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Item Type	Article
Authors	Swart, R;Schutte, A.E;van Rooyen, J.M;Mels, C.M.C
Citation	Swart R, Schutte AE, van Rooyen JM, Mels CMC. Selenium and large artery structure and function: a 10-year prospective study. Eur J Nutr. 2019 Dec;58(8):3313-3323. doi: 10.1007/s00394-018-1875-y.
Publisher	Springer Nature
Download date	2026-04-13 15:03:11
Link to Item	https://pubmed.ncbi.nlm.nih.gov/30523433/



Selenium and large artery structure and function: a 10-year prospective study

R. Swart¹ · A. E. Schutte^{1,2} · J. M. van Rooyen^{1,2} · Catharina M. C. Mels^{1,2}

Received: 14 August 2018 / Accepted: 1 December 2018 / Published online: 6 December 2018
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Abstract

Purpose Despite selenium's beneficial effects in counteracting oxidative stress, inflammation, and vascular endothelial dysfunction, controversial results exist regarding the long-term associations between selenium and atherosclerosis, arterial stiffness, and hypertension. We investigated in normal and selenium-deficient groups (and the total group), whether serum selenium relates to measures of large artery structure and function over 10 years.

Methods This longitudinal study included black adults from rural and urban areas in South Africa. Serum selenium and blood pressure were measured at baseline ($N=987$). At follow-up, carotid intima media thickness (IMT), cross-sectional wall area (CSWA), carotid-femoral pulse wave velocity (c-fPWV), and blood pressure were measured ($N=718$). Selenium deficiency was classified as serum levels $< 8 \mu\text{g}/100 \text{ ml}$.

Results In multivariable-adjusted regression analyses performed in the normal selenium group, c-fPWV after 10 years was negatively associated with baseline selenium ($\beta = -0.09$; $p = 0.016$). In the normal selenium group, baseline (but not 10 years) blood pressure also associated negatively with baseline selenium ($\beta = -0.09$; $p = 0.007$). Both IMT ($\beta = 0.12$; $p = 0.001$) and CSWA ($\beta = 0.10$; $p = 0.003$) after 10 years associated positively with baseline selenium in the total, normal, and selenium-deficient groups.

Conclusion We found a long-term vascular protective association of selenium on arterial stiffness and blood pressure in Africans with normal selenium levels, supporting the notion that selenium fulfills a vascular protective role. In contrast, we found a potential detrimental association between selenium and carotid wall thickness, particularly evident in individuals within the highest quartile of serum selenium.

Keywords Carotid intima media thickness · Atherosclerosis · Pulse wave velocity · Arterial stiffness · Blood pressure · Micronutrient

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s00394-018-1875-y>) contains supplementary material, which is available to authorized users.

✉ Catharina M. C. Mels
carina.mels@nwu.ac.za

¹ Hypertension in Africa Research Team (HART), North-West University, Private Bag X1290, Potchefstroom 2522, South Africa

² Medical Research Council, Unit for Hypertension and Cardiovascular Disease, North-West University, Potchefstroom, South Africa

Introduction

Rapid socio-economic development and urbanization as experienced by many black South Africans are associated with a nutrition transition [1]. These changes in dietary patterns and nutrient intake reflect the move from traditional foods to more processed and convenient foods, and may be accompanied by micronutrient deficiencies [2]. This in turn is related to an increased prevalence of non-communicable diseases [2], such as hypertension and cardiovascular disease (CVD). It is well established that black populations have a higher prevalence of hypertension and, therefore, increased CVD incidence and mortality when compared to their white counterparts [3].

Selenium is an important dietary micronutrient present in various dietary sources including meat, Brazil nuts,

intestines, seafood, cereals, cheese, and milk [4]. Apart from a high prevalence of CVDs, black populations also tend to have a high prevalence of selenium deficiency [5], which may be due to increased consumption of maize products—a poor source of selenium [6]. The functions of selenium range from antioxidative [7] to regulatory functions in processes such as the inflammatory response as well as proliferation and differentiation of immune cells [8, 9]. Selenium's functions are carried out by selenoproteins, including glutathione peroxidase (GPx) [10], which are present in the arterial wall [11].

Inconsistent results on the protective roles of selenium on CVD were found in randomized-controlled trials in a recent review [12]. Intervention studies indicated that selenium has a protective effect against the development of CVD [13, 14], including atherosclerotic CVD [12]. This was also seen in a recent cross-sectional study in white men, in which vascular protective associations with selenium and GPx were found [5]. Others reported that selenium deficiency may lead to increased blood pressure [15], arterial stiffness [5], and atherosclerosis [16]. In contrast, no significant effect of selenium on CVD mortality [17] and coronary heart disease [18] were indicated in two meta-analyses which included several randomized-controlled trials. However, it was found that selenium lowered inflammation and oxidative stress, thereby having a protective effect on coronary arteries [18].

Collectively, it is known that selenium exerts beneficial effects on oxidative stress, inflammation, and endothelial dysfunction, but controversial results exist on the long-term associations of selenium on thickening of the carotid wall, the development of arterial stiffness, and increased blood pressure. We, therefore, investigated in normal and selenium-deficient adults as well as in the total group, whether serum selenium levels are related to measures of large artery structure [carotid intima media thickness (IMT) and cross-sectional wall area (CSWA)] and function (blood pressure and arterial stiffness) over 10 years.

Materials and methods

Study design and participants

The international Prospective Urban and Rural Epidemiology (PURE) study focuses on the societal determinants of non-communicable diseases in urban and rural areas in low-, middle-, and high-income countries [19]. This sub-study is embedded in the South African leg of the PURE study and includes data collected at baseline (2005) and

after 10 years (2015) in the North West Province, South Africa.

A total of $N = 1265$ participants of the $N = 2010$ who participated at baseline were included, based on the following criteria: (i) participants who took part in both the baseline and 10-year follow-up phase ($N = 923$); (ii) participants who passed away over the course of 10 years ($N = 342$). We excluded $N = 277$ participants with missing baseline and follow-up cardiovascular and/or missing baseline selenium data. A total of $N = 987$ participants (Fig. 1) were, therefore, analyzed in the baseline phase and $N = 718$ participants were analyzed in the follow-up phase. From the $N = 718$ participants, $N = 81$ participants were randomly selected to determine their serum selenium levels at follow-up.

Experimental protocol

The detailed experimental protocol for data collection was previously described [20]. Briefly, all the participants were fully informed about the protocol of the study, and all gave written informed consent. The study fulfilled the requirements as stated in the Declaration of Helsinki for

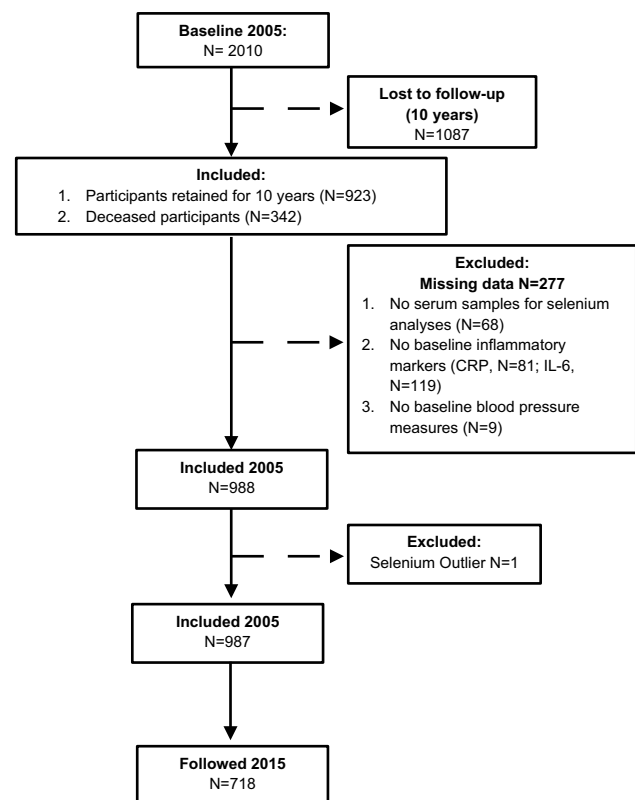


Fig. 1 Layout of the sub-study

investigation in human participants and was approved by the Health Research Ethics Committee of the North-West University.

Anthropometric measurements

Weight and height were taken in triplicate with calibrated instruments by trained anthropometrists and body mass index (BMI) was calculated.

Questionnaires

Demographic, socio-economic, and lifestyle information were obtained by trained field workers. The adapted BAE-CKE questionnaire was used to determine the physical activity index [21].

Cardiovascular measurements

Blood pressure measurements were conducted, while the participants were seated upright with the right arm supported at heart level (in duplicate, 5-min apart). Brachial systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured with a validated OMRON device (Omron Healthcare, Kyoto, Japan) at baseline and follow-up. According to International and South African Guidelines [22], hypertension was classified as SBP ≥ 140 and/or DBP ≥ 90 mmHg or use of anti-hypertensive medication. Pulse pressure (PP) was calculated as the difference between SBP and DBP. Mean arterial pressure (MAP) was calculated as $MAP = DBP + (PP/3)$.

The SphygmoCor XCEL device (AtCor Medical Pty. Ltd., Sydney, New South Wales, Australia) was used to determine carotid-femoral pulse wave velocity (c-fPWV) at follow-up. The participant was in the supine position, and of the duplicate readings, the second reading was used for analysis. The distances between the pulsated sites were measured using an infantometer, and 80% of these distances were used as the pulse wave traveled distance [23].

The SonoSite Micromaxx ultrasound system (SonoSite, Inc., Bothell, WA, USA), with a 6–13-MHz linear array transducer was used to obtain the IMT according to the Mannheim Consensus [24]. Images from at least two optimal angles of the left and right common carotid arteries were obtained. The measurements were done on a selected segment of maximum 10 mm with good image quality. It was performed by a single reader using a semi-automated program, namely the Artery Measurement Systems (AMS) II v1.139 (Chalmers University of Technology, Gothenburg,

Sweden) to determine intima media thickness of the far wall (IMT_f) and near wall (IMT_n). The CSWA was calculated to confirm structural changes in luminal diameter: $CSWA = \pi(d/2 + CIMT)^2 - \pi(d/2)^2$, where d denotes the luminal diameter [25].

Biochemical analyses

Blood samples (90 mL in 2005, and 30 mL in 2010 and 2015) from fasting participants were obtained from brachial antecubital vein branches with a sterile-winged infusion set. Samples were prepared according to standard procedures. Blood collection took place from 7:00 a.m. to 11:00 a.m. All samples were stored at -80 °C until biochemical analyses were performed. In the rural areas, the blood samples were frozen at -18 °C for no longer than 5 days and then stored in the laboratory at -80 °C until biochemical analyses were performed. Samples were centrifuged at $2000 \times g$ for 15 min at 10 °C within 30 min after collection. For blood lipids [total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglycerides], gamma glutamyl transferase (GGT), and C-reactive protein (CRP), tubes not containing anti-coagulants were used. For plasma glucose, sodium fluoride tubes were used.

Serum selenium levels were analyzed with an inductively coupled plasma mass spectrometry (ICP-MS) method and serum selenium deficiency was classified as selenium levels < 8 $\mu\text{g}/100$ ml [26]. Glucose levels were determined in sodium fluoride plasma samples with the Vitros DT6011 Chemistry Analyzer (Ortho-Clinical Diagnostics, Rochester, New York, USA) in 2005 and a Cobas Integra 400 plus analyzer (Roche, Basel, Switzerland) in 2015. Gamma glutamyl transferase and the lipid profile including TC, LDL-C, HDL-C, and triglycerides as well as high sensitivity CRP were determined in serum with a Konelab20i™ auto-analyzer, (Thermo Fisher Scientific, Vantaa, Finland) in 2005 and a Cobas Integra 400 plus (Roche, Basel, Switzerland) in 2015. Both the intra-assay coefficient and inter-assay coefficient of variation were $< 10\%$.

Statistical analyses

Statistical analyses were performed with Statistica 13.3 (TIBCO Software, Palo Alto, California, USA). Aligned with the objective of the study, we divided the population group into selenium-deficient and normal selenium groups. Data were expressed as arithmetic mean and standard deviation for normally distributed variables. Variables with a non-Gaussian distribution (glucose,

triglycerides, CRP, GGT, c-fPWV, IMTf, IMTn, and CSWA) were logarithmically transformed and the central tendency and spread represented by the geometric mean and the 5th and 95th percentile intervals. Means and proportions were compared between the normal selenium group and the selenium-deficient group, using independent *t* tests and Chi-square tests, respectively. We used the analyses of covariance (ANCOVAs) to compare cardiovascular measurements (at 10-year follow-up) including SBP, c-fPWV, IMT, and CSWA by quartiles of baseline selenium levels, while adjusting for age and sex, and SBP were additionally adjusted for baseline SBP. The c-fPWV, IMT, and CSWA were additionally adjusted for MAP.

We further performed multivariable adjusted regression analyses to determine the associations of cardiovascular measurements with selenium. The models were compiled with either follow-up SBP, c-fPWV, IMT, or CSWA as dependent variables, and baseline selenium as the main independent variable. The following covariates were considered for entry into the models: baseline age, sex, BMI, waist circumference, self-reported smoking, GGT, self-reported alcohol use, glucose, glycated hemoglobin, physical activity index, CRP, total cholesterol, HDL-C, LDL-C, and triglycerides. Based on the literature [27, 28] and bivariate correlations between potential covariates and the dependent and main independent variables, we selected the covariates to be included in multivariate regression analyses. We also tested for multicollinearity using the variance inflation factor (VIF) and the tolerance value was above 0.1, indicating no multicollinearity. The following covariates were entered into the final models: age, sex, BMI, self-reported smoking, physical activity index, GGT, CRP, glucose, and LDL-C. In models where c-fPWV, IMT, and CSWA were the dependent variables, we additionally entered MAP at follow-up as a covariate.

Results

The baseline and follow-up characteristics, stratified according to baseline selenium levels, are shown in Table 1. Participants with selenium deficiency were younger, and had lower BMI, but higher GGT ($p=0.005$) and CRP levels ($p<0.001$) and reported to use more tobacco ($p<0.001$) when compared to those with normal selenium levels at baseline. Mean selenium levels of the normal selenium group were $12.7 \pm 3.41 \mu\text{g}/100 \text{ ml}$ compared to the selenium-deficient group with $6.12 \pm 1.67 \mu\text{g}/100 \text{ ml}$ ($p<0.001$). After 10 years, the selenium levels (done in a randomly selected subgroup) of the selenium-deficient group restored to normal levels, and there was no difference between selenium levels

of the baseline normal selenium and selenium-deficient groups. At follow-up, the group with selenium deficiency at baseline reported higher alcohol use ($p=0.023$), but displayed lower total cholesterol ($p=0.025$) and LDL-C ($p=0.041$) compared to the normal selenium group. No differences in the cardiovascular profile were observed at both baseline and follow-up, when comparing the normal selenium group with the selenium-deficient group. Deceased participants ($N=217$) had significantly lower baseline selenium levels ($p<0.001$) compared to those who survived over 10 years (Supplementary Table 1).

We investigated SBP, c-fPWV, IMT, and CSWA at follow-up by quartiles of baseline selenium levels while adjusting for baseline values of age and sex as well as follow-up MAP and baseline SBP (Fig. 2). A positive trend for IMT ($p \text{ trend}=0.004$) and CSWA ($p \text{ trend}=0.033$) with increasing baseline selenium quartiles was found. However, we found no trends for SBP ($p=0.745$) and c-fPWV ($p=0.332$) with increasing baseline selenium quartiles.

Using multivariable-adjusted regression analyses, we reviewed, in the total group, associations of 10-year follow-up cardiovascular measurements (SBP, c-fPWV, IMT, CSWA) with baseline selenium (Table 2). We found a positive association between IMT and selenium ($\beta=0.12$; $p=0.001$) as well as between CSWA and selenium ($\beta=0.10$; $p=0.003$).

When dividing the total group into normal and selenium-deficient groups at baseline (Table 3), we confirmed the positive associations between IMT and selenium in the normal ($\beta=0.12$; $p=0.003$) and selenium-deficient groups ($\beta=0.23$; $p=0.034$). A positive association was also found between CSWA and selenium in the normal selenium group ($\beta=0.10$; $p=0.006$), but not in the selenium-deficient group. In addition, a negative association between c-fPWV and selenium ($\beta=-0.09$; $p=0.016$) was evident in the normal selenium group, but not in the selenium-deficient group ($\beta=0.03$; $p=0.78$).

Supplementary Table 2 shows the associations between SBP and baseline selenium. We reviewed cross-sectional analyses using baseline SBP, and longitudinal associations between follow-up SBP and baseline selenium. We found a negative association between baseline SBP and selenium only in the normal selenium group ($\beta=-0.08$; $p=0.007$), with no associations with SBP ($p=0.44$) at follow-up.

Sensitivity analyses

When excluding HIV infected participants ($N=210$) at baseline and follow-up, the results remained mostly the same, except for the positive association between IMT and selenium in the selenium-deficient group ($N=118$)

Table 1 Characteristics of the study population at baseline and after 10 years, stratified according to normal and deficient baseline selenium levels

	Baseline (<i>N</i> =987)			10 year follow-up (<i>N</i> =718)		
	Normal Se	Se deficient ^c	<i>p</i> values	Normal Se	Se deficient	<i>p</i> values
<i>N</i>	845	142		637	81	
Sex [women, (%)]	546 (64.6)	82 (57.8)	0.115	438 (68.8)	52 (64.2)	0.406
Age (years)	50.7 ± 10.2	48.8 ± 9.58	0.042	59.1 ± 9.15	56.4 ± 8.26	0.014
Anthropometric measures						
Height (m)	1.60 ± 0.08	1.61 ± 0.09	0.244	1.59 ± 0.08	1.60 ± 0.09	0.360
Body mass (kg)	62.7 ± 16.2	60.4 ± 18.0	0.137	65.3 ± 17.4	66.2 ± 20.7	0.699
Body mass index (kg/m ²)	25.6 ± 6.77	23.4 ± 7.05	0.057	25.9 ± 7.10	25.8 ± 7.76	0.966
Cardiovascular measures						
Systolic blood pressure (mmHg)	133 ± 24.6	132 ± 24.7	0.560	134 ± 25.7	134 ± 25.7	0.989
Diastolic blood pressure (mmHg)	87.7 ± 14.6	87.6 ± 14.3	0.965	85.5 ± 13.6	86.4 ± 13.2	0.613
Mean arterial pressure (mmHg)	103 ± 17.0	102 ± 17.2	0.780	102 ± 16.6	102 ± 16.4	0.793
Pulse pressure (mmHg)	45.7 ± 15.4	44.4 ± 14.4	0.370	48.3 ± 16.7	47.5 ± 17.4	0.700
c-fPulse wave velocity (m/s) ^a	–	–	–	8.61 ± 0.08	8.55 ± 0.08	0.776
Intima media thickness near wall (mm) ^a	–	–	–	0.65 ± 0.09	0.62 ± 0.09	0.071
Intima thickness far wall (mm) ^a	–	–	–	0.65 ± 0.08	0.64 ± 0.08	0.221
Cross-sectional wall area (mm ²) ^a	–	–	–	13.3 ± 0.11	13.0 ± 0.11	0.392
Biochemical variables						
Selenium (µg/100 ml) ^b	12.7 ± 3.41	6.12 ± 1.67	<0.001	17.5 ± 5.23	18.7 ± 7.31	0.567
Glucose (mmol/l)	4.86 (3.50; 6.70)	4.78 (3.70; 6.30)	0.363	5.32 (4.05; 7.74)	5.21 (3.84; 9.82)	0.523
C-reactive protein (mg/l)	3.16 (0.28; 37.8)	5.06 (0.43; 51.9)	0.001	3.44 (0.43; 33.9)	3.65 (0.19; 43.8)	0.712
Total cholesterol (mmol/l)	5.04 ± 1.34	4.85 ± 1.43	0.122	4.62 ± 1.14	4.30 ± 1.17	0.025
High-density lipoprotein cholesterol (mmol/l)	1.52 ± 0.63	1.47 ± 0.66	0.340	1.39 ± 0.57	1.34 ± 0.54	0.484
Low-density lipoprotein cholesterol (mmol/l)	2.94 ± 1.15	2.79 ± 1.15	0.162	2.63 ± 1.02	2.37 ± 1.4	0.041
Triglycerides (mmol/l)	1.13 (0.54; 2.88)	1.18 (0.58; 2.67)	0.404	1.14 (0.54; 2.77)	1.14 (0.55; 2.72)	0.991
Lifestyle and medication use						
Physical activity index	7.30 ± 1.77	7.15 ± 1.83	0.368	5.08 ± 1.76	4.83 ± 1.65	0.224
γ-Glutamyl transferase (U/l)	56.4 (19.8; 344)	70.6 (21.2; 442)	0.005	37.8 (11.6; 212)	41.9 (12.3; 369)	0.354
Alcohol use, <i>n</i> (%)	364 (43.3)	67 (47.9)	0.313	183 (29.2)	33 (41.8)	0.023
Tobacco use, <i>n</i> (%)	448 (53.1)	90 (63.8)	0.018	237 (37.7)	38 (48.1)	0.075
HIV infected, <i>n</i> (%)	142 (16.8)	19 (13.4)	0.302	118 (18.6)	12 (14.8)	0.411
Hypertension medication, <i>n</i> (%)	149 (17.6)	22 (15.5)	0.533	187 (29.9)	21 (26.9)	0.585
Hypertensive status, <i>n</i> (%)	452 (53.5)	74 (52.1)	0.761	377 (59.2)	55 (67.9)	0.131

Data are expressed as arithmetic mean ± standard deviation, geometric mean (5th and 95th percentile boundaries) or % of *N*. *p* values for comparison between groups were obtained with independent *t* tests and Chi-square tests

^aAdjusted for mean arterial pressure

^bSelenium data in 2015 available for *N*=81

^cSelenium deficiency at baseline < 8 µg/100 ml. Values in bold indicate statistical significance (*p* < 0.05)

which was now borderline significant ($\beta = 0.24$; $p = 0.051$). We also excluded participants with diabetes at baseline ($N = 165$) and follow-up ($N = 174$); however, our main results were still significant. We also added hypertension status of participants at baseline and follow-up

as covariates into the multiple regression model and our main results remained significant, except for the positive association of IMT with selenium ($\beta = 0.22$; $p = 0.17$) and the inverse association of cfPWV with selenium in the normal selenium group ($\beta = -0.09$; $p = 0.11$).

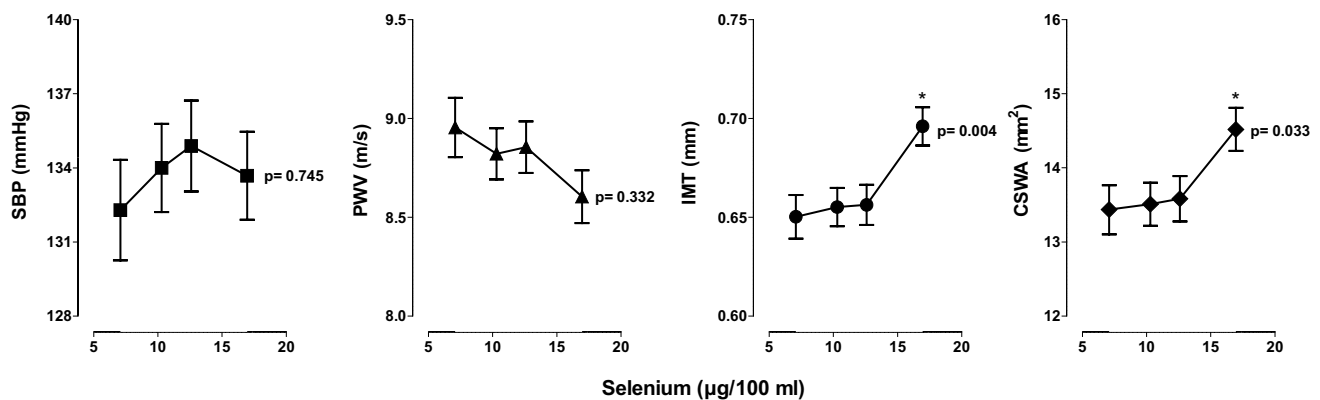


Fig. 2 Quartiles of baseline selenium levels plotted against 10 year follow-up systolic blood pressure (SBP), pulse wave velocity (PWV), carotid intima media thickness (IMT), and cross-sectional wall area (CSWA), adjusted for age and sex. The c-fPWV, IMT, and CSWA

were additionally adjusted for mean arterial pressure and SBP was additionally adjusted for baseline SBP. Asterisk indicates difference between quartile 1 and 4 ($p < 0.05$). Spread represents standard error

Discussion

High exposure to selenium has been linked to possible adverse cardiometabolic effects including hyperlipidemia [29] and diabetes [30]. From the literature, it is evident that “further epidemiological studies and randomized clinical trials across populations with different selenium status should be conducted to determine the causal effect of selenium on cardiovascular disease and risk factors” [31]. Therefore, in this longitudinal study, which included a black population from urban and rural areas of the North West Province of South Africa, we investigated whether serum selenium relates to large artery structure (IMT and CSA) and function (blood pressure and arterial stiffness) over 10 years. We found consistent positive independent associations of selenium with carotid wall thickness. We also found a protective inverse association of selenium with arterial function (blood pressure and c-fPWV), but only in Africans with normal selenium levels—where 14% of our population presented with selenium deficiency.

The positive association between carotid wall thickness and selenium after 10 years is in contrast with most other studies, which found selenium to be protectively associated against thickening of the intima media [16, 32–34]. One study failed to link selenium (measured in toenails) with the measures of subclinical atherosclerosis [35]. It is noteworthy to mention that, in our multivariable-adjusted regression model, along with serum selenium, other pro-atherogenic factors such as age, inflammation (CRP) and LDL-C [36, 37] were also independently associated with carotid wall thickness—laying credence to our selenium finding. To the best of our knowledge, only one study reported findings which

support our findings [38]. In this study, the effect of selenium on histopathological changes in an animal model of cockerel was investigated, and it was found that optimal selenium levels induced atherosclerosis via inflammation and smooth muscle proliferation in the media of blood vessels [38]. In our study, IMT and CSA values were the highest in the fourth selenium quartile (Fig. 2), with a mean selenium level of 16.96 µg/100 ml. However, a narrow selenium range of 5.5–14.5 µg/100 ml is known to have significant protective benefits against CVD [39] and some studies indicated that increased selenium intake in people with adequate-to-high selenium status may lead to adverse effects [40]. Selenium supplementation is, therefore, known to only benefit those with low selenium levels [40]. This corresponds well with the previous reviews, concluding that there is a U-shaped relationship between selenium and CVD [31, 40, 41].

However, since our study population did not have extremely high selenium levels, it may also be possible that genetic single-nucleotide polymorphisms (SNP) of selenoproteins such as GPx may in part explain our finding. It was previously found that specific SNPs may influence selenium’s metabolism and utilization and thereby the synthesis of selenoproteins and the responses to environmental stressors [42]. A common polymorphism of the GPx1 gene which is known as Pro198Leu, was previously linked to increased risk of CVD including increased IMT [43] and coronary artery calcification [44]. This may suggest that these SNPs may demolish the vascular protective effects of selenium; however, the prevalence of this polymorphism in our population is unknown. Nutrigenetics [45] may also have an influence on the selenium distribution in the body; however, we

Table 2 Multiple regression analyses with 10-year follow-up cardiovascular measures as dependent variables and baseline serum selenium, in the total group ($N=690$)

	Systolic blood pressure (mmHg)	
	Adjusted $R^2=0.09$; $p<0.001$	
	β value (95% CI)	p value
Selenium ($\mu\text{g}/100$ ml)	-0.03 (-0.10; 0.04)	0.418
Age (years)	0.25 (0.18; 0.33)	< 0.001
Sex (male/female)	0.11 (0.03; 0.19)	0.007
Body mass index (kg/m^2)	0.10 (0.01; 0.19)	0.026
Physical activity index	0.16 (0.09; 0.24)	< 0.001
Tobacco use	0.01 (-0.07; 0.08)	0.867
γ -Glutamyl transferase (U/l)	0.10 (0.02; 0.17)	0.013
Glucose (mmol/l)	0.05 (-0.02; 0.13)	0.155
C-reactive protein (mg/l)	-0.001 (-0.08; 0.07)	0.969
Low-density lipoprotein cholesterol (mmol/l)	-0.06 (-0.13; 0.02)	0.134
	Pulse wave velocity (m/s) ^a	
	Adjusted $R^2=0.29$; $p<0.001$	
	β value (95% CI)	p value
Selenium ($\mu\text{g}/100$ ml)	-0.05 (-0.12; 0.02)	0.163
Age (years)	0.23 (0.16; 0.30)	< 0.001
Sex (male/female)	0.09 (0.01; 0.17)	0.024
Body mass index (kg/m^2)	-0.08 (-0.16; 0.01)	0.067
Physical activity index	-0.03 (-0.10; 0.05)	0.461
Tobacco use	0.02 (-0.05; 0.09)	0.562
γ -Glutamyl transferase (U/l)	0.15 (0.08; 0.23)	< 0.001
Glucose (mmol/l)	0.09 (0.02; 0.16)	0.015
C-reactive protein (mg/l)	0.06 (-0.01; 0.14)	0.079
Low-density lipoprotein cholesterol (mmol/l)	-0.06 (-0.13; 0.01)	0.112
Mean arterial pressure (mmHg)	0.36 (0.29; 0.43)	< 0.001
	Intima media thickness (mm) ^a	
	Adjusted $R^2=0.19$; $p<0.001$	
	β value (95% CI)	p value
Selenium ($\mu\text{g}/100$ ml)	0.12 (0.05; 0.19)	0.001
Age (years)	0.32 (0.25; 0.40)	< 0.001
Sex (male/female)	0.06 (-0.02; 0.14)	0.123
Body mass index (kg/m^2)	0.01 (-0.08; 0.09)	0.864
Physical activity index	0.12 (0.04; 0.19)	0.002
Tobacco use	0.02 (-0.05; 0.10)	0.550
γ -Glutamyl transferase (U/l)	-0.02 (-0.09; 0.05)	0.587
Glucose (mmol/l)	0.01 (-0.06; 0.08)	0.765
C-reactive protein (mg/l)	0.10 (0.03; 0.17)	0.008
Low-density lipoprotein cholesterol (mmol/l)	0.12 (0.05; 0.20)	0.001
Mean arterial pressure (mmHg)	0.13 (0.06; 0.20)	< 0.001
	Cross-sectional wall area (mm^2) ^a	
	Adjusted $R^2=0.23$; $p<0.001$	
	β value (95% CI)	p value
Selenium ($\mu\text{g}/100$ ml)	0.10 (0.04; 0.17)	0.003

Table 2 (continued)

	Cross-sectional wall area (mm ²) ^a	
	Adjusted $R^2 = 0.23$; $p < 0.001$	
	β value (95% CI)	p value
Age (years)	0.32 (0.25; 0.39)	< 0.001
Sex (male/female)	0.14 (0.06; 0.22)	< 0.001
Body mass index (kg/m ²)	0.04 (−0.04; 0.12)	0.319
Physical activity index	0.09 (0.02; 0.17)	0.010
Tobacco use	0.06 (−0.01; 0.14)	0.086
γ -Glutamyl transferase (U/l)	0.03 (−0.04; 0.10)	0.410
Glucose (mmol/l)	0.03 (−0.04; 0.10)	0.398
C-reactive protein (mg/l)	0.05 (−0.02; 0.12)	0.199
Low-density lipoprotein cholesterol (mmol/l)	0.09 (0.01; 0.16)	0.018
Mean arterial pressure (mmHg)	0.22 (0.15; 0.29)	< 0.001

The main independent variables included in the models were baseline selenium, and other baseline covariates included age, sex, body mass index, physical activity index, C-reactive protein, γ -glutamyl transferase, glucose, tobacco use, and low-density lipoprotein cholesterol

^aAdditionally adjusted for follow-up mean arterial pressure. Values in bold indicate statistical significance ($p < 0.05$)

were unable to investigate this due to unavailability of data on genetic factors in our population.

Notwithstanding our finding of a potential detrimental association of selenium on carotid wall thickening, we also found a beneficial association of selenium with arterial stiffness over 10 years and baseline blood pressure, only in the normal selenium group. This finding is well aligned with the previous studies which indicated protective associations of selenium on arterial function [5, 46]. Apart from selenium, we also found independent associations of other risk factors for CVD such as age [47], GGT [48], and glucose [49] to be independently associated with arterial function. In spontaneous hypertensive rats, increased selenium intake showed protective effects on degenerative changes and elastin degradation in the vessel walls, suggesting that selenium deficiency may lead to severe degenerative changes in the vessel walls [50]. In addition, we previously found a protective association between GPx activity and arterial stiffness in white men (aged 20–65 years) [5], although this association was not directly with selenium, selenium performs its roles via the expression of selenoproteins such as GPx [51]. We also previously found an independent protective association between 24-h blood pressure and selenium [5]. However, the other studies conducted on participants older than 50 years of age found no beneficial effect of antioxidant intake on arterial stiffness, carotid atherosclerosis [52], or blood pressure [53]. Notably, in the 14% of our population studied with selenium deficiency, the beneficial association with arterial stiffness was also absent.

The results of this study should be interpreted within the context of its strengths and limitations. This was a well-controlled 10-year prospective study performed in an understudied black population. The limitations included a lack of dietary data to relate dietary selenium intake with serum selenium levels and cardiovascular measures. From a physiological viewpoint, serum selenium is a more accurate estimate of current selenium status than dietary intake data. Furthermore, c-fPWV and IMT data were not collected at baseline and no data were available on selenoproteins such as GPx, in this study population. While the results from this study were consistent after multiple adjustments, residual confounding cannot be excluded due to unknown factors associated with selenium, c-fPWV, IMT, CSWA, and blood pressure. The participants of this study were recruited from the North West Province and cannot be seen as representative of the entire South African population.

Conclusion

We found a potential detrimental association between selenium and carotid wall thickening, particularly evident in individuals within the highest quartile of serum selenium levels. We also found long-term protective associations of serum selenium with arterial stiffness and blood pressure in Africans with normal selenium levels, thereby supporting the notion that selenium fulfills a vascular protective role.

Table 3 Multiple regression analyses in the normal and selenium-deficient groups with 10-year follow-up cardiovascular measures as dependent variables

	c-fPulse wave velocity (m/s) ^a			
	Normal Se (N=637)		Se deficient (N=81) ^b	
	Adjusted R ² =0.27; p<0.001		Adjusted R ² =0.42; p<0.001	
	β value (95% CI)	p value	β value (95% CI)	p value
Selenium (μg/100 ml)	−0.09 (−0.17; −0.02)	0.016	0.03 (−0.17; 0.22)	0.775
Age (years)	0.22 (0.14; 0.30)	< 0.001	0.28 (0.08; 0.48)	0.008
Sex (male/female)	0.09 (0.003; 0.17)	0.042	0.09 (−0.14; 0.32)	0.458
Body mass index (kg/m ²)	−0.08 (−0.17; 0.01)	0.092	−0.15 (−0.38; 0.08)	0.198
Physical activity index	−0.02 (−0.09; 0.06)	0.693	−0.01 (−0.22; 0.19)	0.891
Tobacco use	0.001 (−0.08; 0.08)	0.986	0.17 (−0.04; 0.37)	0.113
γ-Glutamyl transferase (U/l)	0.16 (0.08; 0.23)	< 0.001	0.11 (−0.10; 0.32)	0.301
Glucose (mmol/l)	0.09 (0.01; 0.17)	0.021	0.13 (−0.07; 0.33)	0.197
C-reactive protein (mg/l)	0.08 (−0.001; 0.15)	0.054	0.05 (−0.14; 0.24)	0.588
Low-density lipoprotein cholesterol (mmol/l)	−0.05 (−0.13; 0.03)	0.216	−0.18 (−0.38; 0.03)	0.097
Mean arterial pressure (mmHg)	0.35 (0.27; 0.42)	< 0.001	0.39 (0.18; 0.60)	0.001
	Intima media thickness (mm) ^a			
	Adjusted R ² =0.18; p<0.001		Adjusted R ² =0.23; p=0.003	
	β value (95% CI)	p value	β value (95% CI)	p value
	β value (95% CI)	p value	β value (95% CI)	p value
Selenium (μg/100 ml)	0.12 (0.04; 0.19)	0.003	0.23 (0.02; 0.44)	0.034
Age (years)	0.33 (0.26; 0.41)	< 0.001	0.21 (−0.01; 0.42)	0.061
Sex (male/female)	0.04 (−0.04; 0.12)	0.314	0.16 (−0.09; 0.41)	0.207
Body mass index (kg/m ²)	0.02 (−0.07; 0.11)	0.677	−0.03 (−0.27; 0.22)	0.833
Physical activity index	0.13 (0.05; 0.21)	0.001	0.03 (−0.19; 0.25)	0.789
Tobacco use	0.01 (−0.07; 0.09)	0.857	0.15 (−0.06; 0.37)	0.173
γ-Glutamyl transferase (U/l)	−0.02 (−0.10; 0.06)	0.615	−0.11 (−0.33; 0.11)	0.324
Glucose (mmol/l)	0.01 (−0.07; 0.08)	0.889	0.08 (−0.14; 0.29)	0.473
C-reactive protein (mg/l)	0.08 (0.01; 0.16)	0.034	0.16 (−0.05; 0.36)	0.137
Low-density lipoprotein cholesterol (mmol/l)	0.13 (0.05; 0.20)	0.001	0.07 (−0.15; 0.29)	0.518
Mean arterial pressure (mmHg)	0.11 (0.04; 0.19)	0.004	0.32 (0.09; 0.54)	0.007
	Cross-sectional wall area (mm ²) ^a			
	Adjusted R ² =0.22; p<0.001		Adjusted R ² =0.25; p=0.001	
	β value (95% CI)	p value	β value (95% CI)	p value
	β value (95% CI)	p value	β value (95% CI)	p value
Selenium (μg/100 ml)	0.10 (0.03; 0.18)	0.006	0.21 (0.001; 0.42)	0.053
Age (years)	0.34 (0.26; 0.41)	< 0.001	0.13 (−0.08; 0.34)	0.232
Sex (male/female)	0.11 (0.03; 0.19)	0.006	0.30 (0.05; 0.54)	0.020
Body mass index (kg/m ²)	0.04 (−0.05; 0.13)	0.384	0.07 (−0.17; 0.31)	0.580
Physical activity index	0.11 (0.03; 0.18)	0.007	0.0005 (−0.22; 0.22)	0.997
Tobacco use	0.06 (−0.02; 0.14)	0.133	0.09 (−0.13; 0.30)	0.425
γ-Glutamyl transferase (U/l)	0.02 (−0.05; 0.10)	0.552	−0.004 (−0.22; 0.21)	0.969
Glucose (mmol/l)	0.04 (−0.04; 0.11)	0.345	0.01 (−0.21; 0.22)	0.954
C-reactive protein (mg/l)	0.04 (−0.04; 0.12)	0.304	0.07 (−0.13; 0.27)	0.484
Low-density lipoprotein cholesterol (mmol/l)	0.09 (0.02; 0.17)	0.016	0.02 (−0.20; 0.23)	0.872
Mean arterial pressure (mmHg)	0.20 (0.13; 0.27)	< 0.001	0.36 (0.14; 0.58)	0.002

The main independent variables included in the models were baseline selenium, and other baseline covariates included age, sex, body mass index, physical activity index, C-reactive protein, γ-glutamyl transferase, glucose, tobacco use, and low-density lipoprotein cholesterol

^aAdditionally adjusted for follow-up mean arterial pressure. Values in bold indicate statistical significance ($p < 0.05$)

^bSelenium deficiency at baseline $< 8 \mu\text{g}/100 \text{ ml}$

Acknowledgements We would like to thank all the participants, students, and supporting staff of the PURE study and particularly: (1) PURE-SA research team, field workers, and office staff at the North-West University, South Africa. (2) PURE-International: The PURE project office staff at the Population Health Research Institute (PHRI), Hamilton Health Sciences, and McMaster University, ON, Canada.

Author contributions RS was responsible for the planning, writing, and composition of the manuscript as well as the statistical analyses. CMC, AES, and JMvR gave recommendations for the framework, writing, and composition of the manuscript as well as the methodology. They also supervised the statistical analyses and helped with the formulation of the tables and figures.

Funding This project was funded by the South African Netherlands Research Programme on Alternatives in Development, North-West University, Population Health Research Institute, Roche Diagnostics (South Africa) and South African Medical Research Council, South African National Research Foundation (NRF), and South African Sugar Association (SASA) for the analyses (Grant number: Project 249). Opinions expressed and conclusions are those of the authors and are not necessarily to be attributed to the NRF.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interests.

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