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Differential associations between selenoprotein P and distal sensorimotor polyneuropathy in people with and without diabetes: KORA F4/FF4 study

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ABSTRACT

Background: Oxidative stress is a risk factor for distal sensorimotor polyneuropathy (DSPN). Selenoprotein P is a protein with antioxidant properties but has not been investigated in the context of DSPN. This study aimed to assess the associations between selenoprotein P and DSPN in people without and with type 2 diabetes (T2D).
Methods: Cross-sectional and prospective analyses were based on 1053 (including 217 with T2D) and 513 participants (including 79 with T2D), respectively, aged 61–82 years from the population-based KORA F4 survey. DSPN at baseline (KORA F4) and in the follow-up survey KORA FF4 was defined based on the Michigan Neuropathy Screening Instrument. Serum levels of full-length selenoprotein P were quantified by ELISA. Associations between selenoprotein P and prevalent or incident DSPN were estimated using logistic regression analysis adjusting for multiple confounders.
Results: Selenoprotein P levels were not associated with prevalent DSPN in the total sample. However, there was a significant interaction by diabetes status. Higher levels of selenoprotein P were associated with lower odds of prevalent DSPN in individuals without T2D (fully adjusted model: OR 0.825 [95 % CI 0.682, 0.998], $p = 0.0476$), but not in those with T2D (OR [95 % CI] 1.098 [0.829, 1.454], $p = 0.5132$; $p_{interaction} = 0.0488$). Selenoprotein P levels were not associated with incident DSPN over a follow-up of 6.5 years.
Conclusion: In individuals without T2D from the older general population, lower selenoprotein P levels were associated with a higher prevalence of DSPN. Whether the antioxidant properties of selenoprotein P are responsible for the observed associations remains to be elucidated in future research.

1. Introduction

Selenoprotein P is a hepatokine that transports the trace element selenium from the liver to extrahepatic organs [1,2]. Several lines of evidence suggest that selenoprotein P has antioxidant properties [3]. In line with these potential protective effects, lower circulating levels of

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selenoprotein P are associated with higher incidence of cardiovascular events and heart failure as well as higher mortality rates in epidemiological studies [4–6]. In contrast, studies based on mouse models and clinical cohorts implicated that selenoprotein P is positively associated with key features of type 2 diabetes pathology, such as insulin resistance and beta-cell dysfunction [7–9].

Distal sensorimotor polyneuropathy (DSPN) is one of the most common complications of type 2 diabetes [10,11] but also occurs in people without diabetes with older age, obesity and prediabetes as significant risk factors [12,13]. One of the mechanisms linking (pre)diabetes and DSPN is oxidative stress [14–16]. Several pro- and antioxidative protein biomarkers from serum or plasma have been found to be associated with prevalent and/or incident DSPN [15,17,18] but selenoprotein P has not yet been investigated in this context. Of note, experimental studies on DSPN are hampered by the lack of validated animal models so that population-based studies are invaluable to investigate potential protective or risk biomarkers.

In addition to the antioxidant activity, several studies also point towards neuroprotective effects of selenoprotein P. Selenoprotein P deficiency leads to severe neurological dysfunction in the central nervous system affecting multiple brain regions [19–22]. However, reports on phenotypes related to the peripheral nervous system are lacking.

Based on these links between selenoprotein P, oxidative stress and cardiometabolic and neurological conditions, we hypothesised that lower circulating levels of selenoprotein P are associated with higher prevalence and incidence of DSPN. Therefore, we aimed to assess this association in a population-based study of older adults. Given the aforementioned positive association with type 2 diabetes, we also aimed to investigate if the presence of diabetes interacted with the association between selenoprotein P and DSPN.

2. Study population and methods

2.1. Study population

This study used data from the Cooperative Health Research in the Region of Augsburg (KORA) F4 (2006–2008) and the KORA FF4 surveys (2013–2014). Both studies are follow-up examinations of the population-based KORA S4 survey (1999–2001) conducted in Augsburg and two adjacent counties in Southern Germany as described previously [23–25].

An overview of the study design is given in Fig. 1. The study samples for the cross-sectional and prospective analyses are similar to those from previous studies on biomarkers and DSPN in KORA F4/FF4 [25,26]. Analyses were based on participants in the age range of 61–82 years at KORA F4 (n = 1161) because the neuropathy examination was not performed in younger participants. Of these, 21 had no measurements of selenoprotein P. In addition, 87 individuals were excluded because of missing data for the Michigan Neuropathy Screening Instrument (MNSI) score (examination part) at F4, diabetes forms other than type 2 diabetes (type 1 diabetes, drug-induced diabetes or unclear glucose tolerance status), high alcohol consumption (≥60 g/day for women and ≥80 g/day for men) or missing covariables for statistical analysis, so the cross-sectional analyses were conducted in 1053 participants.

For the prospective analysis, individuals with prevalent DSPN at F4 (n = 183) and with missing data for the MNSI score or non-participation at FF4 (mainly because people had died, moved out of the study area, were too sick for participation, refused to participate or could not be contacted) (n = 355) needed to be excluded, leaving a sample of 515 individuals. The mean follow-up time was 6.5 years.

2.2. Measurement of selenoprotein P

For the measurement of serum concentrations of full-length selenoprotein P, a sandwich ELISA system to measure full-length selenoprotein P was used, keeping laboratory personnel blinded to information on study participants, as described previously [27]. Human selenoprotein P as standard was purified from human plasma, and human frozen plasma was provided by the Japanese Red Cross Tohoku Block Blood Center (No. 25J0012). Briefly, 96-well microtiter plates were coated with rat anti-human selenoprotein P monoclonal antibody AA3, washed and incubated in Block Ace Powder (UK–B80, KAC, Kyoto, Japan). After washing the wells, a selenoprotein P standard or diluted serum sample was added to each well and incubated. After washing, horseradish peroxidase-conjugated anti-human selenoprotein P monoclonal antibody AH5 was added and incubated. Finally, TMB Peroxidase Substrate (5120-0047, SeraCare Life Sciences, Gaithersburg, MD, USA) was added to each well, incubated in the dark, and the reactions were stopped by the addition of sulphuric acid. The absorbances were read at 450 nm in a SpectraMax iD5 (Molecular Devices, San Jose, CA, USA). We determined at least three points in each serum sample, and the average value was used for analysis. This assay was shown to be highly reproducible when identical samples are compared regarding either intra-assay or inter-assay variation, with the relative standard deviations within

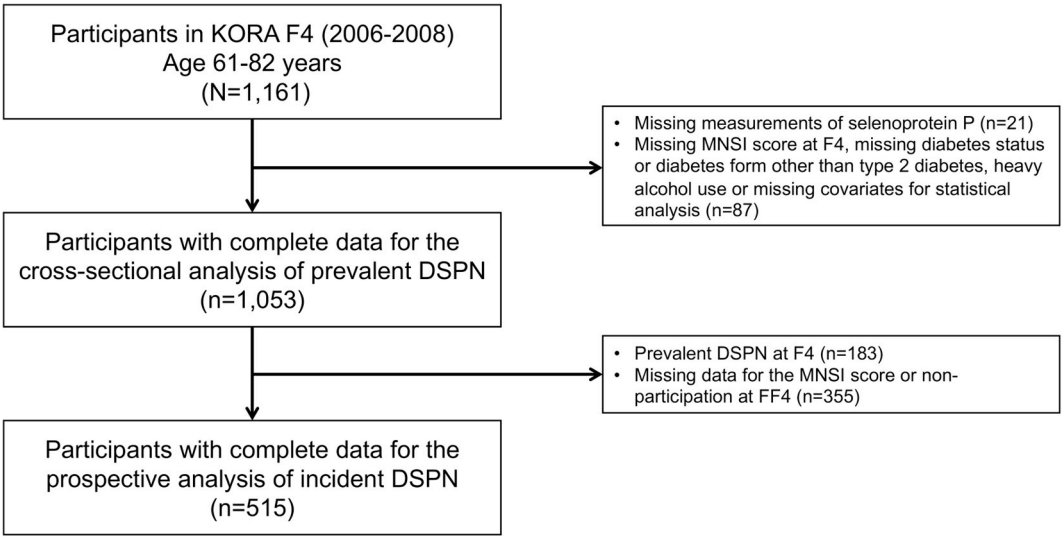

Fig. 1. Flow chart of the study population for the cross-sectional and prospective analysis.
DSPN, distal sensorimotor polyneuropathy; KORA, Cooperative Health Research in the Region of Augsburg; MNSI, Michigan Neuropathy Screening Instrument.

determinations being under 5 % and 10 %, respectively.

2.3. Assessment of DSPN and covariates

The clinical examination at baseline (F4) and follow-up (FF4) contained all items of the MNSI, i.e. the appearance of feet, foot ulceration, ankle reflexes and vibration perception threshold at the great toes. Vibration perception was determined using the Rydel-Seiffer graduated C 64 Hz tuning fork [28]. Normal vibration perception threshold took into account age-dependent threshold values [29]. The MNSI score also included the bilateral assessment of touch/pressure sensation with a 10-g monofilament (Neuropen) [30] so that the total MNSI score ranged from 0 to 10. Prevalent and incident DSPN were defined based on an MNSI score of >3 points [25], which is in line with the diagnostic criteria for possible DSPN [31].

2.4. Assessment of anthropometric, demographic, clinical, metabolic and lifestyle-related variables

The assessment of anthropometric, demographic and lifestyle variables has been described in detail before [24,25]. All participants without known diabetes received a standard 75-g oral glucose tolerance test (OGTT) [24]. Glucose tolerance categories were defined using fasting and 2-h glucose levels according to the 2003 American Diabetes Association criteria [32]. Known type 2 diabetes in KORA F4 was defined as self-reported and subsequently validated by the responsible physician, or as current use of glucose-lowering medication. Glucose and haemoglobin A1c (HbA1c) were determined using the hexokinase method (Dimension RxL instrument, Dade Behring, Newark, NJ, USA) and by cation-exchange high-performance liquid chromatographic, photometric assays (Adams HA 8160 Hemoglobin Analysis System, Menarini Diagnostics, Florence, Italy), respectively. Serum lipids were also measured using a Dimension RxL instrument (Dade Behring).

Hypertension was defined as current hypertension (≥140/90 mmHg) or known hypertension controlled by medication. The estimated glomerular filtration rate (eGFR) was calculated from serum creatinine (Chronic Kidney Disease Epidemiology Collaboration 2009). Alcohol consumption was graded as none (0 g/day), moderate (<20 g/day for women and <40 g/day for men) and high (20–<60 g/day for women and 40–<80 g/day for men). History of stroke and myocardial infarction were self-reported by the study participants.

2.5. Statistical analysis

Baseline characteristics of study participants are given as means (SD) for continuous variables and counts (%) for categorical variables. Independent samples *t*-test or Pearson's χ^2 test were used to assess for differences by DSPN status. Fisher's exact test was used for cell sizes smaller than 5.

Associations between selenoprotein P and prevalent or incident DSPN were estimated per 1-μg/ml increase using logistic regression analysis in models of increasing complexity. Model 1 was unadjusted. Model 2 was adjusted for age (years) and sex (male/female). Model 3 was additionally adjusted for waist circumference (cm), physical activity (active/inactive), alcohol consumption (none/moderate/high), smoking status (never/ex/current), HbA1c (mmol/mol), total cholesterol (mmol/l), triglycerides (mmol/l), hypertension (yes/no), prevalent myocardial infarction (yes/no), prevalent stroke (yes/no), use of non-steroidal anti-inflammatory drugs (NSAIDs) (yes/no), use of lipid-lowering drugs (yes/no) and estimated glomerular filtration rate (eGFR; ml/min per 1.73 m^2). Results were expressed as odds ratios (ORs) and 95 % confidence intervals (CIs) for increments of 1 μg/ml in serum levels of selenoprotein P. Analyses were also performed stratified by sex to explore potential sex differences.

In supplementary analyses, we assessed the associations between selenoprotein P and the MNSI score (continuous) at baseline and prospectively. We used linear regression analysis with the same three models described earlier and results were expressed as β estimates and 95 % CIs. Models for the prospective analysis of the MNSI score at KORA FF4 were adjusted for the MNSI score at baseline (F4).

Effect modification by glycaemic status (normal glucose tolerance and prediabetes vs. type 2 diabetes) was assessed using interaction terms and *p* values for interaction terms were reported ($p_{interaction}$).

All statistical analyses were conducted with SAS version 9.4 (SAS Institute, Cary, NC, USA). p values < 0.05 were considered to indicate statistical significance.

3. Results

3.1. Study population

The characteristics of the cross-sectional sample (n = 1053) overall and stratified by prevalence of DSPN and diabetes status are shown in Table 1. Briefly, in the total sample, individuals with prevalent DSPN (n = 183) were older, more likely to be male, had a higher BMI and an overall less favourable metabolic and lifestyle profile compared to those without prevalent DSPN (n = 870) (all $p < 0.05$). Differences between individuals with and without DSPN were similar or sometimes less pronounced in the subgroup with normal glucose tolerance or prediabetes (n = 836) than in the subgroup with diabetes (n = 217).

Serum concentrations of selenoprotein P were normally distributed as shown for the total study sample in Supplementary Fig. 1. Selenoprotein P levels were lower in individuals with DSPN compared to those without DSPN in the subgroup without diabetes (mean (SD) 5.8 (1.1) vs. 6.1 (1.1) μg/ml, $p = 0.0086$), whereas no significant differences were seen in the total sample or in individuals with diabetes (both $p > 0.08$; Table 1). Selenoprotein P levels were inversely associated with age (Supplementary Fig. 2).

The characteristics of the prospective sample (n = 515) overall and stratified by incidence of DSPN and diabetes status are shown in Table 2. There were no differences in selenoprotein P levels between individuals without and with incident DSPN neither in the total study sample nor in the subgroups stratified by diabetes status (all $p > 0.30$).

3.2. Cross-sectional association between selenoprotein P and prevalent DSPN

In the total sample, selenoprotein P levels were not associated with prevalent DSPN ($p > 0.08$ for all models, Table 3). However, we observed a significant interaction by diabetes status ($p_{interaction}<0.05$). Higher levels of selenoprotein P were associated with lower odds of prevalent DSPN in all 3 models in individuals without diabetes (model 1: OR 0.795 [95 % CI 0.669, 0.944], $p = 0.0089$; model 2: OR 0.834 [95 % CI 0.700, 0.995], $p = 0.0438$; model 3: OR 0.825 [95 % CI 0.682, 0.998], $p = 0.0476$). In contrast, the ORs for prevalent DSPN were larger than 1.0 in individuals with diabetes but associations were not significant in any model (all $p > 0.30$).

In a sex-stratified analysis, effect estimates for men and women were similar with largely overlapping 95 % CIs between both sexes (Supplementary Tables 1a and 1b).

The findings for prevalent DSPN were confirmed when analysing the association between selenoprotein P and the MNSI score as a continuous variable. As shown in Supplementary Table 2, there was no association in the total sample but a significant interaction with diabetes status ($p < 0.02$ for all models). Selenoprotein P was inversely associated with the MNSI score in individuals without diabetes whereas no association was seen in individuals with diabetes (Fig. 2).

3.3. Prospective association between selenoprotein P and incident DSPN

The associations between selenoprotein P and incident DSPN are shown in Table 4. There were no significant associations identified in the

Table 1
Baseline characteristics of the cross-sectional study population stratified by prevalence of DSPN and T2D status.

Baseline characteristics	Total (n = 1053)				Normal glucose tolerance and Prediabetes (n = 836)			Type 2 diabetes (n = 217)		
	Overall	No DSPN (n = 870)	Prevalent DPSN (n = 183)	*p*	No DPSN (n = 709)	Prevalent DPSN (n = 127)	*p*	No DPSN (n = 161)	Prevalent DPSN (n = 56)	*p*
Age (years)	70.2 (5.3)	69.7 (5.2)	72.6 (5.3)	< **0.0001**	69.4 (5.1)	72.5 (5.4)	< **0.0001**	71.1 (5.4)	72.8 (4.9)	**0.0410**
Sex (male, n,%)	537 (51.0 %)	427 (49.1 %)	110 (60.1 %)	**0.0067**	336 (47.4 %)	70 (55.1 %)	0.1086	91 (56.5 %)	40 (71.4 %)	**0.0495**
BMI (kg/m^2)	28.7 (4.5)	28.4 (4.2)	30.2 (5.2)	< **0.0001**	27.9 (4.0)	29.5 (4.8)	< **0.0001**	30.7 (4.5)	31.9 (5.8)	0.1245
Waist circumference (cm)	98.3 (12.2)	97.1 (11.7)	103.8 (12.9)	< **0.0001**	95.5 (11.2)	101.8 (13.0)	< **0.0001**	104.2 (11.1)	108.4 (11.7)	**0.0152**
Total cholesterol (mmol/L)	5.7 (1.0)	5.8 (1.0)	5.5 (1.0)	**0.0005**	5.8 (1.0)	5.6 (1.0)	**0.0418**	5.4 (1.0)	5.1 (0.9)	**0.0248**
LDL cholesterol (mmol/L)	3.6 (0.9)	3.6 (0.9)	3.4 (0.9)	**0.0028**	3.7 (0.9)	3.5 (0.9)	0.0677	3.4 (0.9)	3.2 (0.8)	0.0666
HDL cholesterol (mmol/L)	1.4 (0.4)	1.4 (0.4)	1.4 (0.3)	**0.0304**	1.5 (0.4)	1.4 (0.3)	0.2300	1.3 (0.3)	1.2 (0.3)	0.5762
Triglycerides (mmol/L)	1.5 (0.9)	1.5 (0.9)	1.4 (0.8)	0.3034	1.4 (0.8)	1.3 (0.7)	0.1343	1.9 (1.4)	1.7 (0.8)	0.3362
HbA1c (%)	5.8 (0.7)	5.7 (0.6)	6.0 (0.8)	< **0.0001**	5.6 (0.3)	5.6 (0.3)	0.0984	6.5 (1.0)	6.8 (1.1)	0.1240
HbA1c (mmol/mol)	39.8 (7.4)	39.4 (6.9)	41.8 (9.1)	< **0.0001**	37.4 (3.5)	38.0 (3.6)	0.0970	48.0 (10.6)	50.5 (11.6)	0.1404
eGFR (ml/min/ 1.73m^2)	76.0 (14.6)	76.8 (14.2)	72.3 (15.9)	**0.0001**	77.6 (13.8)	74.9 (14.5)	**0.0479**	73.6 (15.3)	66.3 (17.5)	**0.0033**
MNSI	2.1 (1.4)	1.7 (1.0)	4.3 (0.9)	< **0.0001**	1.6 (1.0)	4.2 (0.8)	< **0.0001**	1.8 (1.0)	4.7 (1.1)	< **0.0001**
Smoking status (n, %)				0.2465			0.8373			0.1602
Current smoker	77 (7.3 %)	64 (7.4 %)	13 (7.1 %)		52 (7.3 %)	10 (7.9 %)		12 (7.5 %)	3 (5.4 %)	
Former smoker	443 (42.1 %)	356 (40.9 %)	87 (47.5 %)		285 (40.2 %)	54 (42.5 %)		71 (44.1 %)	33 (58.9 %)	
Never smoker	533 (50.6 %)	450 (51.7 %)	83 (45.4 %)		372 (52.5 %)	63 (49.6 %)		78 (48.4 %)	20 (35.7 %)	
Alcohol consumption (n, %)				**0.0011**			0.0553			**0.0074**
None	340 (32.3 %)	277 (31.8 %)	63 (34.4 %)		217 (30.6 %)	39 (30.7 %)		60 (37.3 %)	24 (42.9 %)	
Moderate	602 (57.2 %)	514 (59.1 %)	88 (48.1 %)		424 (59.8 %)	67 (52.8 %)		90 (55.9 %)	21 (37.5 %)	
High	111 (10.5 %)	79 (9.1 %)	32 (17.5 %)		68 (9.6 %)	21 (16.5 %)		11 (6.8 %)	11 (19.6 %)	
Physical activity (n, %)				**0.0088**			0.1061			0.1352
Active	530 (50.3 %)	454 (52.2 %)	76 (41.5 %)		390 (55.0 %)	60 (47.2 %)		64 (39.8 %)	16 (28.6 %)	
Inactive	523 (49.7 %)	416 (47.8 %)	107 (58.5 %)		319 (45.0 %)	67 (52.8 %)		97 (60.2 %)	40 (71.4 %)	
Stroke (n, %)	42 (4.0 %)	27 (3.1 %)	15 (8.2 %)	**0.0014**	18 (2.5 %)	9 (7.1 %)	**0.0076**	9 (5.6 %)	6 (10.7 %)	0.1929
Myocardial infarction (n, %)	63 (6.0 %)	47 (5.4 %)	16 (8.7 %)	0.0833	33 (4.7 %)	9 (7.1 %)	0.2479	14 (8.7 %)	7 (12.5 %)	0.4069
Hypertension (n, %)	653 (62.0 %)	535 (61.5 %)	118 (64.5 %)	0.4493	405 (57.1 %)	70 (55.1 %)	0.6745	130 (80.8 %)	48 (85.7 %)	0.4042
Lipid-lowering drugs (n, %)	260 (24.7 %)	209 (24.0 %)	51 (27.9 %)	0.2728	155 (21.9 %)	31 (24.4 %)	0.5250	54 (33.5 %)	20 (35.7 %)	0.7675
NSAIDs (n, %)	43 (4.1 %)	30 (3.5 %)	13 (7.1 %)	**0.0231**	23 (3.2 %)	7 (5.5 %)	0.2058	7 (4.4 %)	6 (10.7 %)	0.0838
Selenoprotein P (µg/ ml)	6.1 (1.2)	6.1 (1.2)	5.9 (1.1)	0.0816	6.1 (1.1)	5.8 (1.1)	**0.0086**	6.1 (1.4)	6.2 (1.1)	0.5824

Data are given as mean (SD) or counts (%).
Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, haemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MNSI, Michigan Neuropathy Screening Instrument; NSAIDs, non-steroidal anti-inflammatory drugs; T2D, type 2 diabetes.
Bold print indicates statistical significance ($p < 0.05$).

total sample or in either of the subgroups without and with diabetes (all $p > 0.3$). Again, effect estimates were similar between men and women in a sex-stratified analysis (Supplementary Tables 3a and 3b). The same results were obtained when estimating the prospective associations between baseline selenoprotein P levels and the MNSI score as a continuous variable (Supplementary Table 4).

Table 2
Baseline characteristics of the prospective study population stratified by prevalence of DSPN and T2D status.

Baseline characteristics	Total (n = 515)				Normal glucose tolerance and Prediabetes (n = 436)			Type 2 diabetes (n = 79)		
	Overall	No DSPN (n = 386)	Incident DSPN (n = 129)	*p*	No DPSN (n = 333)	Incident DPSN (n = 103)	*p*	No DPSN (n = 53)	Incident DPSN (n = 26)	*p*
Age (years)	68.5 (4.8)	68.0 (4.6)	70.2 (5.0)	< **0.0001**	67.9 (4.6)	69.9 (5.1)	**0.0002**	68.2 (4.6)	71.4 (4.8)	**0.0055**
Sex (male, n,%)	263 (51.1 %)	190 (49.2 %)	73 (56.6 %)	0.1473	160 (48.1 %)	58 (56.3 %)	0.1427	30 (56.6 %)	15 (57.7 %)	0.9268
BMI (kg/m^2)	28.0 (3.9)	27.7 (3.9)	29.1 (4.0)	**0.0004**	27.3 (3.7)	28.6 (3.9)	**0.0029**	30.0 (3.9)	31.0 (3.8)	0.2539
Waist circumference (cm)	96.1 (11.4)	94.9 (11.3)	99.8 (11.0)	< **0.0001**	93.8 (11.0)	98.1 (10.6)	**0.0005**	101.8 (10.3)	106.8 (10.0)	**0.0410**
Total cholesterol (mmol/L)	5.8 (1.1)	5.8 (1.0)	5.6 (1.1)	**0.0161**	5.9 (1.1)	5.6 (1.1)	**0.0370**	5.6 (0.8)	5.4 (1.1)	0.3523
LDL cholesterol (mmol/L)	3.6 (0.9)	3.7 (0.9)	3.5 (1.0)	0.1192	3.7 (1.0)	3.6 (1.0)	0.2058	3.5 (0.7)	3.4 (0.9)	0.5188
HDL cholesterol (mmol/L)	1.4 (0.4)	1.5 (0.4)	1.4 (0.3)	**0.0004**	1.5 (0.4)	1.4 (0.3)	0.0066	1.3 (0.3)	1.2 (0.3)	**0.0403**
Triglycerides (mmol/L)	1.5 (1.0)	1.5 (1.1)	1.6 (0.8)	0.7453	1.4 (0.8)	1.4 (0.7)	0.9018	2.2 (2.0)	2.1 (1.1)	0.7632
HbA1c (%)	5.1 (0.5)	5.7 (0.5)	5.8 (0.7)	**0.0034**	5.5 (0.3)	5.6 (0.3)	0.1661	6.4 (0.7)	6.7 (1.0)	0.0784
HbA1c (mmol/mol)	38.8 (5.9)	38.4 (5.2)	40.1 (7.5)	**0.0055**	37.2 (3.4)	37.6 (3.7)	0.2493	46.1 (7.7)	49.7 (10.6)	0.0857
eGFR (ml/min/ 1.73m^2)	78.6 (13.1)	79.3 (12.8)	76.6 (13.8)	**0.0400**	79.5 (12.9)	77.1 (13.6)	0.1053	78.0 (11.9)	74.4 (14.6)	0.2468
MNSI at baseline (F4)	1.6 (1.0)	1.5 (1.0)	1.9 (1.0)	< **0.0001**	1.5 (1.0)	1.9 (0.9)	0.0016	1.4 (1.0)	2.1 (1.0)	**0.0056**
MNSI at follow-up (FF4)	2.5 (1.5)	1.9 (0.9)	4.4 (0.9)	< **0.0001**	1.8 (1.0)	4.4 (0.9)	< **0.0001**	1.9 (0.9)	4.6 (1.0)	< **0.0001**
Smoking status (n, %)				0.0465			0.0941			0.4259
Current smoker	35 (6.8 %)	21 (5.4 %)	14 (10.9 %)		18 (5.4 %)	10 (9.7 %)		3 (5.7 %)	4 (15.4 %)	
Former smoker	209 (40.6 %)	165 (42.8 %)	44 (34.1 %)		140 (42.0 %)	33 (32.0 %)		25 (47.2 %)	11 (42.3 %)	
Never smoker	271 (52.6 %)	200 (51.8 %)	71 (55.0 %)		175 (52.6 %)	60 (58.3 %)		25 (47.2 %)	11 (42.3 %)	
Alcohol consumption (n, %)				0.9061			0.5273			0.4425
None	159 (30.9 %)	121 (31.3 %)	38 (29.5 %)		105 (31.5 %)	27 (26.2 %)		16 (30.2 %)	11 (42.3 %)	
Moderate	303 (58.8 %)	225 (58.3 %)	78 (60.5 %)		193 (58.0 %)	66 (64.1 %)		32 (60.4 %)	12 (46.2 %)	
High	53 (10.3 %)	40 (10.4 %)	13 (10.1 %)		35 (10.5 %)	10 (9.7 %)		5 (9.4 %)	3 (11.5 %)	
Physical activity (n, %)				**0.0001**			**0.0001**			0.5722
Active	294 (57.1 %)	239 (61.9 %)	55 (42.6 %)		213 (64.0 %)	44 (42.7 %)		26 (49.1 %)	11 (42.3 %)	
Inactive	221 (42.9 %)	147 (38.1 %)	74 (57.4 %)		120 (36.0 %)	59 (57.3 %)		27 (50.9 %)	15 (57.7 %)	
Stroke (n, %)	4 (0.8 %)	3 (0.8 %)	1 (0.8 %)	1.0000	3 (0.9 %)	1 (1.0 %)	1.0000	0 (0.0 %)	0 (0.0 %)	0.1055
Myocardial infarction (n, %)	28 (5.4 %)	19 (4.9 %)	9 (7.0 %)	0.3730	16 (4.8 %)	4 (3.9 %)	1.0000	3 (5.7 %)	5 (19.2 %)	0.1066
Hypertension (n, %)	300 (58.3 %)	216 (56.0 %)	84 (65.1 %)	0.0679	179 (53.8 %)	61 (59.2 %)	0.3295	37 (69.8 %)	23 (88.5 %)	0.0940
Lipid-lowering drugs (n, %)	121 (23.5 %)	88 (22.8 %)	33 (25.6 %)	0.5186	69 (20.7 %)	24 (23.3 %)	0.5764	19 (35.9 %)	9 (34.6 %)	0.9142
NSAIDs (n, %)	7 (1.4 %)	4 (1.0 %)	3 (2.3 %)	0.3746	4 (1.2 %)	1 (1.0 %)	1.0000	0 (0.0 %)	2 (7.7 %)	0.1055
Selenoprotein P (µg/ml)	6.2 (1.2)	6.2 (1.1)	6.1 (1.2)	0.3146	6.2 (1.1)	6.0 (1.2)	0.3001	6.3 (1.2)	6.2 (1.2)	0.7300

Data are given as mean (SD) or counts (%).
Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, haemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MNSI, Michigan Neuropathy Screening Instrument; NSAIDs, non-steroidal anti-inflammatory drugs; T2D, type 2 diabetes.
Bold print indicates statistical significance ($p < 0.05$).

4. Discussion

4.1. Key findings

Our study has three main findings: First, the association between selenoprotein P and prevalent DSPN in older adults from a population-based cohort depends on diabetes status. Second, higher serum levels of selenoprotein P were associated with lower odds of DSPN only in people without type 2 diabetes, whereas this inverse association was not observed in people with type 2 diabetes. Third, selenoprotein P levels were not associated with incident DSPN over a follow-up time of 6.5 years.

4.2. Inverse association between selenoprotein P and DSPN

The association between circulating selenoprotein P and DSPN has

Table 3
Cross-sectional association between serum concentrations of selenoprotein P and prevalent DSPN.

Model	Total sample (n = 1053)	*p*	NGT and prediabetes (n = 836)	*p*	T2D (n = 217)	*p*	$p_{interaction}$
	OR (95 % CI)		OR (95 % CI)		OR (95 % CI)		
1	0.884 (0.770, 1.016)	0.0819	0.795 (0.669, 0.944)	**0.0089**	1.069 (0.844, 1.353)	0.5806	**0.0468**
2	0.934 (0.811, 1.077)	0.3467	0.834 (0.700, 0.995)	**0.0438**	1.138 (0.891, 1.454)	0.3003	**0.0273**
3	0.920 (0.791, 1.071)	0.2826	0.825 (0.682, 0.998)	**0.0476**	1.098 (0.829, 1.454)	0.5132	**0.0488**

Abbreviation: NGT, normal glucose tolerance.
Model 1: unadjusted.
Model 2: adjusted for age and sex.
Model 3: model 2 + adjustment for waist circumference, physical activity, alcohol, smoking status, HbA1c, total cholesterol, triglycerides, hypertension, myocardial infarction, stroke, use of NSAIDs use, use of lipid-lowering drugs and eGFR.
Bold print indicates statistical significance ($p < 0.05$).

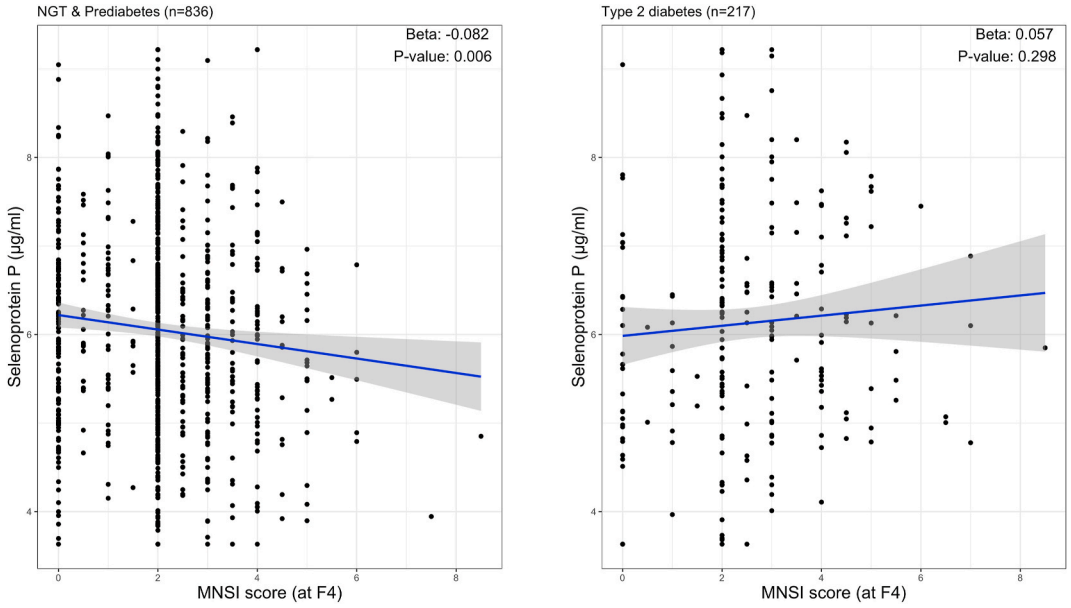

Fig. 2. Association between the MNSI score and serum concentrations of selenoprotein P at baseline (KORA F4) stratified by diabetes status. The shaded area represents the 95 % CI of the linear regression line.

Table 4
Prospective association between serum concentrations of selenoprotein P and incident DSPN.

Model	Total sample (n = 515)	*p*	NGT and prediabetes (n = 436)	*p*	T2D (n = 79)	*p*	$p_{interaction}$
	OR (95 % CI)		OR (95 % CI)		OR (95 % CI)		
1	0.914 (0.767, 1.089)	0.3141	0.901 (0.740, 1.097)	0.3838	0.931 (0.625, 1.388)	0.7261	0.8859
2	0.954 (0.797, 1.141)	0.6054	0.939 (0.769, 1.148)	0.5425	0.945 (0.623, 1.433)	0.7895	0.9636
3	0.957 (0.791, 1.157)	0.6487	0.924 (0.746, 1.144)	0.4662	1.011 (0.592, 1.725)	0.9686	0.9704

Abbreviation: NGT, normal glucose tolerance.
Model 1: unadjusted.
Model 2: adjusted for age and sex.
Model 3: model 2 + adjustment for waist circumference, physical activity, alcohol, smoking status, HbA1c, total cholesterol, triglycerides, hypertension, myocardial infarction, stroke, use of NSAIDs use, use of lipid-lowering drugs and eGFR.
Bold print indicates statistical significance ($p < 0.05$).

not been investigated before so our study extends the literature on this protein biomarker. The observations in the subgroup without type 2 diabetes (i) that people without DSPN had higher selenoprotein P levels than those with DSPN and (ii) that this inverse association was robust to adjustment for multiple confounders are in line with a range of previous studies on selenoprotein P.

The pathogenesis of DSPN is complex and multifactorial. One mechanism that links risk factors such as hyperglycaemia, obesity and older age with neuronal damage is oxidative stress [10,15]. An imbalance between reactive oxygen species (ROS), such as superoxide anion, and both intra- and extracellular scavenger enzymes, such as superoxide dismutases, leads to inflammation and nerve damage so that the inverse association between the antioxidant selenoprotein P and DSPN is biologically plausible. Selenoprotein P affects the redox balance either by direct action to suppress the formation of reactive oxygen species or by supplying selenium to extrahepatic tissues, thus enabling the synthesis of other antioxidant selenoproteins throughout the body [33].

Regarding neuroprotective effects, mechanistic data are limited to mouse models with genetic deficiency of the gene encoding selenoprotein P (*Selenop*, also known as *Sepp1*) and to clinical studies linking

circulating selenoprotein P levels with various neurological conditions. Mice with a deletion of *Selenop* develop severe neuronal and axonal degeneration in the central nervous system when fed a low-selenium diet [19,20,22]. Affected brain regions are characterised by high basal metabolic rates and may be particularly susceptible to oxidative stress resulting from low selenium supply [20]. In humans, studies in small patient cohorts investigated associations between selenoprotein P levels and cognitive impairment or dementia but results were contradictory [27,34]. Therefore, future studies addressing the potential mechanisms linking selenoprotein P and both central and peripheral nerve function are clearly needed.

Oxidative stress also increases the risk of cardiovascular events, heart failure, cancer and mortality [35]. Therefore, it appears plausible that higher selenoprotein P concentrations in the circulation were found associated with a lower incidence of first cardiovascular events and heart failure as well as with lower rates of cardiovascular, cancer-related and all-cause mortality in population-based cohorts [4–6].

A causal relationship between selenoprotein P and DSPN would be supported by a clear temporal relationship, but our study could not observe an association between selenoprotein P and incident DSPN in the prospective analysis. This null finding could on the one hand be possible because the inverse association that we found in people without DSPN was still affected by residual confounding despite our efforts to adjust for multiple covariables. On the other hand, it is also possible that a decrease in selenoprotein P could occur within a shorter timeframe before the onset of DSPN, which could not be detected based on our study design with baseline and follow-up examination being 6.5 years apart. Of note, there is no evidence of a causal link in the other direction because a direct impact of nerve damage in DSPN on lowering selenoprotein P levels in the circulation appears rather unlikely.

4.3. Interaction with diabetes status

In this study, the inverse association between selenoprotein P and prevalent DSPN was not observed in people with type 2 diabetes. Whereas higher circulating levels of selenoprotein P were associated with lower risk for cardiovascular events, cause-specific and all-cause mortality as discussed above [4–6], several studies found positive associations between higher selenoprotein P levels and insulin resistance [36], prevalent prediabetes or type 2 diabetes [37] and the development of hyperglycaemia [9]. These results were corroborated by mouse models in which overexpression of selenoprotein P caused insulin resistance and the genetic deletion or antibody-based neutralisation of selenoprotein P improved insulin sensitivity [7,8].

In contrast, other studies reported inverse associations between selenoprotein P and hyperglycaemia, insulin resistance and gestational diabetes [38–40]. Additionally, selenoprotein P levels were inversely associated with adipose tissue distribution and metabolite profiles that were indicative of a higher risk of type 2 diabetes [38,41].

There may be several reasons for these discrepancies. First, knockdown or overexpression of selenoprotein P in mouse models may indicate a causal relationship but selenoprotein P levels far below or above normal levels could result in substantial oxidative stress due to downregulation of antioxidant defence or reductive stress by elimination of physiological ROS levels, respectively [42], which limits the transferability of these findings to humans. Second, it has been hypothesised that a positive association between selenoprotein P and diabetes might be attributable to reverse causality, i.e. a compensatory upregulation of selenoprotein P levels by hyperglycaemia, insulin resistance, oxidative stress or subclinical inflammation which characterise type 2 diabetes [1,2,5] and also contribute to nerve damage. In this scenario, the degree of upregulation of selenoprotein P levels may not be sufficient to protect against DSPN in the presence of multiple risk factors of DSPN. However, these explanations remain speculative in the absence of further mechanistic evidence.

Results from intervention studies with dietary selenium in type 2 diabetes were inconsistent so far which may be explained by the heterogeneity of study designs and study populations, differences in the background selenium status and differences in selenium dosages in these trials [43]. In generally, people in Europe tend to have lower selenium levels due to less selenium in the soil compared with the US and Asia, which may be relevant for the different effects of selenium on health. Additional research should focus on the role of selenium deficiency, which could represent a potentially easily addressable risk factor in people with type 2 diabetes and/or DSPN by improving the individual nutritional pattern.

4.4. Strengths and limitations

The main strength of this study is its population-based design including older people with and without type 2 diabetes so that the impact of diabetes status on the association between selenoprotein P and DSPN could be assessed. This study design also allowed the analysis of selenoprotein P levels in the physiological range whereas experimental models often exhibit selenoprotein P concentrations far below or above this range. The present study used two types of monoclonal antibodies with known epitopes which allowed the quantification of full-length selenoprotein P. Additionally, our analyses were rigorously adjusted for multiple demographic, anthropometric, metabolic and clinical confounders to assess whether selenoprotein P is independently associated with DSPN.

Limitations of our study include the fact that no data for selenoprotein P levels from the KORA FF4 follow-up survey were available so that we could not analyse the longitudinal associations between changes in selenoprotein P and the MNSI score. We used the examination part of the MNSI to define possible DSPN whereas nerve conduction studies, which were not feasible in this population-based setting, would have been required to confirm the diagnosis of DSPN. Due to the relatively old age at the study baseline, the participation rate in the follow-up study was reduced which resulted in lower statistical power for the prospective analysis compared to the cross-sectional analysis. The selection of older study participants of European descent also means that the data cannot be generalised to younger groups and other ethnicities. This is also important because there are significant geographical variations in selenium levels which might affect studies on the role of selenoproteins [43,44]. Lastly, data for a comprehensive assessment of oxidative stress were not available so that we could not perform mediation analyses for this potential mechanistic pathway.

5. Conclusions

In this study, serum levels of selenoprotein P were inversely associated with prevalent DSPN in people without type 2 diabetes, which could be attributable to the antioxidant properties of selenoprotein P. This association was not seen in people with type 2 diabetes, which may be explained by a complex, but futile upregulation of selenoprotein P which is not pronounced enough to protect against DSPN. We could not observe an association with incident DSPN over a follow-up of 6.5 years so future prospective studies should investigate different timeframes to clarify the temporal relationship between selenoprotein P and the onset of DSPN.

Ethical approval

The KORA surveys were conducted in line with the Declaration of Helsinki and approved by the ethics board of the Bavarian Chamber of Physicians (Munich, Germany; ethics no. for KORA F4/FF4: 06068). All participants provided written informed consent.

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Consent for publication

All authors agree to the content of the paper.

Data availability

The data are subject to national data protection laws. Therefore, data cannot be made freely available in a public repository. However, data can be requested through an individual project agreement with KORA. To obtain permission to use KORA data under the terms of a project agreement, please use the digital tool KORA.PASST (https://epi.helmholtz-muenchen.de/).

CRediT authorship contribution statement

Christian Herder: Conceptualization, Data curation, Funding acquisition, Investigation, Project administration, Supervision, Writing – original draft. **Yoshiro Saito:** Conceptualization, Data curation, Funding acquisition, Project administration, Supervision, Writing – review & editing. **Maria C. Spagnuolo:** Formal analysis, Visualization, Writing – review & editing. **Haifa Maalmi:** Formal analysis, Writing – review & editing. **Misaki Shimizu:** Investigation, Writing – review & editing. **Gidon J. Bönhof:** Investigation, Writing – review & editing. **Keita Suzuki:** Investigation, Writing – review & editing. **Wolfgang Rathmann:** Investigation, Writing – review & editing. **Annette Peters:** Investigation, Writing – review & editing. **Michael Roden:** Funding acquisition, Investigation, Writing – review & editing. **Dan Ziegler:** Investigation, Methodology, Writing – review & editing. **Barbara Thorand:** Data curation, Investigation, Project administration, Supervision, Writing – review & editing. **Toshinari Takamura:** Conceptualization, Project administration, Supervision, Writing – review & editing.

Declaration of competing interest

All authors declare that there are no conflicts of interest in connection with this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.freeradbiomed.2024.07.028.

Abbreviations

CI	Confidence interval
DSPN	Distal sensorimotor polyneuropathy
eGFR	Estimated glomerular filtration rate
HbA1c	Haemoglobin A1c
KORA	Cooperative Health Research in the Region of Augsburg
MNSI	Michigan Neuropathy Screening Instrument
NSAID	Non-steroidal anti-inflammatory drug
OGTT	Oral glucose tolerance test
OR	Odds ratio
ROS	Reactive oxygen species
T2D	Type 2 diabetes

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