Journal of Trace Elements in Medicine and Biology 92 (2025) 127765

Contents lists available at ScienceDirect

Journal of Trace Elements in Medicine and Biology

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

Biomarkers of total selenium and selenium species in paired serum and cerebrospinal fluid samples

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ARTICLE INFO

Keywords:
Biomarkers
Central nervous system
Cerebrospinal fluid
Selenium
Serum
Speciation

ABSTRACT

Background: The validity of biomarkers to estimate exposure to selenium (Se) species and selenoproteins in the central nervous system (CNS) is not well studied.
Methods: Among 83 Italian participants with mild cognitive impairment, we estimated total Se and single Se species concentrations in paired serum and cerebrospinal fluid (CSF) samples using anion exchange chromatography-inductively coupled plasma-dynamic reaction cell-mass spectrometry. In each matrix (serum and CSF), we assessed associations between: 1) paired Se species and 2) total Se and Se species.
Results: The distribution of Se exposure was comparable to that generally found in European populations. We found few consistent patterns for most biomarkers, including total Se and some Se species. An exception was a positive association between the two matrices for selenoprotein-P-bound Se and the inorganic Se form selenate, and an unexpected inverse association for glutathione-peroxidase-bound Se. Total Se was positively associated with some Se species but inversely associated with other Se species in serum, while in CSF the positive association was stronger and more consistent across various Se species.
Conclusions: Concentrations of total Se and single Se species in serum were not strongly correlated with their respective concentrations in CSF, the gold standard to estimate CNS exposure. Furthermore, total Se and selected Se species showed consistent positive correlations within CSF but not serum. Our results suggest that relying on serum Se concentrations to assess CNS exposure can introduce error in human studies.

1. Introduction

Selenium (Se) serves a dual role in human health as both an essential nutrient and a toxic agent, depending on its dose and chemical form, thus underscoring its complex biological profile [1,2]. As essential element, Se is a crucial component of various selenoproteins that have a pivotal role in redox homeostasis, ferroptosis regulation, and immune response. However, at higher exposure levels, Se and some Se species in particular may exert genotoxic, immunotoxic, and pro-oxidant effects [3–8]. In addition to shifting the transcriptome and proteome in a complex manner, Se possesses a very narrow and still not well-defined safe range of intake, largely depending on specific organic and inorganic Se species [1,3,9,10].

Concerning the adverse consequences of Se overexposure in humans, studies have shown associations with type 2 diabetes, skin damage, and neurotoxicity [1,11,12], with some indication of an excess risk of

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https://doi.org/10.1016/j.jtemb.2025.127765
Received 20 August 2025; Received in revised form 17 September 2025; Accepted 23 September 2025
Available online 24 September 2025

neurodegenerative diseases [13–22]. However, the extent of and mechanisms by which Se species are transported into the brain across the blood-brain barrier are not well understood [23–25]. Many uncertainties surround the exact roles and safe levels of Se and its species in the brain, given the extreme scarcity of neuro-epidemiologic studies and the potential for both beneficial and toxic effects of Se and selenoproteins [13,15,16,26–33]. Additionally, there are uncertainties about the most valid biomarkers of Se exposure, since our knowledge of the reliability of blood and urinary Se levels in reflecting dietary intake is still incomplete, as is our understanding of how peripheral biomarkers of exposure correlate with central nervous system (CNS) total Se and Se species concentrations [34–40]. The 'gold standard' CNS exposure biomarker *in vivo* is represented by cerebrospinal fluid (CSF) concentrations for Se and more generally for trace elements, though CSF sampling is only possible for ethical reasons in subjects at risk or affected by some neurological diseases [8,41].

In a cohort of Italian individuals with mild cognitive impairment (MCI), we estimated the association of total Se and Se species concentrations in paired serum and CSF samples at baseline. We also estimated the association between total Se and single Se species within each sample matrix (serum and CNS).

2. Methods

2.1. Study population

At baseline, we collected serum and CSF samples from patients participating in a prospective cohort study at the Neurology Clinic of Modena and Reggio Emilia University Hospital, Italy [42]. The protocol was approved by the Ethics Committee of Modena (AOU no. 2158/19) and Reggio Emilia (AUSLRE no. 2019/0009686). We recruited all 147 subjects receiving a diagnosis of MCI or subjective cognitive decline (SCD) during 2019–2021 at the Modena University Hospital and the Reggio Emilia Hospital according to Petersen's criteria and Jessen's characterization, respectively [43,44]. Individuals whose cognitive impairment was attributed to vascular, traumatic, or other brain lesions, as well as those diagnosed with Parkinson's disease, Huntington's disease, CNS inflammatory conditions, or major psychiatric disorders, were excluded from the study. All participants provided written informed consent before sample collection. In the present study, only participants with an MCI diagnosis who provided both blood and CSF samples, were included. Supplementary Figure S1 provides a study flowchart with details of sample availability.

In brief, serum collection and lumbar puncture were performed on fasting subjects. Blood was drawn from the cubital vein immediately following the lumbar puncture, and serum was subsequently separated. Samples were transported to the adjacent neurology laboratory of each respective hospital within 30 min of collection. They were centrifuged at 4000 x g for 10 min, aliquoted into sterile propylene tubes, and stored at −80°C. For Se speciation analysis, samples were shipped frozen on dry ice by air courier to the Helmholtz Center Laboratory in Munich.

2.2. Laboratory analyses

For Se speciation analysis, we employed a hyphenated system from Perkin Elmer (Rodgau, Germany) comprising a NexSAR gradient HPLC pump, an auto-sampler, and a NexION 300 D ICP-DRC-MS, all operated through Clarity software. Se species were separated using an anion-exchange column (AG-11 combined with AS-11, Thermo Dionex, Idstein, Germany). The sample injection volume was 50 μL. We performed chromatographic separation using two eluents. Eluent A consisted of 10 mM Tris-HAc with 5 % methanol (MeOH), adjusted to pH 8.0. Eluent B contained 50 mM sodium carbonate (Na_2CO_3), 20 mM ammonium acetate (NH_4Ac), and 5 % MeOH, also at pH 8.0. The elution gradient for eluent A was programmed as follows: from 0 to 2 min, the proportion of Eluent A decreased from 100 % to 80 %; from 2 to 8 min, it further decreased to 45 %; from 8 to 10.5 min, it was reduced to 0 %, maintained at 0 % from 10.5 to 14 min, and returned to 100 % from 14 to 16 min. The flow rate was constant at 0.80 mL per minute throughout the run. We operated the ICP-DRC-MS with the following settings: radio frequency power at 1250 W, plasma gas (argon) flow rate at 15 L/min, auxiliary gas flow rate at 1.05 L/min, and nebulizer gas flow rate was 0.92 L/min, optimized daily. The dwell time was 300 ms. Se was monitored using the ^{77}Se, ^{78}Se, and ^{80}Se isotopes. Dynamic reaction cell (DRC) conditions included methane (CH_4) as the reaction gas at a flow rate of 0.58 mL/min and a DRC rejection parameter q of 0.6.

In both serum and CSF, we quantified selenite (Se-IV), selenate (Se-VI), selenomethionin-bound Se (Se-Met), selenocystine-bound Se (Se-Cys_2), thioredoxin reductase-bound Se (Se-TXNRD), glutathione peroxidase-bound Se (Se-GPX), selenoprotein P-bound Se (Se-SELENOP), and human serum albumin-bound Se (Se-HSA). Se species were identified based on retention time matching with corresponding standard compounds for each quantified form Se-IV, Se-VI, Se-Met, Se-Cys_2, Se-GPX, Se-SELENOP, Se-HSA).

Given that SELENOP was not commercially available, we purified it from human serum and CSF following a method based on previously-published protocols [45,46], with some modifications as detailed in reference [25]. Purification was performed using a Heparin-affinity column (Amersham, GE Healthcare Europe GmbH, Munich, Germany).

Human serum albumin (HSA) was prepared at a concentration of 1000 mg/L. To generate selenite-bound HSA (Se-HSA), selenite was added to the HSA stock solution at a final Se concentration of 10 mg/L, followed by incubation for a minimum of 14 days. Peak assignment of Se-HSA in CSF was conducted using both Se-HSA and unmodified HSA standards, with detection based on Se-specific signals and corresponding UV absorbance profiles. Chromatographic data files were processed using Clarity software to perform peak area integration of Se chromatograms. Limits of detection (LODs) were calculated as 10 sigma (σ) criterion of noise close to respective peaks. The determined LODs for Se-species were between 15 and 20 ng/L related to Se and were uniformly set to 20 ng/L for all species.

We quantified total serum Se concentrations using flow injection-ICP-DRC-MS [24]. We compared total Se (set as 100 %) to the quantified and summed Se-species concentrations of the respective chromatograms in the same samples. Recoveries in chromatograms varied between 89 % and 107 %.

2.3. Data analysis

We present distributions of total Se and Se species concentrations in serum and CSF, respectively, using numbers and percentages for categorical variables; and median, interquartile range (IQR), range (minimum and maximum) and violin plots [47] for continuous variables. Values below the LOD were imputed as LOD divided by two [48]. We prioritized Spearman correlation coefficients between variables as shown in the displayed heatmap given the non-normal distribution of data. We also analyzed the associations between total Se and Se species concentrations in serum and CSF, and within each of the two compartments, through restricted cubic spline regression models with knots at three fixed percentiles, i.e., 10th, 50th, and 90th of Se concentrations, adjusting for sex, age, and education (i.e., indicator of socioeconomic status). We used StataSE v 19.0 (StataCorp LCC, College Station, TX, 2025) for all data analysis.

3. Results

Table 1 and Fig. 1 present the age (median 61) and sex (M/F: 37/46) characteristics of the 83 participants, their educational attainment, smoking status, mini-mental state examination score, and the distribution of total Se and of Se species. In serum, Se-SELENOP was the most abundant compound, followed by Se-GPX and Se-IV, while Se-Met was the least abundant. Conversely, in CSF samples, Se-GPX was the most

Table 1
Distribution of age, sex, total Se and Se species in paired serum and cerebrospinal fluid samples of 83 participants with mild cognitive impairment, Modena province, Italy. Values are N (%), median and interquartile range (IQR) and range, if otherwise specified.

Variable	N	%
Sex		
Males	37	44.6
Females	46	55.4
Age		
Median (IQR); range	61 (56 – 64)[a]	41 – 70[b]
< 65 years	64	77.1
≥ 65 years	19	22.9
Educational attainment		
Median (IQR); range	13 (8 – 13)[a]	5 – 18[b]
Primary school	7	8.4
Secondary school	26	31.3
High school	33	39.8
College or more	17	20.5
Smoking habits		
Never smokers	37	44.6
Former smokers	25	30.1
Current smokers	18	21.7
	Median (IQR)	**Min - Max**
Mini-Mental State Examination score	27 (25–29)	16–30
Se species in serum (μg/L)		
Total Se	98.72 (86.50–117.18)	47.45–170.00
Se-SELENOP	38.61 (18.71–60.44)	1.92–107.62
Se-Met	1.60 (0.51–2.87)	0.01–11.44
Se-Cys_2	3.29 (0.01–14.57)	0.01–44.57
Se-GPX	12.42 (4.93–20.33)	0.96–53.06
Se-TXNRD	2.51 (0.91–4.84)	0.01–33.57
Se-IV	12.00 (6.41–16.69)	1.01–66.08
Se-VI	8.69 (5.45–13.60)	0.62–68.69
Se-HSA	2.22 (0.65–4.73)	0.01–33.32
Se species in CSF (μg/L)		
Total Se	3.25 (1.79–6.41)	0.58–19.40
Se-SELENOP	0.69 (0.21–1.73)	0.02–5.23
Se-Met	0.05 (0.02–0.15)	0.01–0.82
Se-Cys_2	0.14 (0.01–0.23)	0.01–0.89
Se-GPX	1.03 (0.52–3.36)	0.17–8.22
Se-TXNRD	0.03 (0.01–0.14)	0.01–1.32
Se-IV	0.11 (0.04–0.38)	0.01–3.14
Se-VI	0.69 (0.28–1.05)	0.06–4.31
Se-HSA	0.01 (0.01–0.03)	0.01–1.04

Abbreviations: IQR, interquartile range, Se-Cys_2, 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. [a]Median and interquartile range; [b]Range.

prevalent compound, followed by Se-SELENOP and Se-VI. Se-HSA exhibited the lowest concentration in CSF. Among the analyzed samples, some had Se species concentrations below the LOD, and this occurred particularly for the CSF concentrations of Se-HSA, Se-TXNRD, and Se-Cys_2 (Supplementary Table S1). Most Se species had a left-skewed distribution, with the exception of total Se and Se-SELENOP in serum.

As shown by the Spearman linear correlation heatmap (Fig. 2), correlations between total Se and Se species in both serum and CSF were heterogeneous, and generally stronger within the same matrix. Se-Cys_2 in serum was inversely associated with most other species, apart from a positive association with Se-VI in both matrices and with Se-GPX in serum. Se-Cys_2 in CSF was inversely correlated with all species, except for Se-GPX in serum. A heterogenous pattern emerged for Se-HSA, in both serum and CSF, though its associations with the other Se species were generally weak. Two key Se forms, Se-GPX and Se-SELENOP, showed variable associations with Se forms in both matrices; while there was a strong positive association between Se-SELENOP and Se-GPX in CSF, there was a strong inverse association between these two species in serum. Se-Met tended to show inverse correlations with the other Se species, particularly with concentrations in the other compartment (serum vs. CSF).

Spline regression analyses of the relation between CSF and serum Se concentrations (Fig. 3), adjusted for potential confounders, showed heterogeneous and generally non-linear patterns of association, with few exceptions (e.g., a monotonic inverse association for Se-GPX in the two matrices, and the positive association for Se-VI and to a much lesser extent Se-IV). For total Se and the remaining Se compounds, patterns of association were either U-shaped (for total Se) or inversely U-shaped (for Se-Cys_2, Se-TXNRD and Se-HSA). For Se-Met, after an initial decrease in CSF concentrations with increasing serum levels, the association plateaued, while Se-SELENOP showed a positive association at its lowest range, followed by a flattening of the curve.

Concerning the association between total Se and the single Se compounds within the same compartment, the direction of this association in serum was generally positive and nearly linear (Fig. 4), with the exception of a U-shaped association with Se-Met and Se-TXNRD, and a slightly linear inverse association with Se-Cys_2. The association of Se-GPX with total Se was flat up to certain value and then shifted upward at 20 μg/L. The strongest (positive) association between total Se and Se species was observed for Se-IV, with an almost linear and steep pattern of the curve.

Regarding CSF concentrations (Fig. 5), the associations between total Se and Se species were generally positive, almost linear, and characterized by a much steeper slope than that observed in serum. Exceptions were the U-shaped association between total Se and Se-Cys_2, and the slight inverse U-shaped association with Se-VI. Concerning the latter association, the distributions of observations gave an indication of two positive and linear patterns, with markedly different slopes. Analyses additionally adjusted for smoking gave nearly identical results.

4. Discussion

In this study, concentrations of total Se and Se species in serum did not reliably predict corresponding concentrations in the CNS, as estimated in CSF. This finding indicates that peripheral biomarkers are not appropriate for assessing exposure to Se and its chemical forms in the brain, likely inducing error in the human studies based on the serum/plasma indicators of Se exposure. This work expands on previous findings from a small study with only 24 participants, and further applies, for the first time, a non-linear model to analyze the relation between serum and CSF concentrations of Se and Se species, thus allowing the detection of complex patterns of association and related thresholds [25].

Despite the general lack of association between Se biomarkers across the two matrices, we detected a positive association between serum and CSF levels of Se-VI, a major neurotoxic Se species [17], and of Se-SELENOP, a selenoprotein that is the major transporter of Se and which has both beneficial and adverse health effects [49–51]. For the latter biomarker, however, the positive association was attenuated at the highest levels of exposure, indicating a dose- and species-dependent changing pattern of association between blood and brain levels. It must however be highlighted that we measured Se-SELENOP and not the selenoprotein itself, SELENOP. Though standard SELENOP contains 10 selenocysteine residues, its real content in the human may vary, thus preventing an exact correlation between SELENOP-bound Se and SELENOP itself [49,52–55].

Measurement of protein-bound Se also indicated an unexpected inverse association between blood and CNS concentrations of Se bound to the selenoprotein glutathione peroxidase, a finding that suggests the potential lack of validity of peripheral biomarkers to assess its relation with CNS endpoints, at least for some Se species. Additionally, the inverse association between serum and CSF concentrations of Se-Cys_2 and of Se-HSA at the highest concentrations, as well as the inverse relations between total Se and Se-TXNRD in serum and between total Se and Se-VI in CSF, are intriguing and difficult to explain. Concerning Se-GPX, the Se content of this enzyme may not directly and linearly reflect external Se exposure/intake, but rather represent a reactive stress-induced enzyme

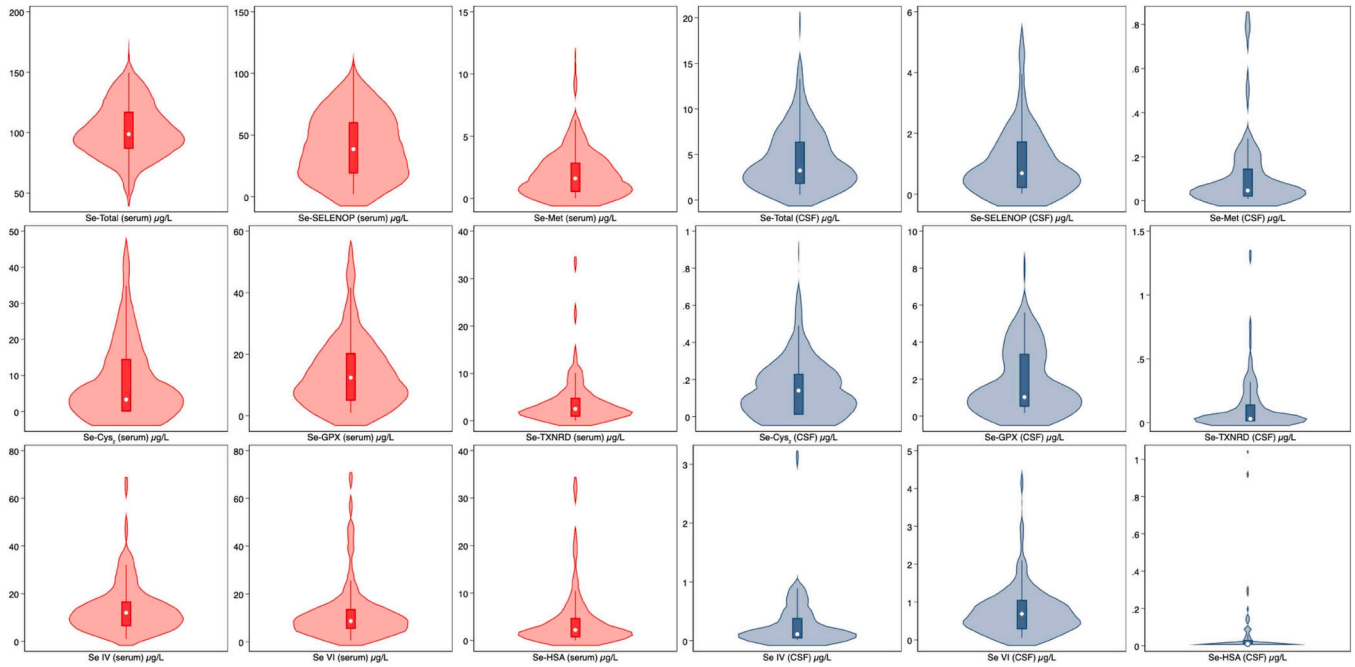

Fig. 1. Violin plots of selenium compounds in paired serum (red) and cerebrospinal fluid (blue) samples (n = 83 participants). **Abbreviations**: Se-Cys_2, selenocystine-bound selenium; Se-GPX, glutathione peroxidase-bound selenium; Se-HSA, human serum albumin-bound selenium; Se-Met, selenomethionine-bound selenium; Se-SELENOP, selenoprotein P-bound selenium; Se-TXNRD, thioredoxin reductase-bound selenium; Se-IV, selenite; Se-VI, selenate.

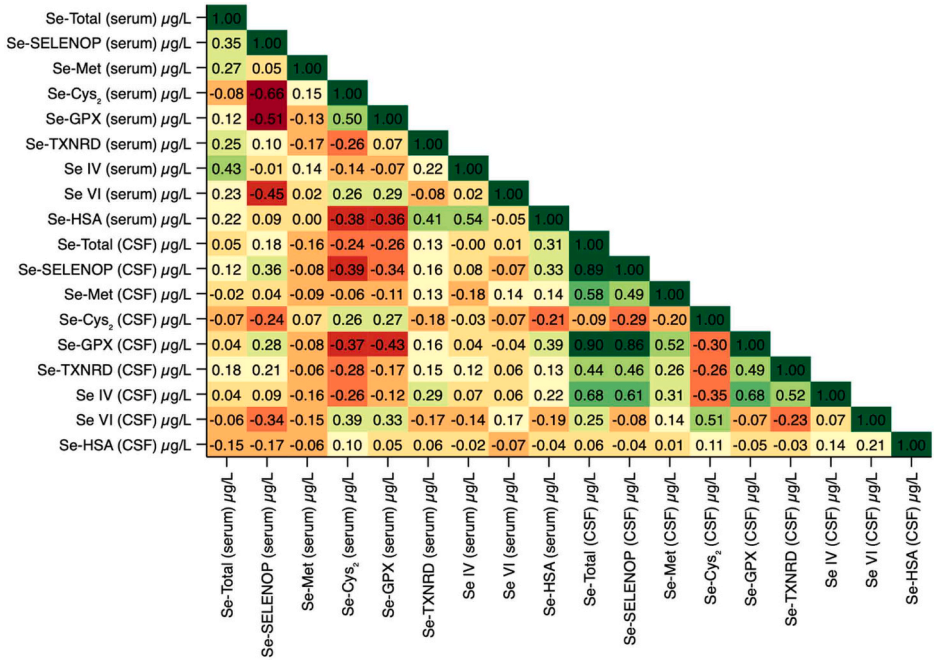

Fig. 2. Spearman correlation heatmap of biomarker concentrations of total Se and Se species in paired serum and cerebrospinal fluid (CSF) samples of 83 participants with mild cognitive impairment. The color scale indicates the strength and direction of the correlation, with values ranging from −1 (strong negative correlation, dark red) to + 1 (strong positive correlation, dark green). Intermediate colors represent varying levels of correlation. Values along the top diagonal represent self-correlations (coefficient = 1).

upregulation, a compensatory phenomenon known to occur for some antioxidant Se-containing enzymes in response to external stressors (paradoxically including Se itself) [4]. Therefore, differences across body districts of Se-GPX or other Se species might also be due, at least in part, to differences in redox status and oxidative stress among these matrices, a possibility that warrants further investigation through markers of oxidative stress. The body maintains a hierarchy of Se retention during deficiency conditions, with the brain among the most protected organs [56]. Notably, despite this prioritization, Se-GPX levels in serum did not correlate with those in CSF in our study, suggesting that peripheral Se biomarkers may not reliably reflect Se status or selenoprotein activity within the CNS. This aspect is also relevant for Se-SELENOP, which showed a (linear) positive correlation between serum and CSF levels at lower concentrations, but eventually reached a

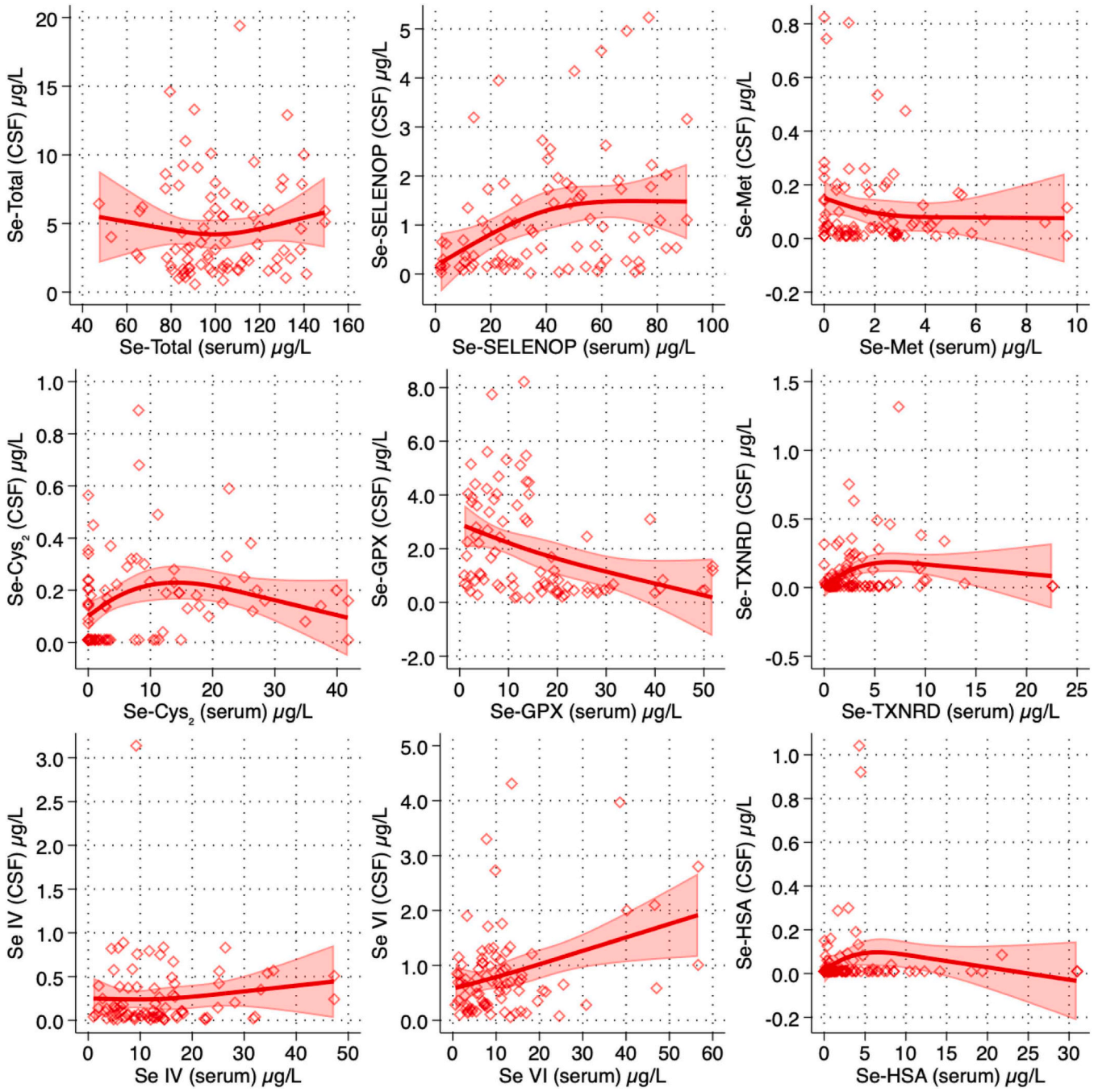

Fig. 3. Association between total Se and Se species concentrations in serum and corresponding concentrations in cerebrospinal fluid (CSF) of 83 participants with mild cognitive impairment. The solid line represents the multivariable analysis (adjusted for sex, age, and educational attainment) with upper and lower confidence interval limits (shaded area). Diamonds represent individual observations. **Abbreviations**: Se-Cys_2, 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.

plateau at higher concentrations.

Considering limitations, the study population comprised participants with cognitive disability, though impairments in cognition were likely to be mild and not expected to have substantially affected Se status, differently from what may occur in dementia patients [57,58]. In addition, our study population had a median intake twice that of the WHO dietary reference value [59] as estimated through their blood levels [60], but at the same time below toxic concentrations [1]. Thus, our findings are potentially applicable to other populations with comparable Se exposures, and in addition no imbalances in Se distribution and selenoprotein synthesis due to the brain prioritization of Se uptake during deficiency states suggested by animal studies [56] is expected to have occurred. Another potential limitation could have been the lack of control for additional factors in addition to sex, age, education and smoking. However, there is little evidence that additional variables not considered in this study, such as other trace elements or neurodegeneration biomarkers, could markedly influence Se status in the CNS [8,19,20,61]. Overall, the low accuracy of serum Se biomarkers in reflecting CNS exposure is disappointing given the challenges of obtaining CSF samples from healthy participants in epidemiologic studies (e.g., physical discomfort associated with CSF sampling). Thus, it would not be ethical or feasible to sample CSF in individuals not affected

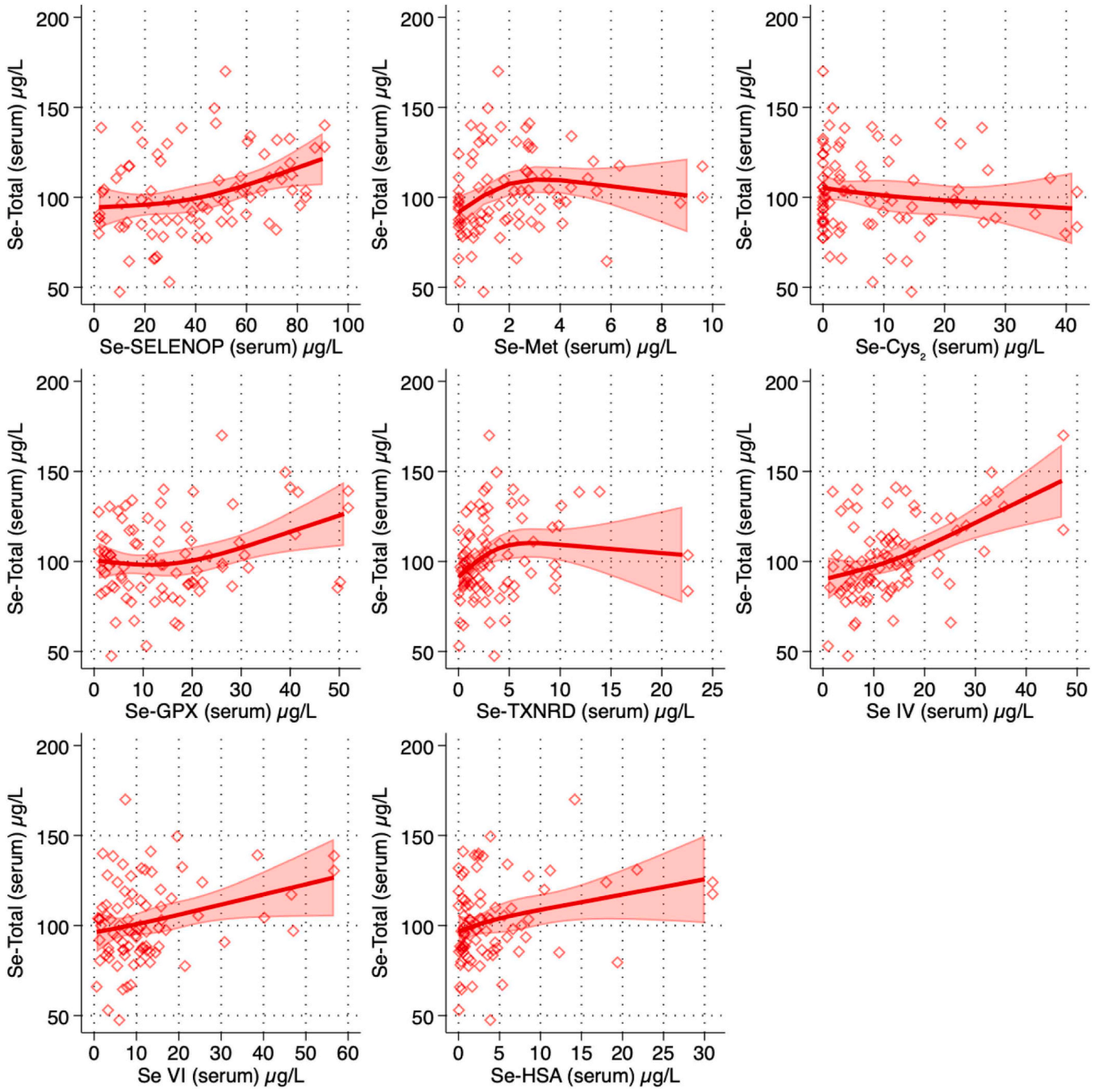

Fig. 4. Association between total Se and Se species concentrations in serum of 83 participants with mild cognitive impairment. The solid line represents the multivariable analysis (adjusted for sex, age, and educational attainment) with upper and lower confidence interval limits (shaded area). Diamonds represent individual observations. **Abbreviations**: Se-Cys_2, 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.

by or at high risk of major neurological disease. We also did not assess all factors that could plausibly influence the relation between peripheral and CNS Se biomarkers concentrations. Possible confounders include genetic factors, in terms of Se metabolism and blood-brain barrier characteristics, and non-genetic factors, such as other chemicals influencing distribution and metabolism of the element and its species. One of these factors could be *APOE ε4* allele status [30,62], possibly influencing Se delivery to the brain and altering its cellular distribution [63]. Furthermore, in serum most Se species were detected above the LOD, whereas in CSF a substantial proportion of measurements fell below the LOD. Notably, Se-HSA, a still not well characterized Se species [64], was the species most frequently below the LOD in CSF, an expected finding given that Se-HSA, like human serum albumin, appears to cross the neural barriers in only small amounts. Overall, there is a clear need to improve the capacity to predict Se CNS concentrations through circulating biomarkers and for all Se species, given the potential relevance of Se deficiency and overexposure to neurological disease, and the remarkable differences in biological effects of the various Se species in the CNS [1,15,23,51].

A strength of our study was the use of Se-species based biomarkers [40], given the limitations of selenoprotein biomarkers at relatively high Se intakes, and the variability of Se content in SELENOP, a major Se

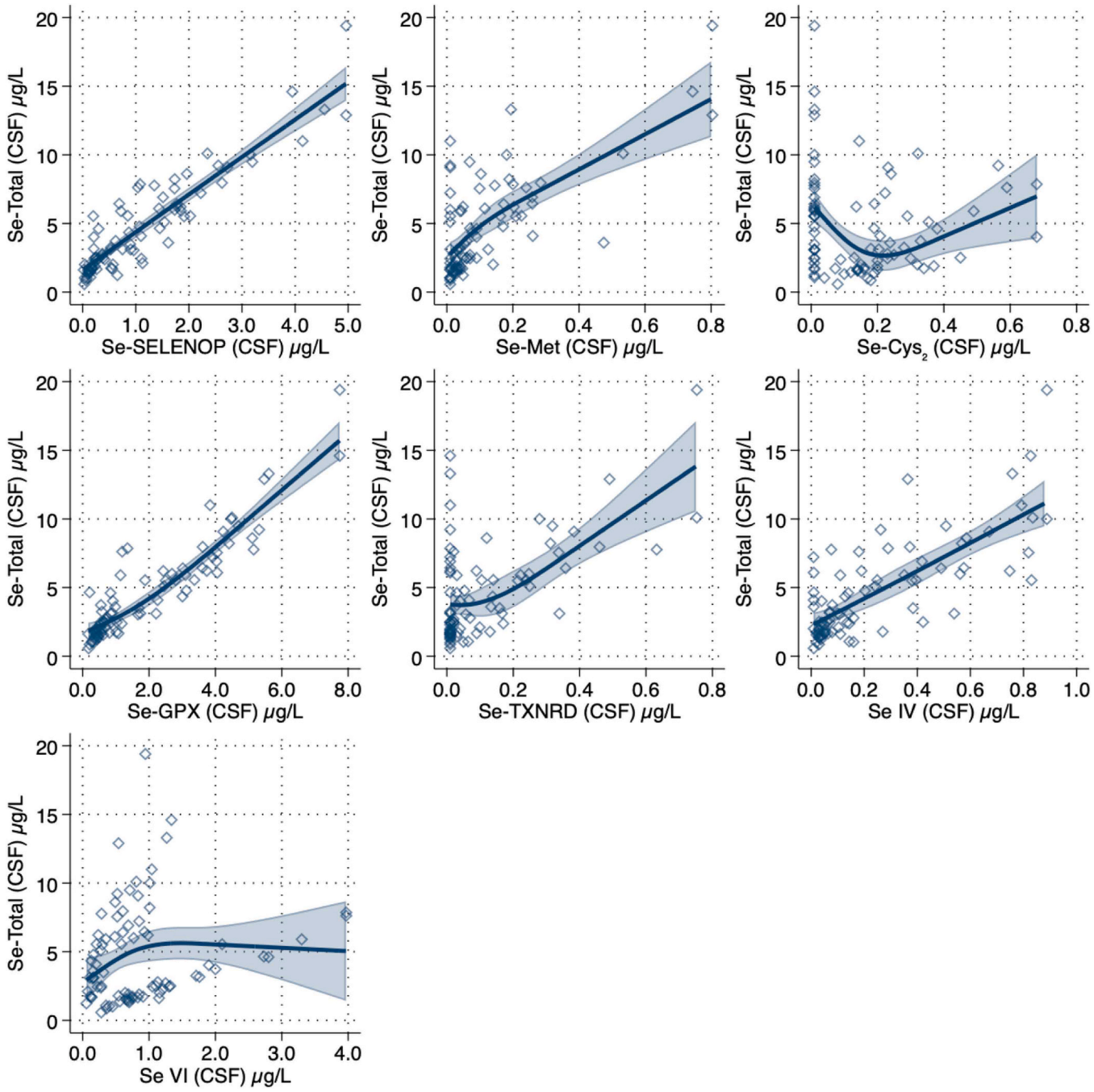

Fig. 5. Association between total Se and Se species concentrations in cerebrospinal fluid (CSF), samples of 83 participants with mild cognitive impairment. The solid line represents the multivariable analysis (adjusted for sex, age, and educational attainment) with upper and lower confidence interval limits (shaded area). Diamonds represent individual observations. **Abbreviations**: Se-Cys_2, 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.

transporter and a selenoprotein with both beneficial and adverse effects [4,20,50,65]. Another strength was the use of a flexible modelling approach in data analysis that does not impose linearity on the associations [66–68].

The limited capacity of serum concentrations of total Se to reflect the serum concentrations of many Se species is a relevant finding with inherent implications for human studies, considering the large toxicological and nutritional differences between Se species and compounds. In addition, our findings point to substantial limitations of the most commonly-used Se biomarker, serum (and plasma) Se, even in experimental studies on the CNS effects of Se [69–71]. Although nutritional guidelines typically rely on blood Se concentrations to assess status, these measures may not accurately reflect Se availability or selenoprotein activity within the brain. Studies of the relation between Se exposure and neurological disease should therefore consider the differences in Se concentrations across body compartments, and the potential for exposure misclassification, when aiming at assessing CNS selenium status. Conversely, total Se in CSF can be a reliable indicator of CSF Se species content, with the exception of Se-VI. However, the extent to which CSF Se biomarkers reflect Se exposure in all brain regions is unknown, given the inability to perform *in vivo* studies [4,72,73].

CRediT authorship contribution statement

Annalisa Chiari: Writing – review & editing, Resources. **Giulia Vinceti:** Writing – review & editing, Resources. **Lauren A. Wise:** Writing – review & editing, Supervision. **Giovanna Zamboni:** Writing – review & editing, Resources, Funding acquisition. **Tommaso Filippini:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Data curation, Conceptualization. **Barbara R. Cardoso:** Writing – review & editing, Supervision. **Marco Vinceti:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Funding acquisition, Conceptualization. **Bernhard Michalke:** Writing – review & editing, Supervision, Methodology, Formal analysis. **Teresa Urbano:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Marcella Malavolti:** Writing – review & editing, Data curation. **Manuela Tondelli:** Writing – review & editing, Resources. **Alessandro Marti:** Writing – review & editing, Resources.

Funding

This study was supported by grant "Departments of Excellence 2018–22" by the Italian Ministry of University and Research (MUR), by grant "PRIN 2022 PNRR" (no. P20229KSXB) from the Italian Ministry of University and Research (MUR) funded by the European Union—Next Generation EU, by grant "UNIMORE FAR 2023" from the University of Modena and Reggio Emilia, and by grant "PRIN 2022" (no. 2022MHMRPR) from the Italian Ministry of University and Research (MUR) funded by the European Union—Next Generation EU.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors would like to thank all MCI participants and their families.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jtemb.2025.127765.

Data availability

The datasets generated and/or analyzed during the current study are not publicly available due to privacy reasons but are available from the corresponding author on reasonable request.

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