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Blood pressure and blood selenium: a cross-sectional and longitudinal population study

Tim S. Nawrot[1], Jan A. Staessen[1]*, Harry A. Roels[2], Elly Den Hond[1], Lutgarde Thijs[1], Robert H. Fagard[1], Anna F. Dominiczak[3], and Harry A. Struijker-Boudier[4]

[1] *Studies Coordinating Centre, Laboratory of Hypertension, Division of Hypertension and Cardiovascular Rehabilitation, Department of Cardiovascular Diseases, Campus Gasthuisberg, University of Leuven, Herestraat 49, Box 702, B-3000 Leuven, Belgium;* [2] *Unité de Toxicologie Industrielle et de Médecine du Travail, Université catholique de Louvain, Bruxelles, Belgium;* [3] *British Heart Foundation Blood Pressure Group, Department of Medicine and Therapeutics, University of Glasgow, Glasgow, United Kingdom; and* [4] *Department of Pharmacology, Cardiovascular Research Institute, University of Maastricht, Maastricht, The Netherlands*

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Aims Western Europeans have low blood levels of selenium (BSe), an antioxidant trace element. In a Flemish population, we investigated the cross-sectional and longitudinal association of blood pressure (BP) with BSe.

Methods and results We randomly recruited 710 subjects (mean age 48.8 years; 51.8% women). We measured BP and BSe and kept participants in follow-up for BP. At baseline, systolic/diastolic BP averaged (SD) 130/77 (17.3/9.2) mmHg. BSe was 97.0 (19.0) μg/L. Of 385 participants with normal baseline BP (<130 and <85 mmHg), over 5.2 years (range 3.4–8.4 years), 139 developed high-normal BP (130–139/85–90 mmHg) or hypertension (≥140/90 mmHg). In multivariate-adjusted cross-sectional analyses of men, a 20 μg/L (∼1 SD) higher BSe was associated with lower BP with effect sizes of 2.2 mmHg systolic (95% CI −0.57 to −5.05; $P = 0.009$) and 1.5 mmHg diastolic (95% CI −0.56 to −2.44; $P = 0.017$). In prospective analyses of men, a 20 μg/L higher baseline BSe was associated with a 37% (95% CI −52 to −17; $P = 0.001$) lower risk of developing high-normal BP or hypertension. None of these associations was significant in women.

Conclusion Deficiency of selenium might be an underestimated risk factor for the development of high BP in European men.

Introduction

The essential trace mineral selenium is of great importance to human health.[1–4] Taken up from the soil, selenium enters the food chain. Animal protein is the main source of dietary selenium, accounting for 66% of the total selenium intake in Western Europe.[5] In many parts of the world, including Western Europe, the concentration of selenium in the soil is <0.5 p.p.m., so the risk of selenium deficiency and the associated detrimental health effects are considerable.

Selenium-dependent enzymes, such as glutathione peroxidase, maintain nitric oxide in its reduced form and protect against oxidative stress. Via this mechanism, selenium deficiency might predispose to cardiovascular disease.[1,3,4] However, the scientific evidence linking cardiovascular disorders to selenium depletion remains equivocal, because most studies including all those focusing on hypertension were cross-sectional or had a case–control design, or because the published reports included only men.[6–8] Some studies in humans showed association between hypertension and oxidative stress,[9,10] or between blood pressure (BP), arterial stiffness, and intake of vitamin C.[11] However, to our knowledge, no prospective population-based study or clinical trial ever investigated the relation between BP and the blood selenium (BSe) concentration. In the framework of the Flemish Study on Environment Genes and Health Outcomes (FLEMENGHO),[12] we therefore assessed both cross-sectionally and longitudinally whether, in a random population sample, BP and the incidence of high-normal BP and hypertension were associated with BSe while adjusting for host factors and lifestyle.

Methods

Study population and data collection

Baseline observations were collected in Belgium from 1985 to 1989.[12] In six rural districts, we identified a random population sample stratified by sex and age (20–39 years vs. 40–59 years vs. ≥60 years) with the aim to recruit equal numbers in each group. The six municipalities provided listings of all inhabitants sorted by address. Households, defined as all subjects living at

*Corresponding author. Tel: +32 16 34 7104; fax: +32 16 34 7106.
E-mail address: jan.staessen@med.kuleuven.be

the same address, were the sampling unit. We gave households consecutive numbers and we generated a random number list by use of the SAS random function. Households with a number matching the random list were invited. Household members >20 years were eligible, but they were no longer included in the cohort if the quota of a sex–age stratum had been met.

Of 1419 randomly selected subjects with a minimum age of 20 years, 1107 (78%) took part in the initial examinations. Compared with the whole sample of 1107 participants, the 312 non-responders had the same sex distribution, but were older [54 (SD 18) vs. 48 (SD 17) years; $P < 0.001$]. From 1991 to 1995, the participants were re-invited. After subjects who had died ($n = 83$) and those who were severely ill ($n = 3$) or who had moved ($n = 7$) were excluded, 1014 persons were left, of whom 823 (81%) again participated. We excluded 113 subjects from the analysis, because their BP ($n = 36$) or BSe concentration ($n = 51$) had not been measured, or because urinary volume or creatinine excretion was outside published limits ($n = 26$).[13] Thus, for the present analysis, the study group totalled 710 subjects (50% of those initially selected).

BP measurements

Five trained nurses measured the participants' sitting BP at two home visits 1–3 weeks apart and thereafter at one follow-up visit. After the subjects had rested for 5 min, the nurses measured BP (phase V diastolic) five times consecutively to the nearest 2 mmHg. Standard cuffs had a 12 × 24 cm inflatable portion, but if upper arm girth exceeded 31 cm, larger cuffs with 15 × 35 cm bladders were employed. Every three months, the nurses passed a test requiring them to read BP from a videotape featuring a falling mercury column with Korotkoff sounds (Blood Pressure Measurement, British Medical Association, London, United Kingdom). In view of the cardiovascular risk associated with high-normal BP,[14] and the high 4-year progression rates from high-normal BP (130–139/85–89 mmHg) to hypertension ($\geq$140/ $\geq$ 90 mmHg) in the present population,[15] we defined high BP as a BP equal or higher than 130 mmHg systolic or 85 mmHg diastolic, or as a condition requiring antihypertensive medications.[16]

Other measurements

We used the same questionnaire at baseline and follow-up to collect information on the participants' medical history, intake of medications, and lifestyle including smoking and drinking habits. The questionnaire also provided information on the menstrual cycle of women. Menopause was defined as continuous amenorrhoea from baseline onwards. By use of published tables,[17] the energy spent in physical activity was calculated from body weight, the time devoted to sports and work, and the type of physical activity.

At baseline, the participants collected a 24 h urine sample in a wide-neck plastic container for the measurement of sodium, potassium, and creatinine. At baseline, we also measured the BSe concentration in duplicate by graphite furnace atomic absorption spectrometry. We included internal standards in each series of study samples. A series of measurements was repeated whenever duplicate determinations of a sample differed by more than 5% or when the deviation from the internal standard exceeded 10%.

Statistical analysis

For database management and statistical analysis, we used SAS software version 8.1 (SAS Institute Inc., Cary, NC, USA). To study the possible confounding structure in our data set, we assessed in women and men separately the distributions of continuous variables (ANOVA) and the proportions of categorical variables (χ^2-statistics) across quintiles of the BSe concentration. Our statistical methods also included single and multiple linear regression.

In the cross-sectional analysis, we tested the interaction between gender and BSe for systolic BP and diastolic BP. Because these interaction terms were statistically significant, we analysed women and men separately. In a first regression step, the linear and quadratic terms of age were forced into the models. We considered covariates for the inclusion in the regression models, which are known to be associated with BP, such as age, body mass index, smoking, the 24 h urinary excretion of sodium and potassium, and in women, additionally menopausal status and the use of contraceptive pills at baseline. Furthermore, we applied sensitivity analyses, in which we further adjusted for physical activity and socio-economic class.

Using multiple Cox regression, we modelled time to high BP with the same adjustments as in the cross-sectional analyses while also accounting for the baseline BP. In Cox regression, we additionally tested whether the addition of a squared term of BSe significantly added to the prediction of high BP. We tested possible non-proportionality of survival rates by means of the PROC LIFETEST, as implemented in the SAS package. All *P*-values refer to two-sided tests.

Results

Baseline characteristics of study participants

The distribution of age (48.9 ± 15.2 vs. 48.6 ± 15.3; $P = 0.76$) and body mass index (26.2 ± 3.6 vs. 26.5 ± 5.8; $P = 0.46$) was similar in 373 women and 346 men. Smoking and use of alcohol were less frequent in women than in men; 123 women (33.0%) were current smokers and 16 women (4.3%) reported intake of alcohol. Among men, these proportions were 170 (49.1%) and 106 (30.6%), respectively. In smokers, the median tobacco use per day was 16 cigarettes (interquartile range 10–25). In drinkers, the median alcohol consumption was 20 g per day (10–50). A total of 143 women (38.3%) reported natural or surgical menopause, 47 (12.6%) used oral contraceptives, and 3 (0.8%) took hormonal replacement therapy. At baseline, the BSe concentration was lower in men than in women (94.8 ± 19.7 vs. 98.9 ± 18.2; $P = 0.0032$) and in smokers compared with non-smokers (93.7 vs. 99.1 μg/L; $P = 0.0001$). Neither in women nor in men, the BSe concentration was significantly associated with age, urinary creatinine, or alcohol intake (*Tables 1* and *2*).

Cross-sectional analysis

We noticed significant sex-by-selenium interactions for both systolic BP ($P = 0.03$) and diastolic BP ($P = 0.004$). We therefore analysed women and men separately. In men, both before (*Figure 1*) and after (*Table 3*) cumulative adjustment for age, body mass index, antihypertensive drug treatment, smoking (0,1), alcohol intake (0,1), and the 24 h urinary excretion of sodium and potassium, systolic BP and diastolic BP at baseline were inversely and independently correlated with the BSe concentration. In men, with adjustments applied as before, systolic BP at follow-up was also inversely correlated with the BSe concentration at baseline (*Table 3*). Sensitivity analyses with men on antihypertensive treatment excluded or with additional adjustments for socio-economic status and the energy spent in physical activity confirmed these associations. In women, neither before (*Figure 1*) nor after (*Table 3*) cumulative adjustment for the aforementioned covariates, as well as menopausal status and contraceptive pill use, BP was not related to BSe.

Table 1 Baseline characteristics by quintiles of BSe in women

Women ($n = 373$), BSe, μg/L	<83	83–94	94–103	103–113	>113	*P*-value for trend
Age, years	49.4 (15.6)	46.3 (16.1)	42.4 (13.8)	45.9 (14.3)	60.0 (11.5)	0.07
Systolic BP, mmHg	131.8 (21.7)	126.5 (18.5)	121.2 (15.2)	127.4 (16.7)	127.5 (18.9)	0.008
Diastolic BP, mmHg	76.9 (9.7)	75.9 (9.1)	73.2 (8.2)	76.9 (9.1)	80.7 (11.0)	0.006
Body mass index, kg/m^2	26.5 (6.2)	25.9 (5.2)	26.2 (6.2)	26.6 (6.7)	26.7 (4.5)	0.84
Menopause, *n*	34 (48.6)	29 (39.5)	21 (29.7)	30 (40.0)	29 (37.8)	0.24
Smokers, *n*	27 (37.5)	25 (32.9)	30 (40.5)	24 (32.0)	19 (25.6)	0.34
Alcohol intake, *n*	4 (5.6)	4 (5.3)	1 (1.4)	1 (1.3)	6 (7.3)	0.23
Energy expenditure, kcal/day	1954 (173–1954)	1954 (789–1954)	1791 (814–1954)	1693 (489–1954)	1954 (977–1954)	0.94
Urinary volume (L/day)	1.7 (0.7)	1.6 (0.7)	1.6 (0.7)	1.7 (0.6)	1.1 (0.7)	0.96
Potassium excretion, mmol/day	54.3 (19.5)	58.8 (18.5)	58.6 (21.1)	59.6 (18.1)	42.2 (28.0)	0.48
Sodium excretion, mmol/day	123.7 (58.0)	156.4 (62.4)	148.6 (72.8)	151.6 (63.5)	112.7 (84.9)	0.02
Urinary creatinine, mmol/day	9.3 (2.6)	10.2 (2.3)	10.3 (2.8)	10.2 (2.4)	6.3 (4.1)	0.06

Values are means (SD), medians (IQR), or *n* (%). By use of published tables, energy spent in physical activity was calculated from body weight, the time devoted to sports and work, and the type of physical activity.

Table 2 Baseline characteristics by quintiles of BSe in men

Men ($n = 346$), BSe, μg/L	<78	78–90	90–101	101–109	>109	*P*-value for trend
Age, years	47.1 (14.1)	46.2 (13.6)	43.8 (15.0)	45.9 (15.5)	46.4 (14.3)	0.69
Systolic BP, mmHg	139.2 (19.8)	131.8 (15.5)	130.3 (13.4)	132.8 (15.3)	130.7 (14.8)	0.005
Diastolic BP, mmHg	81.4 (10.5)	77.1 (8.1)	76.8 (8.2)	77.5 (9.4)	77.8 (8.1)	0.015
Body mass index, kg/m^2	26.4 (4.0)	25.6 (3.2)	25.9 (3.2)	25.7 (3.1)	25.8 (3.4)	0.66
Smokers, *n*	44 (63.8)	36 (54.6)	31 (44.3)	36 (52.9)	23 (31.5)	0.002
Alcohol intake, *n*	25 (35.8)	26 (38.9)	17 (24.4)	16 (23.7)	22 (30.0)	0.19
Energy expenditure, kcal/day	1374 (100–2665)	1379 (566–2605)	1628 (415–2752)	1302 (308–2605)	1558 (581–2606)	0.56
Urinary volume (L/day)	1.6 (0.6)	1.6 (0.5)	1.6 (0.6)	1.6 (0.6)	1.5 (0.6)	0.83
Potassium excretion, mmol/day	66.7 (24.3)	70.9 (21.3)	69.3 (26.1)	71.4 (24.5)	74.7 (22.5)	0.37
Sodium excretion, mmol/day	168.3 (78.3)	201.5 (97.3)	192.8 (106.8)	200.9 (93.3)	207.3 (86.3)	0.11
Urinary creatinine, mmol/day	15.0 (4.2)	14.8 (3.2)	15.9 (4.3)	15.0 (3.9)	15.5 (3.2)	0.45

Values are means (SD), medians (IQR), or *n* (%). By use of published tables, energy spent in physical activity was calculated from body weight, the time devoted to sports and work, and the type of physical activity.

Longitudinal analysis

Follow-up ranged from 3.4 to 8.4 years (median 5.2 years). In women, from baseline to follow-up, systolic BP tended to decrease by 0.53 ± 0.76 (±SE) mmHg ($P = 0.60$) and diastolic BP increased by 1.72 ± 0.53 mmHg ($P = 0.014$). In men, the corresponding changes averaged −2.28 ± 0.76 mmHg ($P = 0.03$) and 2.00 ± 0.44 mmHg ($P = 0.003$), respectively. Of 385 subjects with normal BP at baseline, 139 developed high-normal BP or hypertension, of whom 36 (25.8%) started receiving antihypertensive drug treatment. Thus, the overall incidence of high BP was 36 cases per 1000 person-years. In men, the risk of developing high-normal BP or hypertension was inversely and independently associated with BSe (*Table 4*). A 20 μg/L higher BSe concentration was associated with a 37% (95% CI −52 to −17; $P = 0.001$) lower risk. In women (*Table 4*), baseline selenium did not predict the incidence of high-normal BP or hypertension; the risk associated with a 20 μg higher BSe was 8% (95% CI −10 to 27; $P = 0.41$). To allow for non-linearity, we tested the quadratic term of BSe in multivariate-adjusted Cox models, which already included the linear term of BSe. However, the *P*-values for the quadratic term did not reach significance in women ($P = 0.18$) or in men ($P = 0.22$).

Because the lower selenium quintile included the highest number of smokers, we performed a sensitivity analysis with smokers excluded. A 20 μg/L higher BSe in non-smoking men was associated with a 32% (95% CI −51 to −2; $P = 0.039$) lower risk of high-normal BP or hypertension. Further sensitivity analyses revealed that baseline BP, based on the average of the five BP readings taken at the second home visit, and for additional adjustments for socio-economic class, the energy spent in physical activity, or the 24 h urinary creatinine excretion did not materially alter the reported associations. Our prospective results in men also remained consistent when patients on antihypertensive drug treatment during follow-up were excluded [risk reduction per 20 μg/L higher BSe, 46% (95% CI −37 to −21; $P = 0.001$)].

Discussion

The blood concentration of selenium, an antioxidant trace mineral, is suboptimal (<90 μg/L) in an estimated 50% of Western Europeans.[2,3] In keeping with these published data,[2,3] we found that the 95th percentile of the BSe concentration in our study was 125 μg/L, which is approximately the median of the distribution in the USA.[18]

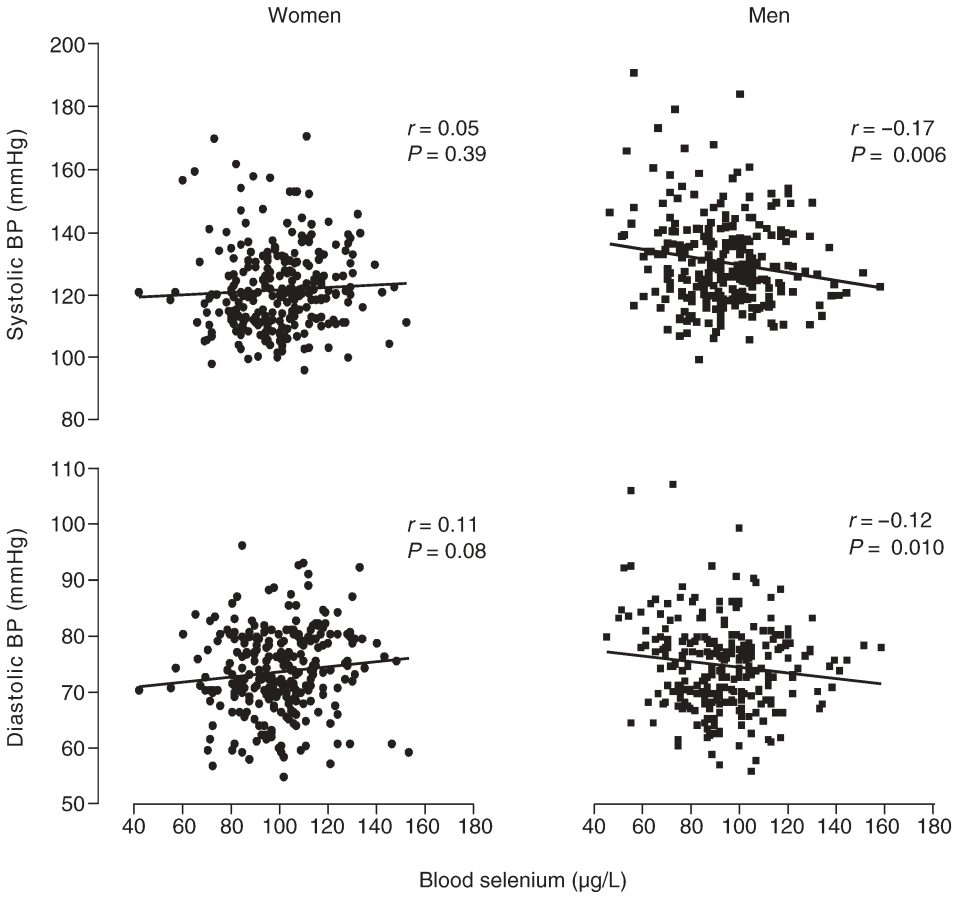

Figure 1 Cross-sectional unadjusted relation between BP and BSe. Left panels represent women and right panels men.

Table 3 Differences in BP associated with a 1 SD increase in BSe in the cross-sectional analysis

BSe (20 μg/L)	Women		Men	
	Difference (95% CI)	*P*-value	Difference (95% CI)	*P*-value
Baseline BP, mmHg				
Systolic pressure	−0.36 (−1.98 to 1.26)	0.67	−2.24 (−0.57 to −5.05)	0.0009
Diastolic pressure	0.74 (−0.18 to 1.66)	0.92	−1.50 (−0.56 to 2.44)	0.017
Follow-up BP, mmHg				
Systolic pressure	1.20 (−0.97 to 2.32)	0.28	−1.73 (−3.44 to −0.02)	0.048
Diastolic pressure	0.54 (−0.29 to 0.12)	0.13	−0.34 (−1.45 to 0.76)	0.54

Differences were adjusted for baseline covariates, including age, body mass index, smoking, 24 h urinary sodium and potassium, and in women, also menopausal status and the use of contraceptive pills. Systolic BP was also adjusted for age squared.

The key finding in our study was that in men, but not women, BP was lower by ∼2 mmHg systolic and 1 mmHg diastolic for each standard deviation increment in BSe. The risk of men developing high-normal BP or hypertension during 5.2 years of follow-up decreased by 37% for each 1 SD increment in the BSe concentration.

To our knowledge, the present results demonstrate for the first time in a prospective epidemiological context that selenium deficiency might be a risk factor for high BP in men. Virtamo *et al.*[8] did not find a relation between BP and serum selenium. However, this study population of 1100 elderly men was not representative for the whole population. A second cross-sectional study of 722 middle-aged Finnish men demonstrated a negative relation between systolic BP and serum selenium.[19] In 1991, Perry *et al.*[6] observed that the intrarenal selenium concentration was 25% lower in hypertensive patients compared with normotensive controls. Rat experiments revealed that administration of sodium selenite via drinking water suppressed the increase in BP in response to infusion of angiotensin II, which has a pro-oxidant activity.[20]

Selenium is a key component of a number functional selenoproteins required for normal health, including the antioxidant glutathione peroxidase enzyme, which prevents oxidation of lipids and phospholipids. In selenium deficiency, a build-up of hydroperoxides inhibits prostacyclin synthetase.

Table 4 Hazard ratios for developing high BP

Predictor at baseline	Hazard ratio (95% CI)	*P*-value
Women		
Age (10 years)	1.28 (1.03–1.57)	0.024
Pre-menopausal	0.83 (0.56–1.24)	0.37
Body mass index (1 kg/m^2)	1.11 (1.07–1.14)	<0.001
Smoking (0,1)	0.91 (0.65–1.28)	0.60
Systolic BP (10 mmHg)	1.31 (0.96–1.77)	0.09
Diastolic BP (5 mmHg)	1.13 (0.77–1.64)	0.55
Urinary sodium (10 mmol/L)	1.02 (1.00–1.08)	0.07
Urinary potassium (10 mmol/L)	1.04 (0.95–1.14)	0.40
BSe (20 μg/L)	1.08 (0.90–1.27)	0.41
Men		
Age (10 years)	1.55 (1.26–1.89)	<0.0001
Body mass index (1 kg/m^2)	1.03 (0.96–1.11)	0.48
Smoking (0,1)	0.80 (0.46–1.38)	0.41
Systolic BP (10 mmHg)	1.95 (1.21–3.11)	0.0065
Diastolic BP (5 mmHg)	0.90 (0.70–1.14)	0.37
Urinary sodium (10 mmol/L)	1.04 (1.00–1.08)	0.05
Urinary potassium (10 mmol/L)	0.91 (0.69–1.01)	0.08
BSe (20 μg/L)	0.63 (0.48–0.83)	0.0013

The hazard ratios are mutually adjusted. High BP includes high-normal BP (130–139/85–89 mmHg), hypertension (≥140/≥90 mmHg), or the start of antihypertensive drug treatment.

This enzyme is responsible for the production of the vasodilatory prostacyclin by the endothelium. Increased oxidative stress stimulates the production of thromboxane, which promotes vasoconstriction and platelet aggregation *in vitro*[21] and in man.[22] Adequate selenium intake therefore helps to maintain adequate nitric oxide concentrations[23] and to reduce LDL oxidation.[24] In selenium-deficient hypercholesterolaemic rats, selenium supplementation enhanced the endothelium-dependent relaxation.[25]

We observed a relation between BP and BSe in men, but not in women. This was not due to sex differences in the range of values of BP and BSe, or to differential linearity in the BP–selenium association. Gender considerably influences the metabolism of reactive oxygen species.[26–28] Indeed, estrogens exert a strong anti-oxidant activity by direct reduction of free radicals and by the stimulation of enzymes, which are crucial for free radical detoxification.[27] In experimental studies, female mitochondria compared with male produced significantly less hydrogen peroxide and had higher levels of reduced glutathione, manganese superoxide dismutase, and glutathione peroxidase.[28] Thus, the more elaborate anti-oxidative mechanisms in women might explain why we failed to observe any association between BP and BSe. Furthermore, animal and human studies revealed differences in the distribution of selenium across tissues.[29] For instance, women compared with men have higher levels of selenium in toenails, whereas their dietary selenium intake is similar.[30]

Our study should be interpreted within the context of its possible limitations. Observational studies, even if prospective and based on predefined hypotheses, do not prove causality. Indeed, we cannot exclude with certainty that the protective effect of selenium on the development of high-normal BP or hypertension might, owing to other factors, strongly associate with selenium, such as dietary protein intake. On the other hand, our findings are representative for a Western European population. We implemented and maintained a rigorous quality control programme for the measurements of BP and BSe. Nurses visited the participants at home to increase the participation rate and to reduce bias due to attrition in a long-term longitudinal study.

If confirmed, our finding may have important implication for public health. Indeed, a population-wide reduction in systolic pressure by 2 mmHg is likely to result in a 7% decrease in coronary heart disease and a 10% decrease in stroke.[31] Such protective effect could be obtained by a mere increase in the average BSe concentration by 20 μg/L. This would require an enrichment of the daily intake of selenium by 13 μg from an estimated 50 μg per day.[32,33] At present, soil fortification with selenium is being discussed by the European Union.[34] Our study might inform the decision process. Finally, a recent Framingham publication[14] also underscored the potential implications of our current findings. It reported that high-normal BP compared with optimal BP (>120/>80 mmHg) was associated with a 1.6–2.5-fold increase in the cardiovascular risk.

In conclusion, deficiency of the antioxidant selenium, which is prevalent in Western Europe, might be an underestimated risk factor for the development of high-normal BP or hypertension in men.

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