise the associations we detected. Berthold et al., in one of the few studies investigating this association in subgroup analysis, also reported strong evidence of an association in women but little if any association in men [24]. In addition, the risk of hypertension associated with selenium exposure was greater in women compared with men in a study carried out within the US National Health and Nutrition Examination Survey (NHANES) [45]. Sex-specific differences in the effects of selenium on human health have also been noted for diabetes and cancer, although few trials have included women [3, 6]. If the sex differences are real, they might be due to differences in selenium metabolism, biological activity and requirements in the two sexes [48].

As is typical in nonexperimental studies, we could not rule out the possibility of systematic errors and unmeasured or residual confounding, and therefore the associations we found must be considered with caution. However, environmental and biomonitoring data collected in the study area have not suggested the occurrence of any relevant change, in addition to the increased selenium levels, of any trace element or organic contaminant in the environment and the population we investigated. The area investigated in this study is located at the foot-hills of the Himalayas, and the selenium appears to have been washed down from the rocks through rain water over a short period of time. As a consequence, the possibility of confounding between those with higher and lower exposure to selenium may be less of a concern in our study. We are also aware of an additional potential source of heterogeneity in our study, i.e. the fact that the subjects with missing values for serum selenium levels had different average hair (but not nail) selenium levels, compared with those with blood measurements available. This could at least partially explain the discrepancies between findings using different biomarkers.

In this study, we were able to assess the relationship between selenium and BP levels over a wide range of exposure, taking the opportunity to investigate this issue in a population chronically exposed to high levels of environmental selenium. The sources of selenium exposure in our population were most likely to have been vegetables, cereals and other foods (including those of animal sources) of local origin, due to the high selenium soil content [22]. However, we could not assess single chemical forms of selenium in foods, a limitation which has also affected previous studies investigating the selenium-blood pressure association as well as other health outcomes [2, 3, 8]. No information was in fact available regarding the types of selenium found in the study area soil and crops. Differences in selenium bioavailability and in both the toxicological and the nutritional properties of the organic and inorganic selenium species have been extensively highlighted [3, 4, 49]. For instance, the neurotoxic effects of selenium have been selectively associated to single selenium species, depending on the type of neurodegenerative disease [9, 18, 50].

In our study, hair selenium levels but not nail selenium content were associated with BP levels and hypertension prevalence, while the pattern for serum selenium was more inconsistent. It may be that the selenium species positively associated with BP are those not stored in nail [16], thus reducing the ability of nail selenium levels to detect any association between exposure and the aforementioned endpoint. Further weakening the ability of this

biomarker to reflect selenium exposure and therefore its reliability in epidemiologic investigation, we did not observe any increase in nail selenium content among adults who were long-term residents in a seleniferous area, while the converse was true for both serum and hair selenium concentrations.

Another potential limitation of the present study is an inadequate ascertainment of hypertension and BP levels. For instance, record-linkage to hospital discharges or other sources of administrative data to validate hypertension diagnoses or retrieve additional cases was not possible. However, attempts were made to elicit self-reported information regarding previous antihypertensive drug treatment. In addition, participants' selenium status was unknown to both study subjects and investigators during the collection of anthropometric and clinical data, including blood pressure (which was collected by only one physician for the entire study population). Thus, differential misclassification of BP and hypertensive status in relation to selenium exposure status seems an unlikely possibility. In addition, in our study participant height was not measured, thus precluding the calculation of the body mass index, a factor which may both affect BP and to some extent serum selenium [20]. Finally, we must acknowledge a major limitation of the present study, its cross-sectional design, which hinders the identification of causal associations and which suggests caution in the interpretation of study findings.

In conclusion, our results appear to add to the evidence suggesting that chronic selenium overexposure may increase BP levels. Such relationship, particularly if occurring also at low levels of selenium exposure, might be of considerable public health relevance.

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Table 1. Main characteristics of study population.

	All	N=680	Men	N=267	Women	N=413
	N	(%)	N	(%)	N	(%)
Age (year)[a]	43	(32-52)	45	(30-54)	42	(34-50)
Age categories (years)						
<30	133	(19.6)	63	(23.6)	70	(17.0)
30-39	135	(19.8)	47	(17.6)	88	(21.3)
40-49	183	(26.9)	56	(21.0)	127	(30.7)
50-59	177	(26.0)	71	(26.6)	106	(25.7)
>60	52	(7.7)	30	(11.2)	22	(5.3)
Village						
Baghauran	56	(8.2)	30	(11.2)	26	(6.3)
Barwa	158	(23.2)	57	(21.4)	101	(24.4)
Jaadli	101	(14.9)	39	(14.6)	62	(15.0)
Mehind Pur	126	(18.5)	41	(15.4)	85	(20.6)
Nazar Pur	43	(6.3)	19	(7.1)	24	(5.8)
Rakra Dhaha	55	(8.1)	20	(7.5)	35	(8.5)
Simbly	141	(20.7)	61	(22.8)	80	(19.4)
Caste						
Lower caste	413	(60.8)	157	(58.8)	256	(62.0)
Artisan	5	(0.7)	2	(0.8)	3	(0.7)
Upper caste	262	(38.5)	108	(40.4)	154	(37.3)
Occupation						
Labourer			100	(37.5)	-	
Service			30	(11.2)	-	
Business			24	(9.0)	-	
Cultivator			113	(42.3)	-	
Serving outside for money			-		20	(4.8)
Working at home			-		354	(85.7)
Not reported			-		39	(9.4)
Education						
No schooling/NR	157	(23.1)	35	(13.1)	122	(29.5)
Below Matric	269	(39.6)	100	(37.5)	169	(40.9)
Matric	149	(21.9)	73	(27.3)	76	(18.4)
Above Matric	105	(15.4)	59	(22.1)	46	(11.1)
Duration of stay (years)[a]	27	(20-40)	40	(24-52)	23	(18-30)
Weight (kg)[a]	62	(52-72)	69	(58-78)	59	(50-68)
Comorbidities						
Not in list	553	(81.3)	219	(82.0)	334	(80.8)
Diabetes	21	(3.1)	9	(3.4)	12	(2.9)
Hypertension	100	(14.7)	37	(13.9)	63	(15.3)
Tuberculosis	6	(0.9)	2	(0.7)	4	(1.0)
Total SES score[ab]	24	(21-28)	24	(21-28)	24	(21-28)
SES categories						
<20	90	(13.2)	42	(15.7)	48	(11.6)
20-24	257	(37.8)	95	(35.6)	162	(39.2)
25-29	206	(30.3)	80	(30.0)	126	(30.5)
≥30	127	(18.7)	50	(18.7)	77	(18.6)

[a]Median (interquartile range).

[b]SES (socioeconomic status) score based on: caste, education and occupation of the householder, education and occupation of householder's wife, type of family (nuclear or joint), family size, land holding and dimension (in acres), number of agricultural instruments, house type (kacha, pacca, or mixed), number of rooms, number/type of house utilities, type of water supply (hand pump or piped).

Table 2. Serum, hair and nail selenium levels (median and interquartile range, IQR) according to participants' characteristics.

	Serum (µg/L)			Hair (µg/g)			Nail (µg/g)		
	N	50th	IQR	N	50th	IQR	N	50th	IQR
All participants	238	171.30	(111.73-400.51)	521	1.25	(0.75-2.42)	513	5.69	(4.37-8.42)
Sex									
Men	107	238.91	(130.73-427.80)	187	1.46	(0.88-3.53)	182	5.86	(4.39-8.19)
Women	131	159.12	(99.29-344.33)	334	1.15	(0.73-2.19)	331	5.69	(4.26-8.50)
Age categories (years)									
<30	47	269.31	(118.20-339.40)	99	1.25	(0.86-2.56)	99	5.77	(4.44-7.66)
30-39	44	159.05	(120.44-307.57)	103	1.18	(0.72-1.99)	102	5.67	(4.76-8.14)
40-49	64	223.46	(115.51-420.03)	148	1.22	(0.78-2.79)	144	5.72	(4.32-8.42)
40-59	62	133.74	(99.16-409.05)	131	1.22	(0.69-2.25)	128	5.61	(4.07-8.92)
≥60	21	256.51	(159.87-592.33)	40	1.76	(0.89-4.20)	40	6.20	(4.24-10.24)
Village									
Baghauran	40	318.75	(277.61-371.83)	35	3.91	(2.38-5.14)	32	6.63	(5.03-8.66)
Barwa	30	541.35	(204.71-618.60)	153	1.22	(0.74-2.13)	153	7.01	(5.52-11.19)
Jaadli	3	240.40	(238.91-409.05)	80	0.82	(0.61-1.05)	80	4.91	(4.07-5.53)
Mehind pur	43	210.51	(69.84-567.50)	98	1.82	(1.18-2.76)	95	5.56	(3.90-8.73)
Nazar Pur	26	452.22	(170.20-878.40)	38	2.33	(1.15-5.48)	38	5.85	(4.49-8.42)
Rakra Dhaha	35	92.91	(85.53-100.72)	20	0.75	(0.57-1.19)	20	5.34	(4.26-6.40)
Simbly	61	133.94	(118.38-156.84)	97	1.20	(0.72-2.07)	95	5.45	(3.37-8.23)
Living in area									
<10 years	12	119.99	(70.92-184.57)	31	1.02	(0.67-1.75)	30	6.27	(5.17-9.32)
≥10 years	226	180.71	(114.73-404.47)	490	1.26	(0.78-2.50)	483	5.69	(4.27-8.42)

Table 3. Median blood pressure levels (interquartile range) and prevalence of hypertension in the study population.

	All	**N=680**	**Men**	**N=267**	**Women**	**N=413**
	N	(%)	N	(%)	N	(%)
Hypertension[a]						
Total	228	(33.5)	91	(34.1)	137	(33.2)
Anamnestic	100	(14.7)	37	(13.9)	63	(15.3)
Newly diagnosed	128	(18.8)	54	(20.2)	74	(17.9)
Systolic blood pressure[b]	118	(100-130)	120	(104-130)	112	(100-130)
Diastolic blood pressure[b]	80	(70-80)	80	(70-82)	80	(70-80)

[a]Systolic BP ≥140 mm Hg, diastolic BP≥90 mm Hg or history of hypertension.
[b]Median (interquartile range).

Table 4. Linear regression analysis of systolic blood pressure levels according to selenium biomarker levels. Results presented as coefficients (beta) with the corresponding 95% confidence interval (CI), in both unadjusted and adjusted models.

	Crude estimate			Adjusted for age (and sex in the whole group)		
	β	95% CI	*P*	β	95% CI	*P*
All participants						
Se serum (N=238)	0.008	(-0.002 to 0.018)	*0.116*	0.008	(-0.002 to 0.017)	*0.116*
Se hair (N=521)	0.776	(-0.106 to 1.659)	*0.085*	0.787	(-0.053 to 1.628)	*0.066*
Se nail (N=513)	0.386	(-0.080 to 0.852)	*0.104*	0.333	(-0.108 to 0.773)	*0.139*
Participants without history of hypertension						
Se serum (N=207)	0.007	(-0.004 to 0.018)	*0.197*	0.006	(-0.004 to 0.016)	*0.227*
Se hair (N=446)	0.737	(-0.177 to 1.651)	*0.114*	0.667	(-0.203 to 1.536)	*0.133*
Se nail (N=439)	0.234	(-0.250 to 0.719)	*0.343*	0.175	(-0.281 to 0.632)	*0.451*
Men						
Se serum (N=107)	-0.002	(-0.016 to 0.013)	*0.826*	0.000	(-0.014 to 0.014)	*0.984*
Se hair (N=187)	0.294	(-0.847 to 1.436)	*0.612*	0.498	(-0.581 to 1.577)	*0.364*
Se nail (N=182)	-0.086	(-0.954 to 0.783)	*0.846*	-0.018	(-0.838 to 0.802)	*0.965*
Men without history of hypertension						
Se serum (N=95)	-0.003	(-0.017 to 0.011)	*0.717*	-0.001	(-0.015 to 0.012)	*0.831*
Se hair (N=162)	0.264	(-0.939 to 1.468)	*0.665*	0.425	(-0.714 to 1.564)	*0.462*
Se nail (N=157)	-0.064	(-0.992 to 0.863)	*0.891*	-0.044	(-0.921 to 0.834)	*0.922*
Women						
Se serum (N=131)	0.014	(-0.000 to 0.029)	*0.052*	0.011	(-0.002 to 0.024)	*0.088*
Se hair (N=334)	1.278	(-0.054 to 2.611)	*0.060*	0.998	(-0.257 to 2.254)	*0.119*
Se nail (N=331)	0.538	(-0.024 to 1.100)	*0.061*	0.421	(-0.109 to 0.951)	*0.119*
Women without history of hypertension						
Se serum (N=112)	0.013	(-0.002 to 0.029)	*0.092*	0.009	(-0.005 to 0.023)	*0.194*
Se hair (N=284)	1.151	(-0.239 to 2.542)	*0.104*	0.850	(-0.453 to 2.154)	*0.200*
Se nail (N=282)	0.344	(-0.234 to 0.922)	*0.242*	0.227	(-0.315 to 0.770)	*0.410*

	Adjusted for age, sex and history of hypertension			Adjusted for age, sex, history of hypertension and socioeconomic status		
	β	95% CI	*P*	β	95% CI	*P*
All participants						
Se serum (N=238)	0.008	(-0.001 to 0.018)	*0.090*	0.006	(-0.003 to 0.016)	*0.209*
Se hair (N=521)	0.795	(-0.035 to 1.626)	*0.061*	0.636	(-0.190 to 1.462)	*0.131*
Se nail (N=513)	0.358	(-0.076 to 0.793)	*0.106*	0.286	(-0.147 to 0.718)	*0.195*
Participants without history of hypertension						
Se serum (N=207)				0.004	(-0.006 to 0.014)	*0.421*
Se hair (N=446)				0.508	(-0.352 to 1.369)	*0.246*
Se nail (N=439)				0.114	(-0.338 to 0.565)	*0.621*
Men						
Se serum (N=107)	0.000	(-0.013 to 0.014)	*0.955*	-0.003	(-0.017 to 0.011)	*0.688*
Se hair (N=187)	0.508	(-0.572 to 1.589)	*0.355*	0.349	(-0.746 to 1.443)	*0.531*
Se nail (N=182)	-0.000	(-0.822 to 0.822)	*1.000*	-0.048	(-0.868 to 0.771)	*0.907*
Men without history of hypertension						
Se serum (N=95)				-0.004	(-0.018 to 0.009)	*0.527*
Se hair (N=162)				0.167	(-0.983 to 1.317)	*0.774*
Se nail (N=157)				-0.083	(-0.949 to 0.783)	*0.850*
Women						
Se serum (N=131)	0.012	(-0.001 to 0.025)	*0.081*	0.010	(-0.002 to 0.023)	*0.112*
Se hair (N=334)	0.976	(-0.254 to 2.206)	*0.119*	0.883	(-0.331 to 2.096)	*0.154*
Se nail (N=331)	0.443	(-0.075 to 0.961)	*0.094*	0.357	(-0.159 to 0.873)	*0.174*
Women without history of hypertension						
Se serum (N=112)				0.008	(-0.006 to 0.022)	*0.240*
Se hair (N=284)				0.833	(-0.448 to 2.114)	*0.202*
Se nail (N=282)				0.154	(-0.383 to 0.691)	*0.573*

Table 5. Linear regression analysis of diastolic blood pressure levels according to selenium biomarker levels. Results presented as coefficients (beta) with the corresponding 95% confidence interval (CI), in both unadjusted and adjusted models.

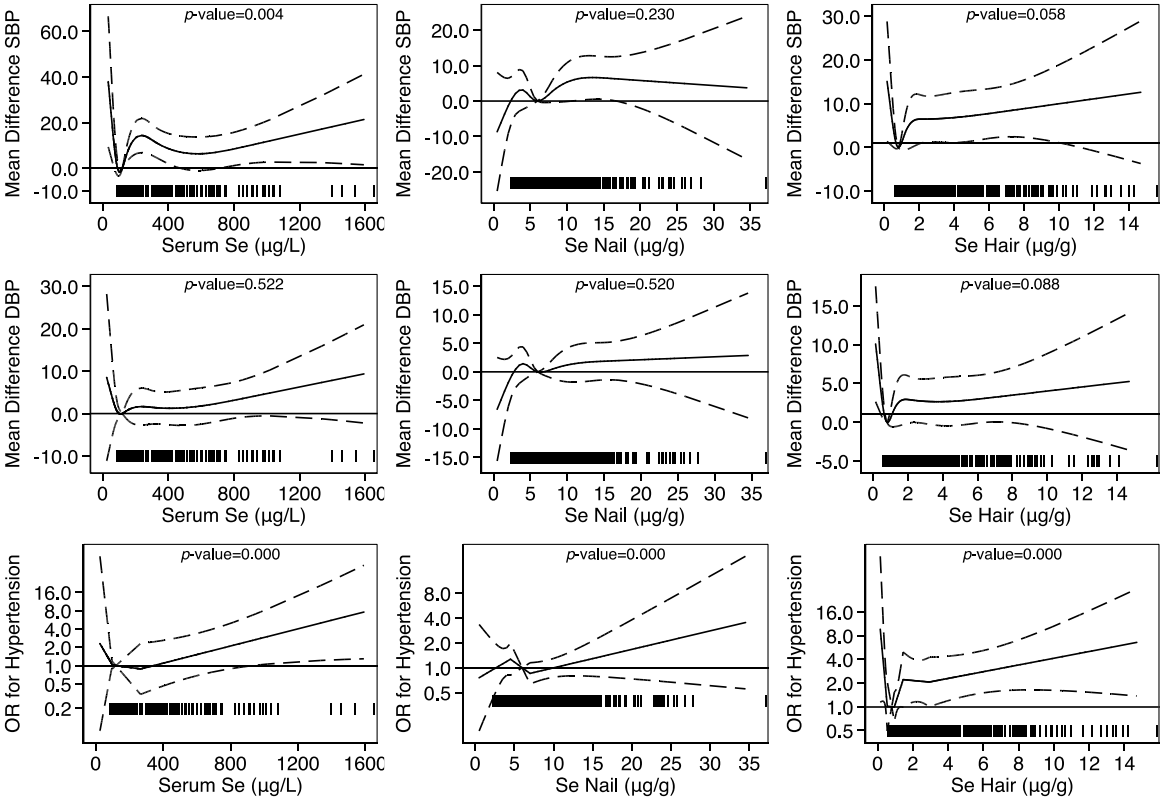
	Crude model			Adjusted for age (and sex in the whole group)		
	β	95% CI	*P*	β	95% CI	*P*
All participants						
Se serum (N=238)	0.005	(-0.001 to 0.010)	*0.104*	0.004	(-0.001 to 0.010)	*0.121*
Se hair (N=521)	0.192	(-0.265 to 0.649)	*0.409*	0.205	(-0.246 to 0.657)	*0.372*
Se nail (N=513)	0.135	(-0.106 to 0.376)	*0.272*	0.115	(-0.121 to 0.352)	*0.339*
Participants without history of hypertension						
Se serum (N=207)	0.004	(-0.002 to 0.09)	*0.158*	0.004	(-0.002 to 0.009)	*0.185*
Se hair (N=446)	0.230	(-0217 to 0.677)	*0.313*	0.214	(-0.224 to 0.653)	*0.337*
Se nail (N=439)	0.042	(-0.195 to 0.280)	*0.727*	0.019	(-0.212 to 0.250)	*0.872*
Men						
Se serum (N=107)	0.000	(-0.008 to 0.008)	*0.983*	0.000	(-0.007 to 0.008)	*0.906*
Se hair (N=187)	0.079	(-0.537 to 0.695)	*0.800*	0.153	(-0.450 to 0.755)	*0.618*
Se nail (N=182)	-0.055	(-0.520 to 0.411)	*0.817*	-0.031	(-0.487 to 0.424)	*0.893*
Men without history of hypertension						
Se serum (N=95)	0.000	(-0.008 to 0.008)	*0.983*	0.000	(-0.008 to 0.008)	*0.954*
Se hair (N=162)	0.075	(-0.555 to 0.705)	*0.815*	0.132	(-0.484 to 0.749)	*0.672*
Se nail (N=157)	-0.121	(-0.602 to 0.360)	*0.619*	-0.114	(-0.585 to 0.357)	*0.633*
Women						
Se serum (N=131)	0.007	(0.000 to 0.015)	*0.061*	0.006	(-0.001 to 0.014)	*0.092*
Se hair (N=334)	0.330	(-0.348 to 1.009)	*0.339*	0.241	(-0.424 to 0.906)	*0.477*
Se nail (N=331)	0.193	(-0.094 to 0.480)	*0.187*	0.157	(-0.125 to 0.438)	*0.275*
Women without history of hypertension						
Se serum (N=112)	0.007	(-0.001 to 0.014)	*0.093*	0.005	(-0.002 to 0.012)	*0.171*
Se hair (N=284)	0.384	(-0.274 to 1.041)	*0.252*	0.274	(-0.361 to 0.909)	*0.397*
Se nail (N=282)	0.097	(-0.179 to 0.373)	*0.491*	0.054	(-0.212 to 0.321)	*0.690*
	Adjusted for age, sex and history of hypertension			Adjusted for age, sex, history of hypertension and socioeconomic status		
	β	95% CI	*P*	β	95% CI	*P*
All participants						
Se serum (N=238)	0.004	(-0.001 to 0.009)	*0.140*	0.003	(-0.002 to 0.009)	*0.248*
Se hair (N=521)	0.207	(-0.244 to 0.658)	*0.367*	0.160	(-0.293 to 0.612)	*0.448*
Se nail (N=513)	0.121	(-0.115 to 0.358)	*0.313*	0.099	(-0.138 to 0.336)	*0.412*
Participants without history of hypertension						
Se serum (N=207)				0.003	(-0.003 to 0.008)	*0.357*
Se hair (N=446)				0.170	(-0.269 to 0.609)	*0.447*
Se nail (N=439)				0.001	(-0.230 to 0.232)	*0.994*
Men						
Se serum (N=107)	0.001	(0.007 to 0.009)	*0.869*	0.000	(-0.008 to 0.008)	*0.923*
Se hair (N=187)	0.151	(-0.453 to 0.756)	*0.622*	0.145	(-0.471 to 0.762)	*0.643*
Se nail (N=182)	-0.033	(-0.490 to 0.425)	*0.889*	-0.037	(-0.497 to 0.423)	*0.874*
Men without history of hypertension						
Se serum (N=95)				-0.001	(-0.009 to 0.007)	*0.809*
Se hair (N=162)				0.081	(-0.549 to 0.711)	*0.800*
Se nail (N=157)				-0.123	(-0.595 to 0.348)	*0.606*
Women						
Se serum (N=131)	0.006	(-0.002 to 0.013)	*0.140*	0.005	(-0.002 to 0.012)	*0.185*
Se hair (N=334)	0.234	(-0.427 to 0.896)	*0.486*	0.199	(-0.459 to 0.857)	*0.533*
Se nail (N=331)	0.162	(-0.118 to 0.443)	*0.255*	0.128	(-0.152 to 0.409)	*0.369*
Women without history of hypertension						
Se serum (N=112)				0.005	(-0.003 to 0.012)	*0.214*
Se hair (N=284)				0.268	(-0.363 to 0.899)	*0.404*
Se nail (N=282)				0.030	(-0.236 to 0.296)	*0.825*

Table 6. Prevalence odds ratio (OR) of hypertension (newly and previously diagnosed, or newly diagnosed only) associated with 1-standard deviation increase in biomarkers of selenium exposure[a].

	All subjects			Men			Women		
	OR	**(95% CI)**	***P***	**OR**	**(95% CI)**	***P***	**OR**	**(95% CI)**	***P***
Serum selenium									
Hypertension	N=238 (80/158)			N=107 (34/73)			N=131 (46/85)		
Crude model	1.13	(0.87 to 1.46)	*0.377*	1.00	(0.66 to 1.50)	*0.988*	1.23	(0.87 to 1.75)	*0.242*
Sex and age-adjusted model	1.14	(0.86 to 1.52)	*0.346*	1.05	(0.69 to 1.62)	*0.809*	1.19	(0.82 to 1.73)	*0.370*
Additionally adjusted for SES	1.09	(0.82 to 1.45)	*0.568*	0.99	(0.64 to 1.54)	*0.981*	1.14	(0.78 to 1.68)	*0.503*
Newly-diagnosed hypertension	N=207 (49/158)			N=95 (22/73)			N=112 (27/85)		
Crude model	1.33	(1.00 to 1.77)	*0.052*	1.09	(0.69 to 1.70)	*0.718*	1.54	(1.04 to 2.27)	*0.031*
Sex and age-adjusted model	1.35	(1.00 to 1.83)	*0.049*	1.14	(0.72 to 1.82)	*0.580*	1.49	(0.99 to 2.25)	*0.055*
Additionally adjusted for SES	1.28	(0.94 to 1.74)	*0.117*	1.07	(0.67 to 1.70)	*0792*	1.43	(0.94 to 2.18)	*0.092*
Hair selenium									
Hypertension	N=521 (181/340)			N=187 (65/122)			N=334 (116/218)		
Crude model	1.19	(1.00 to 1.42)	*0.048*	1.15	(0.85 to 1.54)	*0.367*	1.24	(1.00 to 1.54)	*0.055*
Sex and age-adjusted model	1.23	(1.02 to 1.49)	*0.030*	1.26	(0.92 to 1.73)	*0.153*	1.20	(0.95 to 1.51)	*0.121*
Additionally adjusted for SES	1.20	(0.99 to 1.45)	*0.064*	1.23	(0.89 to 1.70)	*0.202*	1.18	(0.93 to 1.49)	*0.185*
Newly-diagnosed hypertension	N=446 (106/340)			N=162 (40/122)			N=284 (66/218)		
Crude model	1.28	(1.05 to 1.55)	*0.014*	1.26	(0.91 to 1.73)	*0.167*	1.30	(1.01 to 1.66)	*0.039*
Sex and age-adjusted model	1.31	(1.06 to 1.61)	*0.011*	1.36	(0.97 to 1.91)	*0.079*	1.25	(0.97 to 1.63)	*0.090*
Additionally adjusted for SES	1.27	(1.03 to 1.57)	*0.025*	1.31	(0.92 to 1.84)	*0.131*	1.24	(0.05 to 1.63)	*0.115*
Nail selenium									
Hypertension	N=513 (178/335)			N=182 (64/118)			N=331 (114/217)		
Crude model	1.05	(0.88 to1.26)	*0.575*	0.97	(0.72 to 1.32)	*0.871*	1.09	(0.87 to 1.36)	*0.456*
Sex and age-adjusted moel	1.03	(0.85 to 1.25)	*0.743*	1.01	(0.74 to 1.38)	*0.949*	1.04	(0.82 to 1.31)	*0.774*
Additionally adjusted for SES	1.00	(0.83 to 1.21)	*0.994*	1.00	(0.73 to 1.37)	*0.989*	0.99	(0.77 to 1.26)	*0.927*
Newly-diagnosed hypertension	N=439 (104/335)			N=157 (39/118)			N=282 (65/217)		
Crude model	1.11	(0.90 to 1.37)	*0.312*	1.06	(0.75 to 1.51)	*0.728*	1.14	(0.88 to 1.48)	*0.320*
Sex and age-adjusted model	1.09	(0.88 to 1.36)	*0.416*	1.08	(0.76 to 1.54)	*0.654*	1.09	(0.83 to 1.43)	*0.543*
Additionally adjusted for SES	1.07	(0.85 to 1.3)	*0.574*	1.07	(0.75 to 1.53)	*0.702*	1.05	(0.79 to 1.39)	*0.744*

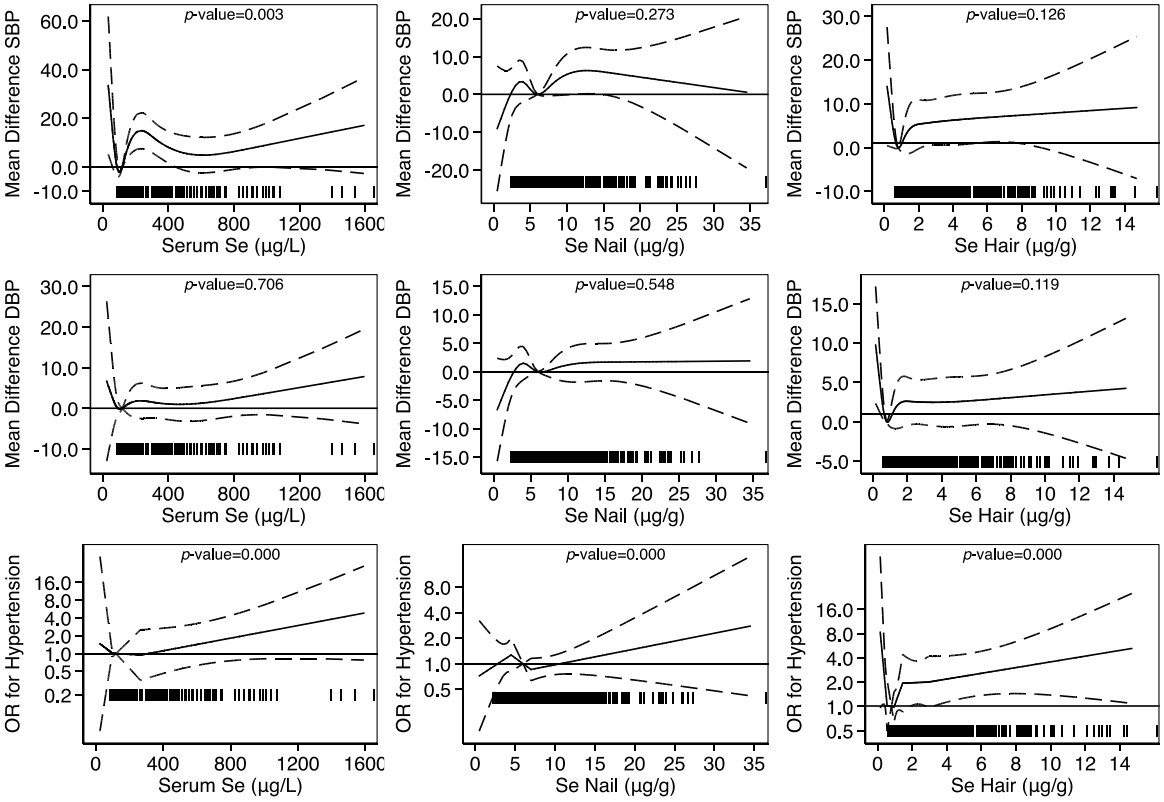
[a]Standard deviation computed for overall population and for males and females, respectively. Sex specific estimates adjusted for age only. SES: socioeconomic status

Figure 1. Restricted cubic spline regression analysis for differences in blood pressure levels and prevalence of hypertension (newly or previously diagnosed) according to selenium biomarker levels. Results presented as mean difference for systolic and diastolic blood pressure and as prevalence odds ratio of hypertension at various levels of selenium compared to those measured at 120 µg/L of serum, 6 µg/g of nail and 0.8 µg/g of hair selenium, respectively, with their 95% confidence interval (CI), in a multivariable model adjusted for age, sex, and (for SBP-DBP) history of hypertension.

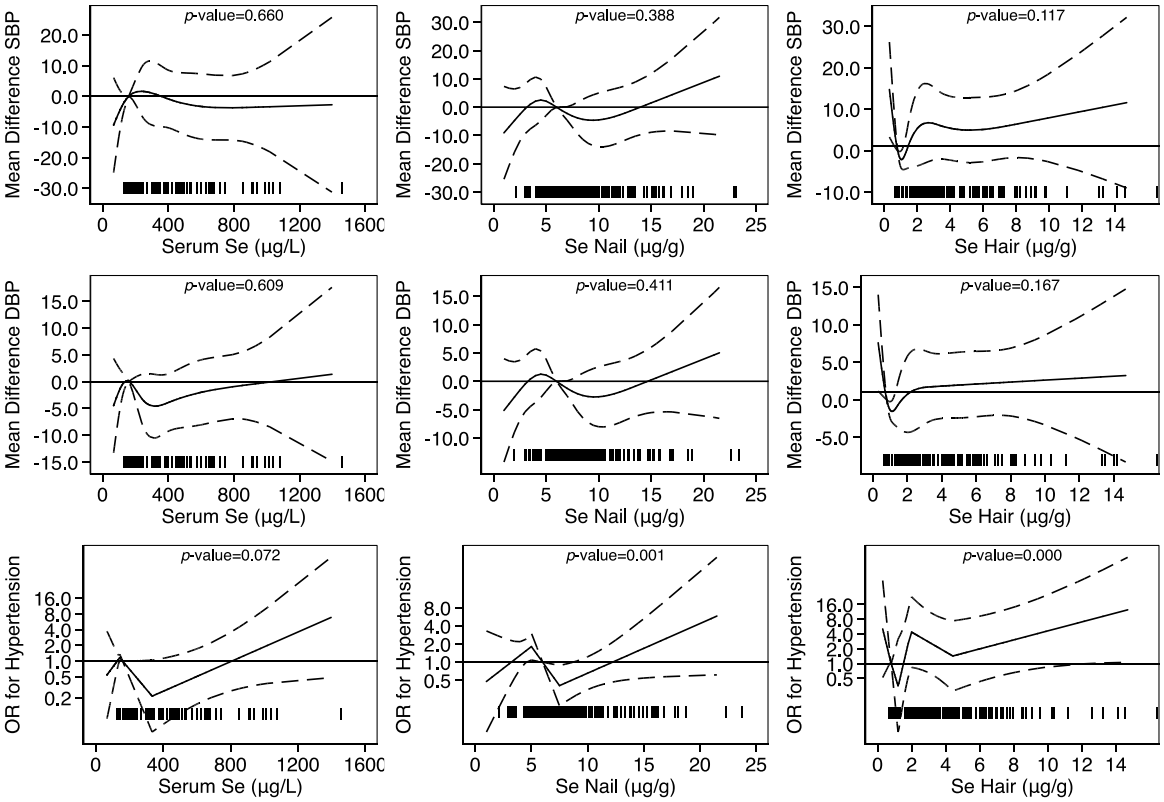


Supplemental Figures

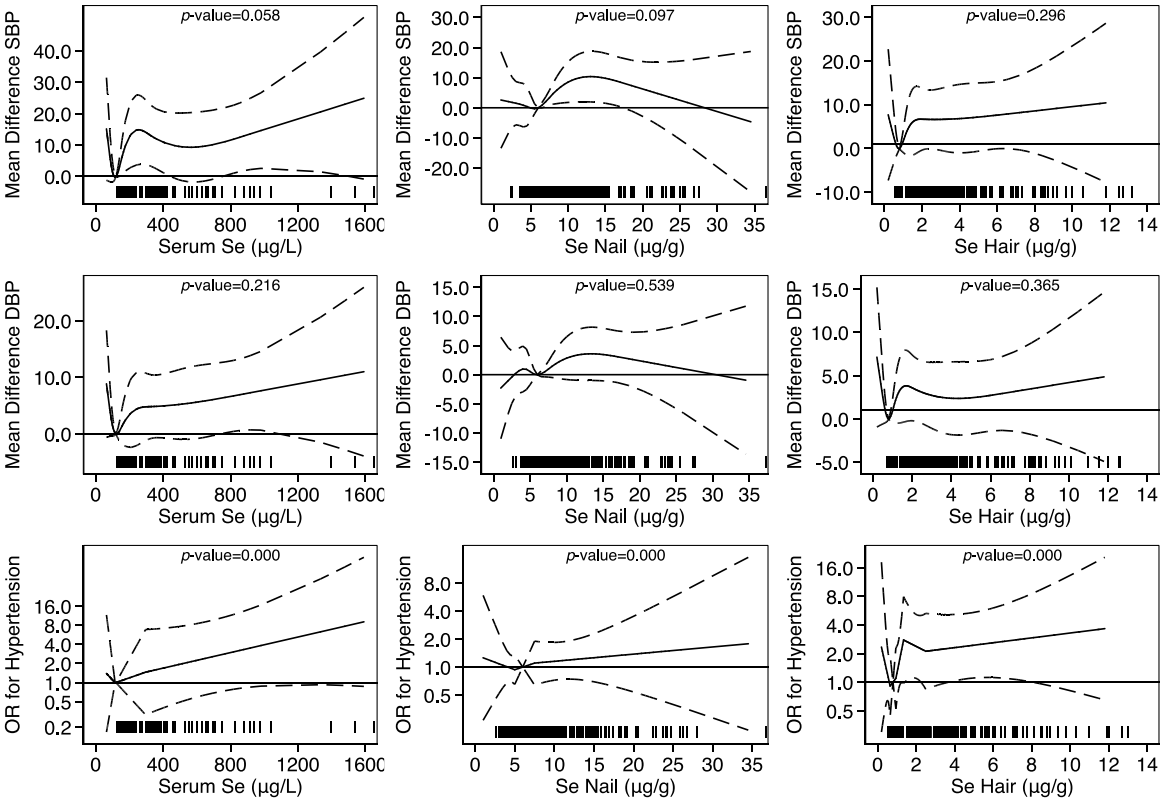
Supplemental Figure S1. Restricted cubic spline multivariable regression analysis for differences in blood pressure levels and prevalence of hypertension (newly or previously diagnosed) according to selenium biomarker levels in the study population. Results presented as mean difference for systolic and diastolic blood pressure and as prevalence odds ratio of hypertension at various levels of selenium compared to those measured at 120 µg/L of serum, 6 µg/g of nail and 0.8 µg/g of hair selenium, respectively, with their 95% confidence interval (CI), in a multivariable model adjusted for age, sex, history of hypertension (for SBP-DBP), and socioeconomic status.



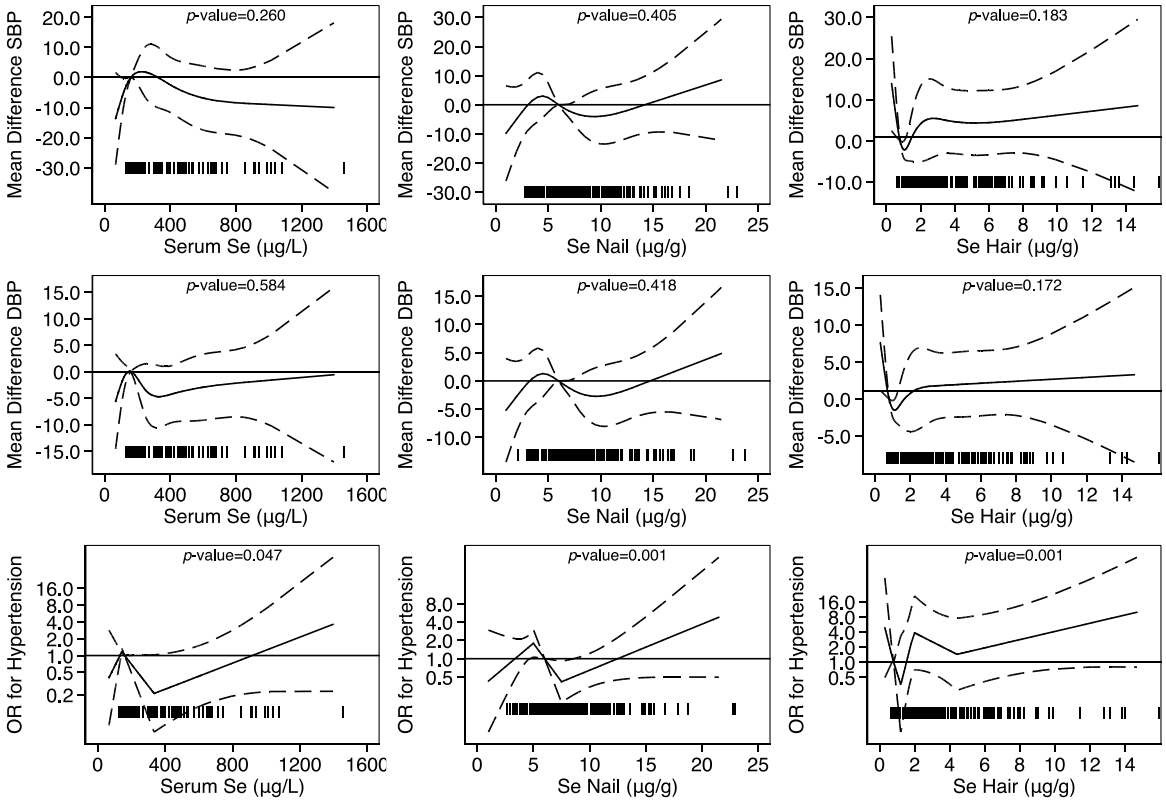
Supplemental Figure S2. Restricted cubic spline multivariable regression analysis for differences in blood pressure levels and prevalence of hypertension (newly or previously diagnosed) according to selenium biomarker levels in men. Results presented as mean difference for systolic and diastolic blood pressure and prevalence odds ratio of hypertension at various levels of selenium compared to those measured at 160 µg/L of serum, 6 µg/g of nail and 0.8 µg/g of hair selenium, respectively, with their 95% confidence interval (CI), in a multivariable model adjusted for age and history of hypertension (for SBP-DBP).



Supplemental Figure S3. Restricted cubic spline multivariable regression analysis for differences in blood pressure levels and prevalence of hypertension (newly or previously diagnosed) according to selenium biomarker levels in women. Results presented as mean difference for systolic and diastolic blood pressure and prevalence odds ratio of hypertension at various levels of selenium compared to those measured at 120 µg/L of serum, 6 µg/g of nail and 0.8 µg/g of hair selenium, respectively, with their 95% confidence interval (CI), in a multivariable model adjusted for age and for history of hypertension (for SBP-DBP).



Supplemental Figure S4. Restricted cubic spline multivariable regression analysis for differences in blood pressure levels and prevalence of hypertension (newly or previously diagnosed) according to selenium biomarker levels in men. Results presented as mean difference for systolic and diastolic blood pressure and prevalence odds ratio of hypertension at various levels of selenium compared to those measured at 160 µg/L of serum, 6 µg/g of nail and 0.8 µg/g of hair selenium, respectively, with their 95% confidence interval (CI), in a multivariable model adjusted for age, history of hypertension (for SBP-DBP), and socioeconomic status.



Supplemental Figure S5. Restricted cubic spline multivariable regression analysis for differences in blood pressure levels and prevalence of hypertension (newly or previously diagnosed) according to selenium biomarker levels in women. Results presented as mean difference for systolic and diastolic blood pressure and prevalence odds ratio of hypertension at various levels of selenium compared to those measured at 120 µg/L of serum, 6 µg/g of nail and 0.8 µg/g of hair selenium, respectively, with their 95% confidence interval (CI), in a multivariable model adjusted for age, history of hypertension (for SBP-DBP), and socioeconomic status.