Nutrition Research 122 (2024) 44–54

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/NTR

Original Research

Adherence to the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet and exposure to selenium species: A cross-sectional study

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ARTICLE INFO

Article history:
Received 4 August 2023
Revised 1 December 2023
Accepted 1 December 2023

Keywords:
Cognitive decline
MIND diet
Neurodegeneration
Prevention
Selenium
Selenium species

ABSTRACT

Selenium is a trace element found in many chemical forms. Selenium and its species have nutritional and toxicologic properties, some of which may play a role in the etiology of neurological disease. We hypothesized that adherence to the Mediterranean-Dietary Approach to Stop Hypertension Intervention for Neurodegenerative Delay (MIND) diet could influence intake and endogenous concentrations of selenium and selenium species, thus contributing to the beneficial effects of this dietary pattern. We carried out a cross-sectional study of 137 non-smoking blood donors (75 females and 62 males) from the Reggio Emilia province, Northern Italy. We assessed MIND diet adherence using a semiquantitative food frequency questionnaire. We assessed selenium exposure through dietary intake and measurement of urinary and serum concentrations, including speciation of selenium compound in serum. We fitted non-linear spline-based regression models to investigate the association between MIND diet adherence and selenium exposure concentrations. Adherence to the MIND diet

Abbreviations: BMI, body mass index; CI, confidence interval; DASH, Mediterranean-Dietary Approach to Stop Hypertension; DRC, dynamic reaction cell; ICP-MS, inductively coupled plasma-mass spectrometry; MIND, Mediterranean-DASH Intervention for Neurodegenerative Delay; RCT, randomized controlled trial; Se-Cys, selenocystine-bound selenium; Se-GPX, glutathione-peroxidase-bound selenium; Se-HSA, human serum albumin-bound selenium; Se-Met, selenomethionine-bound selenium; Se-SELENOP, selenoprotein P-bound selenium; Se- TXNRD, thioredoxin reductase-bound selenium.

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https://doi.org/10.1016/j.nutres.2023.12.002

was positively associated with dietary selenium intake and urinary selenium excretion, whereas it was inversely associated with serum concentrations of overall selenium and organic selenium, including serum selenoprotein P-bound selenium, the most abundant circulating chemical form of the metalloid. MIND diet adherence also showed an inverted U-shaped relation with inorganic selenium and particularly with its hexavalent form, selenate. Our results suggest that greater adherence to the MIND diet is non-linearly associated with lower circulating concentrations of selenium and of 2 potentially neurotoxic species of this element, selenoprotein P and selenate. This may explain why adherence to the MIND dietary pattern may reduce cognitive decline.

1. Introduction

The Mediterranean-Dietary Approach to Stop Hypertension (DASH) Intervention for Neurodegenerative Delay (MIND) diet is a dietary pattern that has been shown in several studies to reduce the risk dementia and cognitive decline [1–5]. It is mainly based on dietary components from the DASH and the Mediterranean diets, which each showed protective effects on cognitive decline in nonexperimental and experimental human studies, including randomized controlled trials (RCT) [6,7]. MIND diet entails high consumption of natural plant-based foods and low rations of foods with elevated intake of animal and high saturated fat, such as butter or margarine, instead favoring a high consumption of foods associated with slower cognitive decline, such as berries and green leafy vegetables [8,9]. The main source of fat in the MIND diet is olive oil, and consumption of 1 glass per day of wine is not discouraged [10].

Selenium is a metalloid generally present in trace amounts in the environment and foods as well as tobacco smoke. The role of selenium in human health has been highly debated because it has both toxic and essential nutritional properties, depending on dose and chemical species [11–14]. Selenium is a component of several enzymes with functions related to antioxidant defense, redox signaling, and homeostasis [15]. Selenium's role in neurodegenerative diseases and cognitive impairment has been investigated in a handful of epidemiological studies, often leading to inconsistent or conflicting results [16–21], with little evidence of beneficial effects from an experimental study [22] and with some indicating adverse effects in an observational cohort study, with reference to inorganic hexavalent selenium and to selenoprotein P [18,23]. RCTs have documented adverse effects of selenium at lower doses than previously believed to be harmful [24,25], and the tolerable upper intake level of this trace element was recently reduced by the European Food Safety Authority in 2023 [26].

In this cross-sectional study, we investigated the extent to which adherence to the MIND diet in a healthy non-smoking population may be associated with selenium exposure ascertained in diet, urine, and serum. We also assessed how the MIND diet could influence concentrations of selected organic and inorganic selenium species in serum.

2. Methods and materials

2.1. Study population

Subjects composing the present study population were selected at the Transfusion Medicine Center of AUSL-IRCCS of Reggio Emilia [27–29], following the approval of the study protocol by the relevant Ethics Committee (AVEN Ethics Committee approval no. 2016/0022799]. A study flowchart is presented in Fig. S1. Overall, 148 healthy blood donors were consecutively contacted for participating in the study during their blood donation, provided they were aged ≥18 years, unaffected by chronic disease including cancer, and non-smokers. A total of 137 subjects were eventually enrolled. All participants provided written informed consent. Personal and medical history data were collected using a questionnaire administered by a clinician at the time of blood donation. Participants also provided fasting blood glucose and urinary samples.

2.2. Dietary assessment

Participants completed a validated semiquantitative food frequency questionnaire derived from that used in the European Prospective Investigation into Cancer and Nutrition, after specific validation in a Northern Italian population [30–32]. The food frequency questionnaire included questions on frequency and quantity of consumption of 188 food items over the previous year, as previously described [33,34]. Adherence to the MIND diet was calculated using a formula developed by Morris et al. using 10 brain-healthy and 5 brain-unhealthy food groups derived from literature on nutrition and cognitive decline [1]. Intake of foods was estimated using a tailored Stata software routine [35]. After summing the frequency of consumption of each food portion, we assigned a concordance score of 0, 0.5, or 1 (Table S1). Thus, higher consumption of foods associated with a healthy brain (green leafy vegetables, other vegetables, berries, nuts, whole grains, fish not fried, beans, and poultry not fried) and lower consumption of red and processed meat, butter and margarine, cheese, fast food, and sweets (e.g., pastries, baked goods) generated higher scores. For wine intake, a score of 1 was assigned if consumption was of 1 unit per day. Otherwise, the score was 0 for no consumption or consumption of more than 1 glass per day;

the score was 0.5 if consumption was less than 1 glass per day. Other types of alcohol were not considered. For olive oil, a score of 1 was assigned if it was the primary cooking fat, otherwise the score was 0. The total score was extrapolated by summing that assigned to each food component, ranging from 0 to 15.

We assessed dietary selenium intake by multiplying trace element concentrations in foods with the pattern of average consumption, based on the dietary assessment [33]. Briefly, vegetables had a low content of selenium, except for cabbage, onion, mushrooms, and garlic. Meat (red or processed), milk and dairy products, eggs, fish, and seafood were the greatest contributors to total daily selenium intake [33].

2.3. *Analytical determination of selenium in urine and serum*

2.3.1. *Urinary selenium*

Urine samples were collected in polypropylene tubes stored at −20 °C. For analysis, urine samples were thawed at room temperature for 2 hours. To dissolve the sediment for the analysis, samples were mixed and heated for 30 minutes at 37 °C. An aliquot of 600 µL was transferred into a polyethylene tube, added to an aqueous solution of nitric acid 0.05% v/v prepared by diluting ultrapure nitric acid (69% TraceSelect, Fluka, France), containing 7.5 µg/L of Scandium-45), Yttrium-89, and Indium-111 (Inorganic Ventures, Inc., Lakewood, NJ, USA) as internal standards. Samples were analyzed by inductively coupled plasma-mass spectrometry (ICP-MS) (X Series II, Thermo Electron Corporation, Rodano, Italy). The instrument was operated in collision cell mode (CCT-Ked), with 3.7 mL/minutes of helium used to reduce interference. Samples were run in triplicate. The calibration curve was prepared in the range of 0.2 to 70 µg/L and the calibration solutions were obtained by diluting a selenous acid standard solution containing selenium at 1 mg/mL (BDH, VWR International, Milan). Ultrapure water (conductivity 0.056 µS/cm) (Milli-Q, Merck, Darmstadt, Germany) was used to prepare all solutions. The quality assurance was assessed using quality controls for metals in urine from Lyphocheck Urine Metals Control (Level-1, Bio-Rad Laboratories, Anaheim, CA, USA) and Seronorm (Level-1, Sero AS, Billingstad, Norway). The limit of quantification was 1.2 µg/L. Accuracy and precision ranged from 90% to 110% and from 7% to 11%, respectively.

2.3.2. *Selenium and selenium speciation analyses*

For speciation of selenium compounds, we used the hyphenated system from Perkin Elmer (Rodgau, Germany) comprising a NexSAR gradient HPLC pump, autosampler, and NexION 300 D inductively coupled plasma-dynamic reaction cell-mass spectrometry (ICP-DRC-MS), completely controlled by Clarity software and the ion exchange-separation column for species separation (AG-11+AS-11 from Thermo Dionex, Idstein, Germany). The sample volume was 50 µL and the flow rate was 0.80 mL/min. The mobile phases and chromatographic gradient were previously published [36]. The experimental settings for ICP-DRC-MS were radio frequency power: 1250 W; plasma gas flow: 15 L Ar/min; auxiliary gas flow: 1.05L Ar/min; nebulizer gas flow: 0.92 L Ar/min; daily optimized, dwell time: and 300 ms. Ions monitored were: ^{77}Se, ^{78}Se, ^{80}Se; DRC reaction gas: CH_4 reaction at 0.58 mL/min, and DRC rejection parameter q: 0.6. The selenium species selenite, selenate, selenomethionine-bound selenium (Se-Met), selenocystine-bound selenium (Se-Cys), thioredoxin reductase–bound selenium (Se-TXNRD), glutathione-peroxidase-bound selenium (Se-GPX), selenoprotein P–bound selenium (Se-SELENOP), and human serum albumin-bound selenium (Se-HSA) were analyzed. Data files from selenium chromatograms were processed with Clarity software for peak area integration. Total serum selenium concentration was measured by ICP sector-field MS. The experimental settings for ICP sector-field MS (ELEMENT II, Thermo Scientific, Bremen, Germany) were as follows: radiofrequency power: 1260 W; plasma gas flow: 16L Ar/min; auxiliary gas flow: 0.85L Ar/min; nebulizer gas flow: 1.085 L Ar/min; daily optimized, dwell time 300 ms, and ions monitored: ^{77}Se, ^{78}Se, high-resolution mode. Five-point calibration curves from 0 to 5000 ng/L were linear with r^2 for the 3 Se isotopes being better than 0.999881. Given budget limitations, we assayed selenium and selenium species in serum for only for the first 104 participants recruited.

2.4. *Data analysis*

We assessed the association between adherence to the MIND diet and selenium exposure as measured in diet, urine, and serum alongside its 95% confidence intervals (CI), using linear and non-linear spline-based regression analyses. In these analyses, we adjusted for sex as discrete variable, along with age, body mass index (BMI), and energy intake as continuous variables. No study participants had missing variables or had to be excluded from multivariable modeling.

We then performed non-linear spline regression analysis, based on a restricted cubic spline model [37,38] using 3 knots at fixed percentiles (10th, 50th, and 90th) of selenium exposure concentrations. To reduce the effect of the outliers by assigning them a lower weight, winsorization was performed for urinary selenium, dietary selenium intake, total serum selenium, and for all selenium species. Sex-stratified analyses were also performed because of sex-related differences in dietary intake and potential varied effects of the MIND diet on selenium exposure by sex [39]. We carried out these analyses using the "mkspline," "regress," "winsor," and "xbcrsplinei" routines in Stata (version 17.0, Stata Corp., College Station, TX, 2021).

3. Results

Table 1 and Fig S2-S4 report the main characteristics of the study population along with mean MIND diet adherence scores and mean urinary, dietary, and serum selenium concentrations, accounting for sex, age, BMI category, smoking, marital status, and educational attainment. Mean MIND diet adherence score was 7.6, which was similar in females (7.9) compared with males (7.3). Females showed higher selenium intake and biomarker concentrations than males. Higher adherence to MIND was associated with normal weight, whereas lower MIND diet adherence was associated with overweight and obesity or being single.

Table 1 – Characteristics of the study population composed of healthy subjects and mean MIND diet adherence, urinary and dietary Se ($n = 137$) and serum Se ($n = 104$) concentrations for each subgroup of the cohort.

Characteristics	All						Males						Females					
	N	%	Urinary Se (μg/L)	Dietary Se (μg/day)	Serum Se (μg/L)	MIND diet	*N*	%	Urinary Se (μg/L)	Dietary Se (μg/day)	Serum Se (μg/L)	MIND diet	*N*	%	Urinary Se (μg/L)	Dietary Se (μg/day)	Serum Se (μg/L)	MIND diet
All subjects	137	100	26.8	84.1	117.4	7.6	62	45.3	29.0	90.0	119.2	7.3	75	54.7	24.9	79.2	115.8	7.9
Age (y)																		
<50	80	58.4	27.2	86.1	116.8	7.6	39	62.9	30.2	91.0	119.0	7.2	41	54.7	24.4	81.5	114.5	7.9
≥50	57	41.6	26.1	81.2	118.4	7.7	23	37.1	27.0	88.3	119.5	7.3	34	45.3	25.5	76.4	117.5	7.9
BMI (kg/m²)																		
<25	74	54.0	25.6	82.2	116.5	8.0	32	51.6	28.5	91.1	116.9	7.6	42	56.0	23.4	75.4	116.1	8.2
≥25–<30	50	36.5	28.6	84.2	119.8	7.2	27	43.6	29.5	87.0	122.1	6.9	23	30.7	27.5	80.9	117.1	7.5
≥30	13	9.5	26.5	94.3	112.0	7.4	3	4.8	30.4	104.3	117.0	6.8	10	13.3	25.4	91.3	110.3	7.6
Smoking history																		
Never	101	73.7	26.1	83.9	117.5	7.6	45	72.6	28.8	88.6	118.9	7.2	56	74.7	23.9	80.2	116.2	7.9
Former	36	26.3	28.7	84.5	117.3	7.8	17	27.4	29.6	93.6	119.9	7.5	19	25.3	27.8	76.4	114.4	8.0
Marital status																		
Married/unmarried partner	97	70.8	26.8	83.1	116.7	7.7	44	71.0	29.7	87.7	117.8	7.4	53	70.7	24.3	79.3	115.7	7.9
Single	26	19.0	27.6	87.7	119.3	7.4	12	19.4	28.8	104.3	121.8	7.1	14	18.7	26.7	73.5	116.7	7.7
Separated/divorced	14	10.2	25.1	84.3	119.0	7.7	6	9.6	24.2	78.0	123.2	6.7	8	10.7	25.7	88.9	114.8	8.4
Educational attainment																		
Elementary school	2	1.5	37.3	147.0	131.5	7.8	2	3.2	37.3	147.0	131.5	7.7	-	-	-	-	-	-
Middle school	20	14.6	26.0	84.8	120.1	7.5	8	12.9	29.5	80.9	126.1	7.2	12	16.0	23.7	87.9	114.7	7.7
High school	66	48.2	23.9	82.7	116.2	7.7	28	45.2	25.0	90.9	114.2	7.2	38	50.7	23.0	76.7	117.9	8.0
College or more	49	35.8	30.6	83.1	117.4	7.6	24	38.7	32.9	87.4	122.5	7.3	25	33.3	28.4	78.9	112.6	7.8

Abbreviations: BMI, body mass index; MIND, Mediterranean-DASH Intervention for Neurodegenerative Delay; Se, selenium.

Figure S5 reports the spline regression analysis showing the association between single components of the MIND diet and total serum selenium concentrations. A monotonic inverse association was found with intake of vegetables (both green leafy and other vegetables), berries, nuts, fish, and poultry. Conversely, a positive association, though not entirely linear, was found for intake of butter/margarine, cheese, whole grain, beans, red meat, pastries and sweets, and wine. After adjustment for age, sex, BMI, and energy intake, spline regression analyses showed a substantially linear association between adherence to the MIND diet and overall selenium exposure as assessed through diet, urinary concentrations, or serum concentrations (Fig. 1). For serum selenium, an inverse association emerged.

When examining the relation between selected MIND diet adherence and selenium compounds in serum, monotonic inverse associations emerged with overall organic selenium and particularly for Se-SELENOP, an almost null association with Se-TXNRD, and a U-shaped pattern of association with Se-GPX, Se-Cys, and Se-Met, although attenuated for the latter, with an inflection point around a MIND diet adherence score of 8. Although selenite did not show a clear pattern of association with MIND diet adherence scores, overall inorganic selenium and the selenate compound exhibited an inverted U-shaped relation, again with an inflection point around 8, as did Se-HSA (Fig. 2).

Overall, unadjusted results were similar to the main analyses (Fig. S6-S7). In sex-specific analyses, there were several differences compared with the overall analysis. Among males, higher levels of adherence to MIND diet (i.e., >8) corresponded with decreased mean urinary and serum selenium concentrations, whereas a positive association emerged among females. Only the results for selenium dietary intake were comparable (Fig. S8). With regard to serum selenium species, different and often opposite trends emerged for males and females, with the only exception being Se-Cys. Among males, the MIND diet showed non-linear inverse associations with total organic selenium and Se-SELENOP, an almost linear inverse association with Se-GPX, a slight positive association with Se-TXNRD, and a generally null association with Se-Met. Adherence to the MIND diet was positively and almost linearly associated with total inorganic selenium and both inorganic species (selenite and selenate), whereas a slight inverse association emerged for Se-HSA (Fig S9). Conversely, among females, we observed U-shaped associations between adherence to the MIND diet and total organic selenium, Se-GPX, and Se-Met. In contrast, we observed inverted U-shaped associations for total inorganic selenium and the 2 inorganic species. J and inverted J associations were observed for Se-SELENOP and Se-HSA, respectively (Fig. S10).

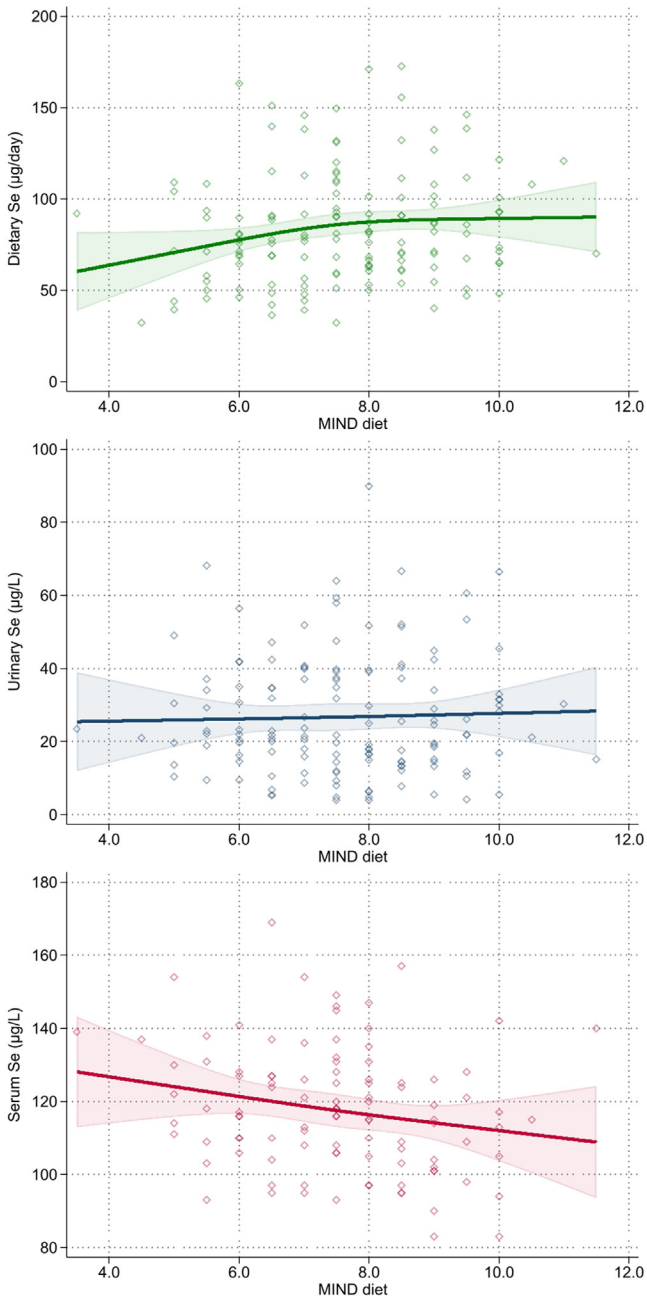

Fig. 1 – Spline regression analysis for the association between MIND diet adherence scores and dietary (n = 137), urinary (n = 137), and serum (n = 104) selenium (Se) concentrations. Analysis adjusted for age, sex, body mass index (BMI), and energy intake. A linear relation emerged between MIND diet adherence and overall selenium exposure, as determined by diet, urine, and serum assessments. Notably, the correlation observed was negative with serum selenium concentrations. MIND, Mediterranean-Dietary Approach to Stop Hypertension Intervention for Neurodegenerative Delay.

4. Discussion

Findings from our cross-sectional study of healthy non-smokers indicate that adherence to the MIND diet influences intake of selenium and selenium species. Our data further support the hypothesis that adherence to the MIND diet counteracts cognitive decline. Greater adherence to the MIND diet demonstrated a positive association with intake and urinary

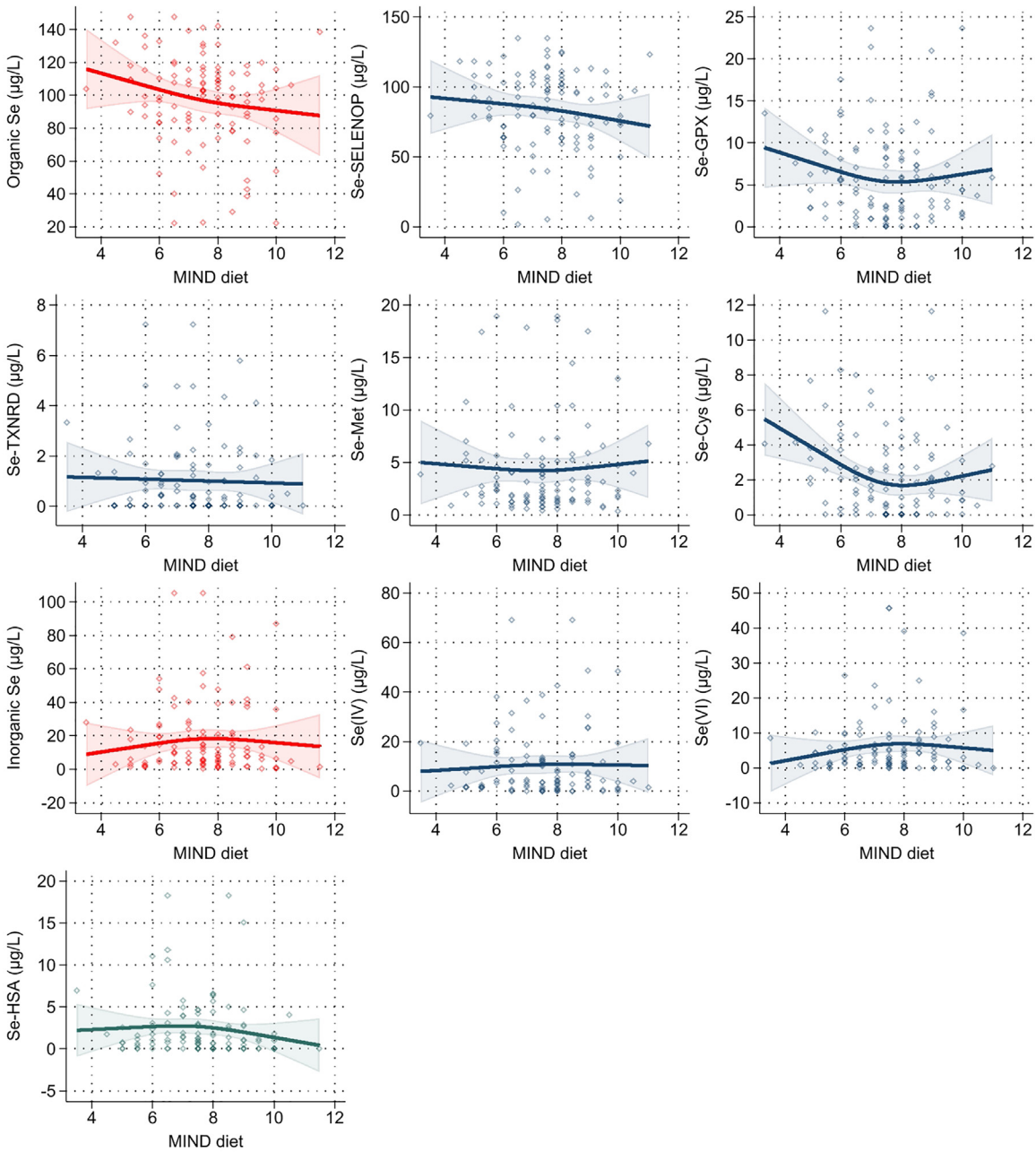

Fig. 2 – Spline regression analysis for the association between MIND diet adherence scores and serum selenium (Se) species concentrations (n = 104). Analysis adjusted for age, sex, body mass index (BMI), and energy intake. Adherence to the MIND diet had varying associations with different serum selenium compounds. Organic selenium and Se-SELENOP showed consistent inverse relationships, whereas Se-TXNRD had minimal correlation. Se-GPX, Se-Cys, and Se-Met displayed a U-shaped pattern. Inorganic selenium and selenate had inverted U-shaped relations, as did Se-HSA. MIND, Mediterranean-Dietary Approach to Stop Hypertension Intervention for Neurodegenerative Delay; Se-Cys, selenocystine-bound selenium; Se-GPX, glutathione-peroxidase-bound selenium; Se-HSA, human serum albumin-bound selenium; Se-Met, selenomethionine-bound selenium; Se-SELENOP, selenoprotein P-bound selenium; Se-TXNRD, thioredoxin reductase-bound selenium; Se(IV), selenite; Se(VI), selenate.

excretion of selenium, as well as diminished serum concentrations of total selenium, mainly because of decreased concentrations of Se-SELENOP, the major selenium transporter in the blood, and of the inorganic species, particularly selenate. Interestingly, both Se-SELENOP and selenate have been suggested to have a neurotoxic potential in a prospective cohort study [18,23]. In addition, we showed an inverse association between MIND diet adherence and Se-HSA concentrations, though this finding is difficult to interpret given the uncertain composition and biological role of Se-HSA [40]. The

opposite patterns of dietary and urinary selenium in relation with MIND diet adherence scores, compared with blood selenium, could be attributable to a higher excretion of the metalloid in subjects with an increased dietary intake because of the MIND diet, possibly from interactions with other dietary constituents [41,42] and consequently lower circulating concentrations of selenium.

In non-occupationally exposed individuals and nonsmokers, exposure to selenium occurs primarily through diet, which is also the major determinant of selenium concentrations in blood (generally in serum or plasma), that represent the most commonly used and most validated biomarkers of selenium exposure in the short to medium term [25,43]. For this reason, serum and plasma selenium concentrations are biomarkers commonly used to assess selenium exposure in epidemiological studies [25]. In our population, urinary selenium concentrations were positively associated with selenium dietary intake, as expected, whereas the association with serum concentrations was negative, suggesting that dietary components of the MIND diet could decrease absorption and increase excretion of the metalloid. This phenomenon could be explained by factors including high consumption of cadmium-rich foods such as fruits and vegetables characterizing the MIND diet [44–46] and therefore an increased selenium excretion from an interaction with this heavy metal [41,42].

Because our study population comprised healthy nonsmokers, we expect that the major contributor to selenium in blood was dietary intake. According to the 2023 report from the European Food Safety Authority on the tolerable upper intake level for selenium, foods that mainly contribute to selenium are meat and meat products, fish and seafood, milk and dairy products, and grains and grain-based products [26]. Accordingly, we found that higher serum selenium concentrations were associated with higher intake of red and processed meats, whole grains, and cheese (though not fish). Conversely, higher intakes of vegetables, berries, nuts, fish, and poultry were associated with lower selenium concentrations. Interestingly, the latter are classified as "brain-healthy" foods [47]. Globally, the MIND diet is composed of foods rich in vitamin E, folate, dietary fiber, carotenoids, flavonoids, and monounsaturated fats, while emphasizing lower intake of saturated fats and *trans* fatty acids [1,10]. In recent years, a growing number of RCTs and observational studies have suggested that the MIND diet may reduce risk of cognitive decline [48,49]. A 2023 study also found that a greater adherence to the MIND diet was inversely associated with postmortem Alzheimer's disease pathology [50]. Another study found an inverse association with dementia incidence only in females [51]. Though the exact mechanisms are not fully understood, foods and nutrients endorsed by the MIND diet have been associated with favorable cognitive and magnetic resonance imaging measures of the brain, such as white matter integrity [52–55]. The MIND diet brain-healthy foods may also act through antithrombotic and anti-inflammatory mechanisms, promoting neuronal signaling and neurogenesis [56,57].

Although the epidemiological evidence produced for the MIND diet envisions it as being protective against Alzheimer's dementia and other forms of dementia, the role of the trace element selenium in the etiology and prevention of cognitive disorders is unclear and debated [21,58]. Selenium in the form of selenoproteins (with at least a selenocysteine residue in its active site) is involved in several biological processes related to neurological disease, from oxidative stress to immune function, with beneficial and less frequently adverse effects having been reported in experimental and observational studies [59]. In fact, although a selenium-deficient diet may lead to oxidative stress because of decreased concentrations of antioxidant selenoproteins, an excessive dietary intake may provoke a redox shift toward a more oxidizing cellular environment, resulting in apoptotic cell death [14,28,60]. Although some studies suggest that excess exposure to selenium and its specific chemical forms may increase the risk of Alzheimer's dementia and amyotrophic lateral sclerosis [61,62], other studies indicate null or beneficial effects on cognitive performance [63–65]. For instance, selenium appeared to correlate with neurofibrillary tangles pathology and amyloid beta levels in some cross-sectional studies [19,66]. Interestingly, selenium supplementation had little effect on dementia prevention in the PREADViSE study, a combination of an RCT with the organic selenium form selenomethionine and a subsequent observational follow-up of the study arms, with a risk ratio of 0.83 (95% CI, 0.60–1.13) [22]. Given the marked differences between selenium species in terms of biological properties, any assessment of the health effects of selenium exposure should specify the selenium compound(s) under investigation [67]. In our study, we observed several differences in relation with adherence to the MIND diet not only according to the biomarker of exposure assessed (i.e., dietary intake, urinary, and serum concentrations), but also to the specific selenium compounds investigated. In addition, several sex differences were observed. Higher adherence to the MIND diet was associated with lower concentrations of overall organic and inorganic selenium in serum, though the association appeared linear in the first case and inverted U-shaped in the latter. Although almost null associations emerged for Se-TXNRD and selenite, higher adherence to MIND diet corresponded with lower concentrations of Se-SELENOP, selenate, and Se-HSA. These results are of particular interest, given that the first 2 compounds have been associated with adverse effects on cognitive decline and dementia risk based on an observational cohort study [19,23,66]. Underlying mechanisms for such association could be related to the onset of insulin resistance, glucose metabolism disruption, and diabetes in the etiology of dementia, and for which selenium, and specifically selenoprotein P, is a hypothesized contributor [25,68–70]. Regarding the inorganic form of selenate, an experimental study conducted in vertebrates found impairment in long-term memory recall when sodium selenate was administered [71]. Selenate was also the inorganic form showing a strong association with Alzheimer's dementia risk. The association observed for Se-HSA needs further investigation, given the uncertain nature of this compound [41]. However, in a previous prospective cohort study, Alzheimer's dementia risk was greater among participants with higher Se-HSA concentrations (risk ratio, 1.7; 95% CI, 0.5–5.3) [18]. Moreover, recent studies reported a positive association between Se-HSA and inorganic selenium species, suggesting inorganic nature of this compound [18,40], an observation of interest given the considerably higher toxicity of inorganic selenium species compared with the organic ones [42].

In our cross-sectional study, we ascertained selenium concentrations and MIND diet adherence at only 1 point in time. Thus, we could not assess temporal variations in adherence to the MIND diet and selenium exposure. In addition, we cannot rule out confounding by unmeasured dietary and nondietary factors. Finally, observed associations were imprecise because of the small sample size.

The inverse association observed between MIND diet adherence and circulating selenium concentrations may be considered either a limitation or a beneficial effect of this dietary pattern, depending on the role attributable to selenium exposure with reference to cognitive decline. However, given the bivalent nature of selenoprotein P and the established neurotoxicity of inorganic selenium including selenate, lower exposure to these neurotoxic selenium species appears to contribute to the protective effect of the MIND diet against cognitive decline. Further studies are warranted to clarify the effects of selenium on cognitive decline, possibly with a longitudinal design, including speciation analysis and assessing the endpoints through neuropsychological evaluation, neuroimaging, and biomarker testing.

Declaration of Competing Interest

Dr. Wise receives consulting fees from Abbvie and the Gates Foundation for work unrelated to the current manuscript. She also receives in-kind donations from Swiss Precision Diagnostics (home pregnancy tests) and Kindara.com (fertility apps) for primary data collection in the PRESTO cohort. The remaining authors declare no conflict of interest.

CRediT authorship contribution statement

Teresa Urbano: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. **Tommaso Filippini:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. **Marcella Malavolti:** Formal analysis, Writing – review & editing. **Silvia Fustinoni:** Formal analysis, Writing – review & editing. **Bernhard Michalke:** Formal analysis, Writing – review & editing. **Lauren A. Wise:** Supervision, Writing – review & editing. **Marco Vinceti:** Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing – review & editing.

Acknowledgment

This study was supported by the grant “Dipartimenti di Eccellenza 2018–2022” awarded to the Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia from the Italian Ministry of University and Research, by the grant “FAR UNIMORE 2023” from the University of Modena and Reggio Emilia, by the grants PRIN 2022 (no. 2022MHMRPR) and PRIN 2022 PNRR (no. P20229KSXB) from the Italian Ministry of University, and by the grants from the “Fondazione Pietro Manodori” and the Local Health Authority of Reggio Emilia. The funding sources had no role in the preparation of this manuscript. We acknowledge the collaboration of Transfusion Medicine Center-Reggio Emilia Hospital personnel, AVIS-Section of Reggio Emilia staff and volunteers, and all blood donors who participated to this study.

Data Statement

Data described in the manuscript, code book, and analytic code will not be made available because of privacy restrictions imposed by the ethics committee, as the informed consent obtained from the participants did not include provision for publicly sharing data. However, a minimal and deidentified dataset may be available from the corresponding author upon reasonable request.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nutres.2023.12.002.

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