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Blood Trace Element Status in Multiple Sclerosis: a Systematic Review and Meta-analysis

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Abstract

The aim of this meta-analysis was to investigate whether the blood concentrations of patients with multiple sclerosis (MS) are associated with those of the healthy control group in terms of trace elements including zinc (Zn), iron (Fe), manganese (Mn), magnesium (Mg), selenium (Se), and copper (Cu). A comprehensive search was performed in online databases including PubMed, Scopus, Embase, and Web of Science for studies, which have addressed trace elements in MS up to July 23, 2020. The chi-square test and I^2 statistic were utilized to evaluate inter-study heterogeneity across the included studies. Weighted mean differences (WMDs) and corresponding 95% CI were considered as a pooled effect size (ES). Twenty-seven articles (or 32 studies) with a total sample comprised of 2895 participants (MS patients (n = 1567) and controls (n = 1328)) were included. Pooled results using random-effects model indicated that the levels of Zn (WMD = − 7.83 mcg/dl, 95% CI = − 12.78 to − 2.87, Z = 3.09, P = 0.002), and Fe (WMD = − 13.66 mcg/dl, 95% CI = − 23.13 to − 4.19, Z = 2.83, P = 0.005) were significantly lower in MS patients than in controls. However, it was found that levels of Mn (WMD = 0.03 mcg/dl, 95% CI = 0.01 to 0.04, Z = 2.89, P = 0.004) were significantly higher in MS patients. Yet, no significant differences were observed in the levels of Mg, Se, and Cu between both groups. This meta-analysis revealed that the circulating levels of Zn and Fe were significantly lower in MS patients and that Mn level was significantly higher than those in the control group. However, it was found that there was no significant difference between MS patients and controls with regard to levels of Mg, Se, and Cu.

Keywords Trace element · Multiple sclerosis · Meta-analysis · Zinc · Iron

Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS). Moreover, it is considered the most common cause of neurological disability in young individuals [42]. This neurological T cell-mediated autoimmune disease is characterized by inflammation, reactive astrogliosis, oligodendrocyte depletion, and demyelination in the brain, spinal cord, and optic nerve [41, 63]. Given that MS affects over 2.5 million people around the world, the disease has turned into an urgent issue in healthcare [13]. MS has three clinical subtypes which include relapsing-remitting MS (RR-MS), primary progressive MS (PPMS), and secondary progressive MS (SPMS) [19]. Despite the still unknown etiology of the disease, it is clear that the interaction between several immunologic, environmental, infectious, and genetic factors account for the pathogenesis of MS [9].

Trace metals are involved in different MS-related pathophysiological mechanisms [39]. Not only are they essential for the synthesis and stability of myelin but they are also required for CNS to function normally [47]. As a trace element which abounds in the human brain, zinc (Zn) comprises a group of several major myelin proteins including myelin basic protein (MBP) with important functional roles in myelin homeostasis,

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regulation of the immune system, and neuronal and oligodendrocyte death, hence its extensive role in MS pathogenesis [3, 8, 9]. Iron (Fe) is critical for normal neuronal metabolisms like mitochondrial energy generation and myelination [30, 31]. However, the excessive iron levels in the brain may cause iron-induced oxidative stress, thereby contributing to the neurodegeneration seen in MS [65]. Manganese (Mn) is an essential trace element with essential roles in normal growth, as well as in cellular homeostasis and development [17]. Despite its importance, excessive levels of Mn are toxic to the CNS and its implications in MS have been defined [39, 62].

In addition, having a significant effect on the nervous system by decreasing the excitability of nerve cells [29], magnesium (Mg) increases the inhibitory effect and decreases the stimulant effect of autonomic ganglia. Moreover, Mg ions prevent excessive stimulation via competition with calcium ions on the nerve endings [32]. Mg deficiency induces dysfunction in lymphocytes or nerve cells which is likely to be implicated in the etiology of MS [11]. Likewise, it is believed that oxidative stress plays a crucial role in the demyelination pathogenesis and neurodegeneration in MS [23, 44]. Furthermore, as a potent antioxidant, selenium (Se) is not only likely to have a positive effect on MS but also its deficiency may be contributed to cell death and have some effects on MS induction [51]. Likewise, copper (Cu) is involved in myelin synthesis and has a significant role in many neurodegenerative diseases [3]. Moreover, it is shown that Cu plays a role in the structure and function of several brain enzymes, as well as in regulating neurotransmitters synthesis, iron metabolism, and oxidative defense. The oxidative damage caused by excessive copper accounts for the role of copper in MS pathology [27, 52, 61].

Previous studies evaluated the associations between the homeostasis status of abnormal trace metals and MS, although they obtained conflicting results. The present systematic review and meta-analysis aimed to summarize the available findings regarding the circulating levels of Zn, Se, Cu, Mg, and Fe in MS patients and healthy controls.

Methods

The protocol for the review was registered with PROSPERO (Provisional registration number: CRD42020204700). After the search strategy was prepared, the online databases including Web of Science (WOS), PubMed, Embase, and Scopus were searched systematically up until July 23, 2020. The following MeSH (Medical Subject Headings) terms and keywords were used for studies on MS and levels of common trace element: ["Multiple sclerosis (MS)" AND "Trace element" OR "Zinc (Zn)" OR "Iron (Fe)" OR "Manganese (Mn) " OR "Magnesium (Mg)" OR "Selenium (Se)" OR "Copper (Cu)"]. The search strategy was supplemented for the Scopus database with more details (Supplementary File. S1). In addition, additional manual searches were conducted according to the reference lists of previous reviews and eligible studies for further pertinent literature.

Study Selection

When the screening process was performed based on the titles and abstracts, two independent authors (FM and SMAK) identified the eligible studies according to the inclusion and exclusion criteria. Any discrepancy in the way the studies were selected was resolved through discussion, resulting in a consensus or consultation with a third author (HA).

Studies were selected in our meta-analysis if they (1) had an original observational design (cross-sectional, case-control, or cohort); (2) investigated the associations between the status of trace elements of interest in both MS patients and controls and, moreover, defined the diagnostic criteria for MS and trace element measurement; (3) presented a sufficient amount of data in order to extract or calculate the mean and standard deviation (SD) for levels of at least a single trace element of interest in both MS patients and controls; 4) were written in English. Moreover, the exclusion criteria were animal studies, reviews, case reports, case series, randomized controlled trials, editorials, letters, abstracts without full texts, and studies without controls or any insufficient data. Additionally, studies that measured trace elements only in cerebrospinal fluid (CSF) or in the whole blood, and those conducted without the inclusion of any MS patients were also excluded.

Data Extraction and Quality Assessment

Standardized data collection sheets were used to extract the following information: first author's name, publication year, the country where the study was conducted, study design, sample size (MS patients/ controls), the main characteristics of subjects, type of MS, the way the blood samples were collected, measurement method for trace elements, and the mean and SD levels of trace elements including Zn, Fe, Mn, Mg, Se, and Cu in both MS patients and controls. Two authors (FM and SO) independently extracted data from the qualified studies, which were then checked by a third author (EN) in terms of data extraction accuracy. If an included study did not directly report the SD in both groups, the equation listed in the Cochrane handbook was used to calculate the SD from standard error of the mean (SEM), interquartile, or range for each eligible study.

The Newcastle–Ottawa Scale (NOS) was applied to determine the risk of bias in the included studies. The three points used for the purpose of critical appraisal included the selection of subjects, comparability of included groups, and outcome/ exposure ascertainment. The NOS scores ranged from 0 to 9. Depending on the type of study, quality scores ≥ 7 in case-

control or cohort designs and ≥ 5 in cross-sectional designs were considered as good quality (Table 1 and Supplementary Table S1).

Statistical Analysis

All of the statistical analyses were conducted using the software STATA 11.0 (STATA Corp, College Station, Texas). The mean and SD of trace elements in both groups (MS patients/controls) were used to pool the data. All measurements of trace elements were converted to an equal unit (mcg/dl). Moreover, we considered weighted mean differences (WMDs) and the corresponding 95% CI as a pooled effect size (ES). The chi-square test and I^2 statistic were utilized to evaluate inter-study heterogeneity across the included studies. Likewise, in the presence of significant heterogeneity (with a $P \leq 0.1$ for chi-square result with I^2 value ≥ 50%), a random-effects model, otherwise, a fixed-effect model was used to combine ESs. Additional methods including subgroup analyses (based on study design, region, type of MS, and blood sampling) and sensitivity analyses were also performed to identify the source of inter-study heterogeneity. Moreover, univariate meta-regression analyses were conducted to assess if the factors including publication year, total sample size, and quality scores were associated with pooled ESs. The quantitative statistics including Egger's linear regression test and Begg's rank correlation test were used to evaluate the potential evidence of publication bias across the included studies in the current meta-analysis.

Results

Literature Search and Study Characteristics

The PRISMA flow diagram for identification and selection of studies in the present systematic review and meta-analysis are shown in Fig. 1. The initial online search in the literature led to the identification of 10,490 records (includes 893 from PubMed, 3721 from Web of Science, 3579 from Scopus, and 2297 from Embase). Upon the removal of duplicate records, the titles and abstracts for 7459 records were screened, leading to the exclusion of 6497 studies. Based on the exclusion criteria (as mentioned before), 962 full-text articles were assessed for eligibility and 935 articles were excluded. Finally, 27 articles (32 studies) were extracted to include in the current meta-analysis [1, 2, 4, 7, 12, 14, 15, 20, 22, 24, 26, 28, 29, 33, 34, 36–38, 40, 43, 45, 49, 53, 55, 57–59, 62]. It is, moreover, noteworthy that all 32 studies included 2895 participants (1567 MS patients and 1328 control group participants).

These studies were conducted mainly in Europe and published between 1980 and 2020. The included studies reported the trace element levels of serum or plasma. Additionally, the main characteristics of the qualified studies are displayed in Table 1.

Main Outcomes

Figure 2 depicts the forest plots for the pooled estimates of the weighted mean differences on trace elements between MS patients and control groups.

Zn Among MS Patients and Controls

The results obtained from the meta-analysis, based on 17 qualified studies using a random-effects model, indicated that Zn levels were considerably lower in MS patients than in those of the controls (WMD = − 7.83 mcg/dl, 95% CI = − 12.78 to − 2.87), along with considerable inter-heterogeneity (I^2 = 99.0%, $P < 0.001$). The findings obtained from the subgroup analyses demonstrated that the heterogeneity decreased within some of subgroups. As observed in Table 2, the pooled effect size did not significantly change in different study designs. However, it was reported that Zn levels decreased in studies conducted among MS patients in Europe (n = 7, WMD = − 11.09 mcg/dl, 95% CI = − 15.85 to − 6.34; I^2 = 79.9%, $P <$ 0.001), America (n = 5, WMD = − 5.34 mcg/dl, 95% CI = − 10.08 to − 0.60; I^2 = 98.5%, $P < 0.001$), and Africa (n = 2, WMD = − 15.44 mcg/dl, 95% CI = − 22.97 to − 7.91; I^2 = 0.0%, P = 0.728). A stratification of studies based on the type of MS revealed significant decreases in Zn Levels among patients with other types of MS (n = 3, WMD = − 14.91 mcg/dl, 95% CI = − 18.03 to − 11.79; I^2 = 0.0%, P = 0.931). Serum Zn reduced significantly among MS patients compared with other blood sampling methods (n = 13, WMD = − 10.52 mcg/dl, 95% CI = − 20.26 to − 0.78; I^2 = 99.2%, $P <$ 0.001). In addition, the meta-regression analysis indicated that the total sample size across the included studies was negatively related to the decreased zinc levels in MS patients (β = − 0.11, P = 0.026) (Table 3). The results of sensitivity analysis also showed that the pooled WMD for Zn levels was stable after the studies were excluded one by one (Supplementary Fig. S1). Moreover, no potential evidence of publication bias was observed across the qualified studies (P = 0.172 for Egger's test and P = 0.410 for Begg's test).

Fe Among MS Patients and Controls

The pooled effect size from 12 qualified studies using a random-effects model indicated that Fe levels in MS patients were lower compared with those in the controls (WMD = − 13.66 mcg/dl, 95% CI = − 23.13 to − 4.19). Their P and I^2 for heterogeneity tests were statistically significant (I^2 = 92.3%, P < 0.001). The findings of subgroup analyses showed that the heterogeneity decreased within some of the subgroups. As shown in Table 2, in comparison with other regions, Fe levels decreased in studies conducted among MS patients in Asia (n = 3, WMD = − 9.98 mcg/dl, 95% CI = − 18.12 to − 1.84; I^2 = 24.8%, P = 0.265). In addition, the subgroup analysis based

Table 1 The main characteristics of included studies

First author	Publication year	Country	Type of study	Sample size (case/control)	Patients	Mean age (case/control)	Blood sampling	Diagnosis criteria	Outcomes	Quality scores
[1]	2008	Egypt	Case-control	20/10	RR-MS	29.94 ± 8.84, NA	Serum	According to [48] supported by clinical examination, MRI of the brain and/or cervical spine and evoked potentials.	Fe	8
[2]	2007	Italy	Case-control	60/124	RR-MS and secondary progressive	38.5 ± 10.4, 44.8 ± 12.7	Serum	McDonald criteria	Mg, Fe, Co, and Zn	7
[4]	2019	Israel	Case-control	63/83	MS	44.7 ± 14.0, 40.6 ± 11.9	Serum	Neurologist based on clinical, laboratory, and MRI findings	Mg and Fe	7
[7]	2019	Austria	Cross-sectional	71/16	MS	46.19 ± 7.83, 31.8 ± 11.6	Serum	McDonald criteria 2010	Fe	7
[12]	2018	Italy	Case-control	38/39	RR-MS	NA	Serum	McDonald criteria	Co	7
[14] #a	1983	USA	Case-control	68/60	MS	NA	Plasma	Clinically	Zn	7
Dore-Duffy et al. #b	1983	USA	Case-control	63/62	MS	NA	Serum	Clinically	Zn	7
[15]	2014	Turkey	Case-control	35/35	RR-MS	38 ± 11, 38 ± 10	Serum	McDonald criteria	Fe	8
[20]	2005	Italy	Case-control	60/60	MS	38.7 ± 9.9, 38.4 ± 9.7	Plasma	McDonald criteria	Mg, Fe, Co, and Zn	7
[22]	2015	Iran	Case-control	50/50	MS	32 ± 3.35, 32 ± 2.65	Serum	NA	Co and Zn	5
[24]	1986	USA	Case-control	45/23	MS	NA	Plasma	Clinically	Zn	6
[26]	1980	Denmark	Case-control	14/12	MS	NA	Serum	Clinically	Se	7
[28]	1989	Greece	Case-control	15/28	MS	34 ± 9.75, 46 ± 14.25	Serum	NA	Mg, Co, and Zn	6
[29]	2017	Poland	Case-control	101/41	Relapsing MS	40.86 ± 10.2, 40.09 ± 14.1	Serum	McDonald criteria	Mg	8
[33] #a	1989	Finland	Cohort	12/7	Mild progressive or remitting MS	46.3 ± 9.25, NA	Serum	MRI of the brain, and by evoked responses	Se	5
Korpela et al. #b	1989	Finland	Cohort	3/6	Active progressive MS	46.3 ± 9.25, NA	Serum	MRI of the brain, and by evoked responses	Se	5
[34]	2002	India	Case-control	15/15	Relapsing MS	NA	Plasma	Poser's criteria	Mg	6
[36]	2007	Iran	Cohort	35/35	MS	31.6 ± 6.6, 35.1 ± 4.5	Serum	Clinical examination and MRI guideline	Mg, Co, and Zn	6
[37]	2020	Lebanon	Case-control	27/42	MS	42.8 ± 12.9 38.3 ± 16.0	Serum	McDonald criteria	Fe and Zn	8
[38]	1983	Italy	Case-control	20/16	MS	37 ± 9.19, 40.81 ± 5.83	Plasma	Criteria of McDonald and Halliday	Se	5
[40]	2020	Brazil	Case-control	174/182	MS	41.9 ± 13.2, 39.5 ± 9.8	Serum	McDonald criteria	Zn	8
[43] #a	2019	Egypt	Case-control	25/12	Relapsing MS		Serum	McDonald's criteria 2017	Zn	5

Table 1 (continued)

First author	Publication year	Country	Type of study	Sample size (case/control)	Patients	Mean age (case/control)	Blood sampling	Diagnosis criteria	Outcomes	Quality scores
						30.88 ± 9.01, 28.28 ± 7.08				
Oraby et al. #b	2019	Egypt	Case-control	25/13	Remission MS	32.28 ± 8.07, 28.28 ± 7.08	Serum	McDonald's criteria 2017	Zn	5
[45]	2018	Germany	Cohort	151/17	MS	43 ± 12, 43 ± 14	Serum	McDonald criteria (2010)	Zn	7
[53]#a	2005	Greece	Case-control	14/20	RR-MS	37.5 ± 5.5, NA	Serum	History or a neurological examination	Fe	6
Sfagos et al. #b	2005	Greece	Case-control	13/20	Chronic p rogressive MS	37 ± 5.5 , NA	Serum	History or a neurological examination	Fe	6
[55]	2019	Italy	Case-control	60/42	RR-MS	37.2 ± 9.06, 40.3 ± 10.86	Serum	[46]	Fe and Co	5
[57]	1989	USA	Cohort	27/33	MS	NA	Plasma	Clinically definite with supporting laboratory data of Poser et al	Co, Se, and Zn	5
[58] #1	2014	Poland	Case-control	101/63	RR-MS	40.86 ± 10.2, 41.12 ± 14.1	Serum	McDonald criteria	Se	7
[59] #2	2017	Poland	Case-control	101/68	RR-MS	40.9 ± 10.2, 40.1 ± 13	Serum	McDonald criteria	Co and Zn	6
[49]	2011	Italy	Case-control	49/49	MS	36.1 ± 6.9, 33.2 ± 6.1	Serum	Expanded disability status scale score (EDSS), routine blood tests, additional tests to rule out alternative conditions mimicking MS, and brain MRI scan	Mg, Fe, Cu, Mn, and Zn	6
[62]	2005	Italy	Case-control	12/12	MS	28.2 ± 7.9, 28.3 ± 8.8	Serum	EDSS	Mg, Fe, Cu, Mn, and Zn	7

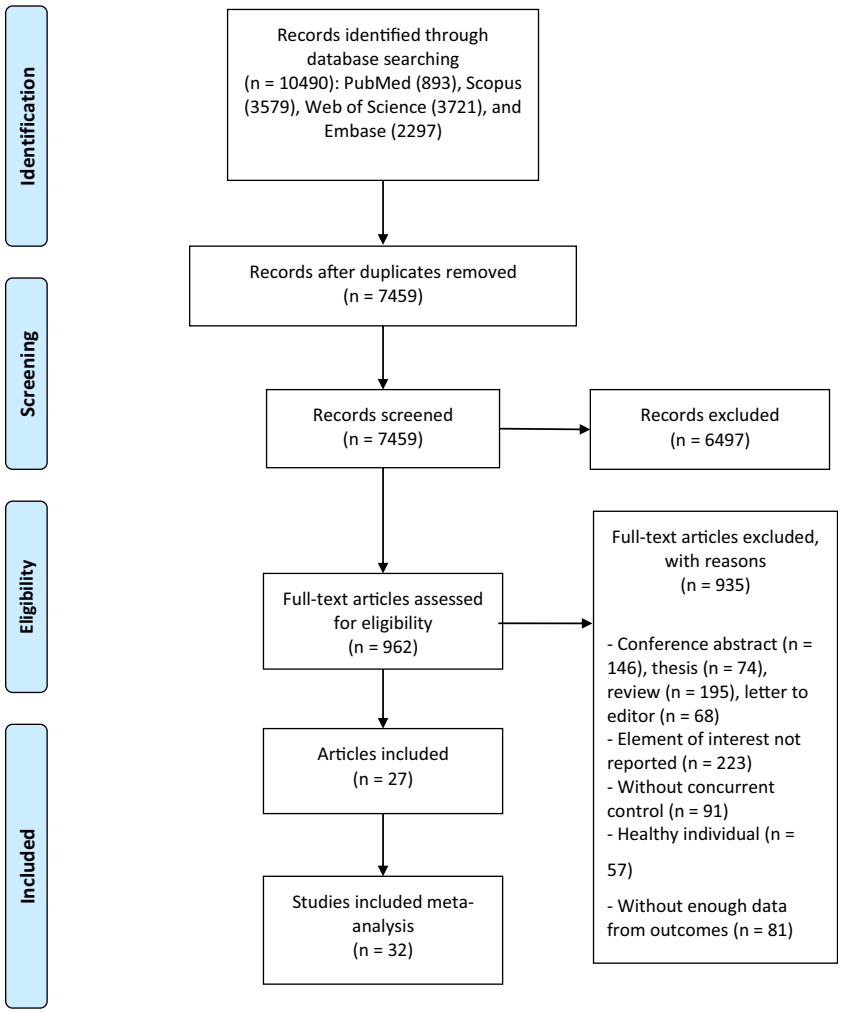

Fig. 1 Flow chart of the studies identification and selection process

on the type of MS indicated significantly decreased levels of Fe in patients with no specific MS (n = 6, WMD = − 23.61 mcg/dl, 95% CI = − 42.42 to − 4.79; I^2 = 90.8%, P = 0.016). Furthermore, Fe levels were shown to be lower in studies with case-control designs (n = 11, WMD = − 13.21 mcg/dl, 95% CI = − 23.00 to − 3.43; I^2 = 92.9%, P <0.001) and in those with serum blood sampling (n = 11, WMD = − 14.77 mcg/dl, 95% CI = − 29.45 to − 0.08; I^2 = 92.9%, P < 0.001). The results obtained from the meta-regression analyses revealed that the studied continuous factors did not have any statistically significant effects on Fe concentrations (Table 3). Moreover, the pooled findings for Fe remained constant in sensitivity analysis (Supplementary Fig. S5). Begg's test (P = 0.583) and Egger's test (P = 0.277) also were estimated to have no significant evidence of publication bias.

Mn Among MS Patients and Controls

In accordance with four qualified studies which were pooled, by using a random-effects model, meta-analysis results indicated that Mn levels were higher in MS patients than in controls (WMD = 0.03 mcg/dl, 95% CI = 0.01 to 0.04), along with considerable inter-heterogeneity (I^2 = 81.5%, P = 0.001). As the number of included studies for this outcome was few, additional analyses could not be conducted to assess the source of inter-study heterogeneity. However, the included studies for Mn were from Europe with a case-control design. Likewise, the sensitivity analysis indicated that the exclusion of the study by Ristori et al. [49] changed the pooled effect size (WMD = 0.03, 95% CI − 0.00, 0.07). Moreover, it should be noted that no potential evidence of publication bias was found across the included studies (P = 0.174 for Begg's test and P = 0.449 for Egger's test).

Mg Among MS Patients and Controls

Nine studies involving 857 subjects have reported Mg levels. The finding of the meta-analysis conducted using a random-effects model showed that Mg levels in MS patients were not significantly different from those in control groups (WMD = − 182.91 mcg/dl, 95% CI = − 419.81 to 53.99). It is noteworthy that additional analyses were conducted, along with the

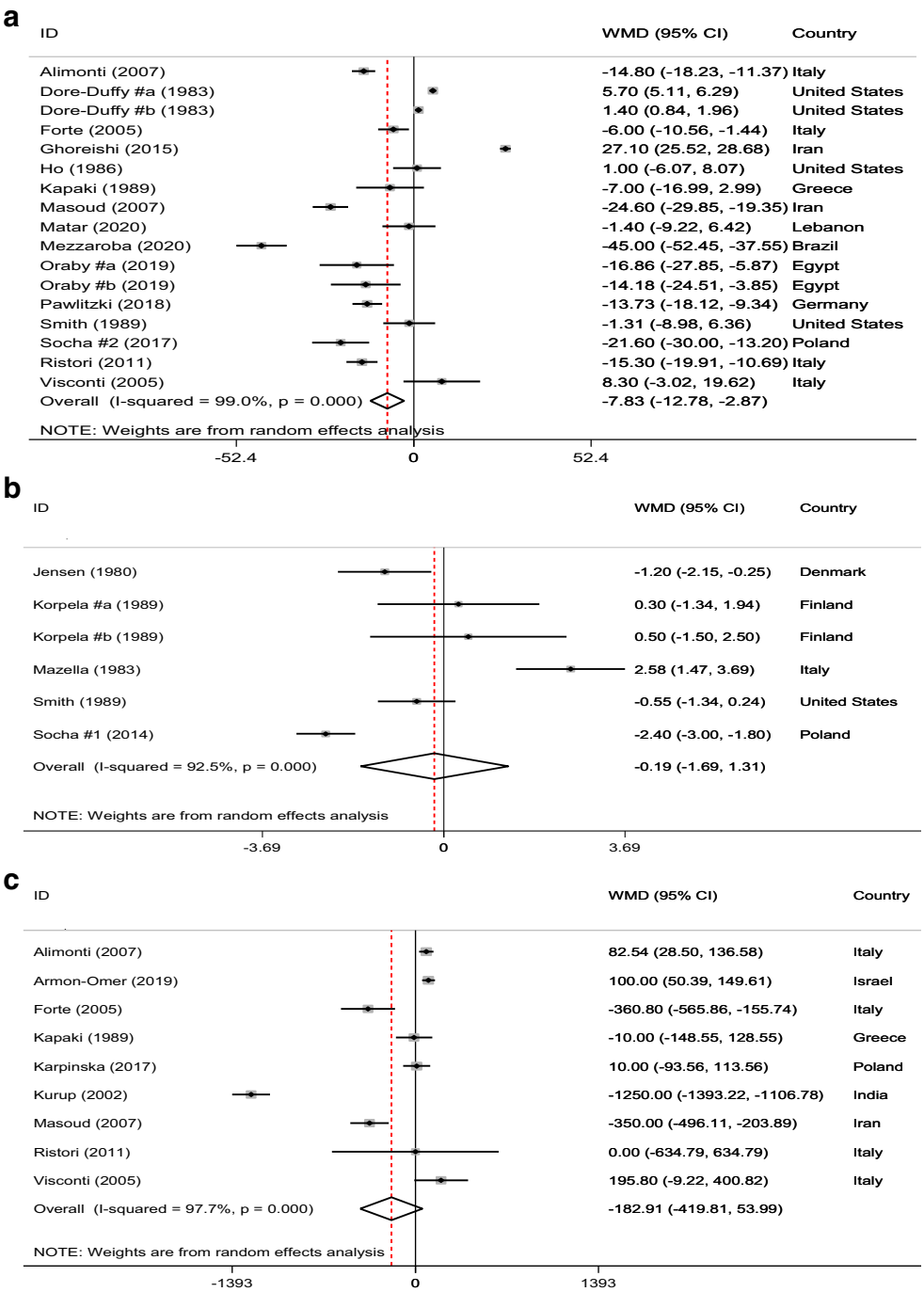

Fig. 2 The forest plots of pooled estimates of the weighted mean differences on Zn (a), Se (b), Mg (c), Cu (d), Fe (e), Mn (f) between MS patients and control groups

reported heterogeneity across the included studies (I^2 = 97.7%, $P < 0.001$). With regard to the subgroup analyses and meta-regression, no significant associations were found between the levels of Mg and MS disease (Tables 2 and 3).

Based on the results of sensitivity analysis of the pooled WMD for Mg levels, we did not find any material change after the studies were excluded one by one (Supplementary Fig. S3). Likewise, no potential evidence of publication bias was found across the included studies ($P = 0.204$ for Begg's test and $P = 0.144$ for Egger's test).

Se Among MS Patients and Controls

The pooled WMD of eight qualified studies showed that Se concentrations among patients with MS were not significantly different from those of the control group (WMD = − 0.19 mcg/dl, 95% CI = − 1.69 to 1.31). The results also revealed considerable heterogeneity across the included studies (I^2 = 92.5%, $P < 0.001$). The subgroups' findings indicated that none of the stratified subgroups was associated with Se concentrations (Table 2). However, the inter-heterogeneity is

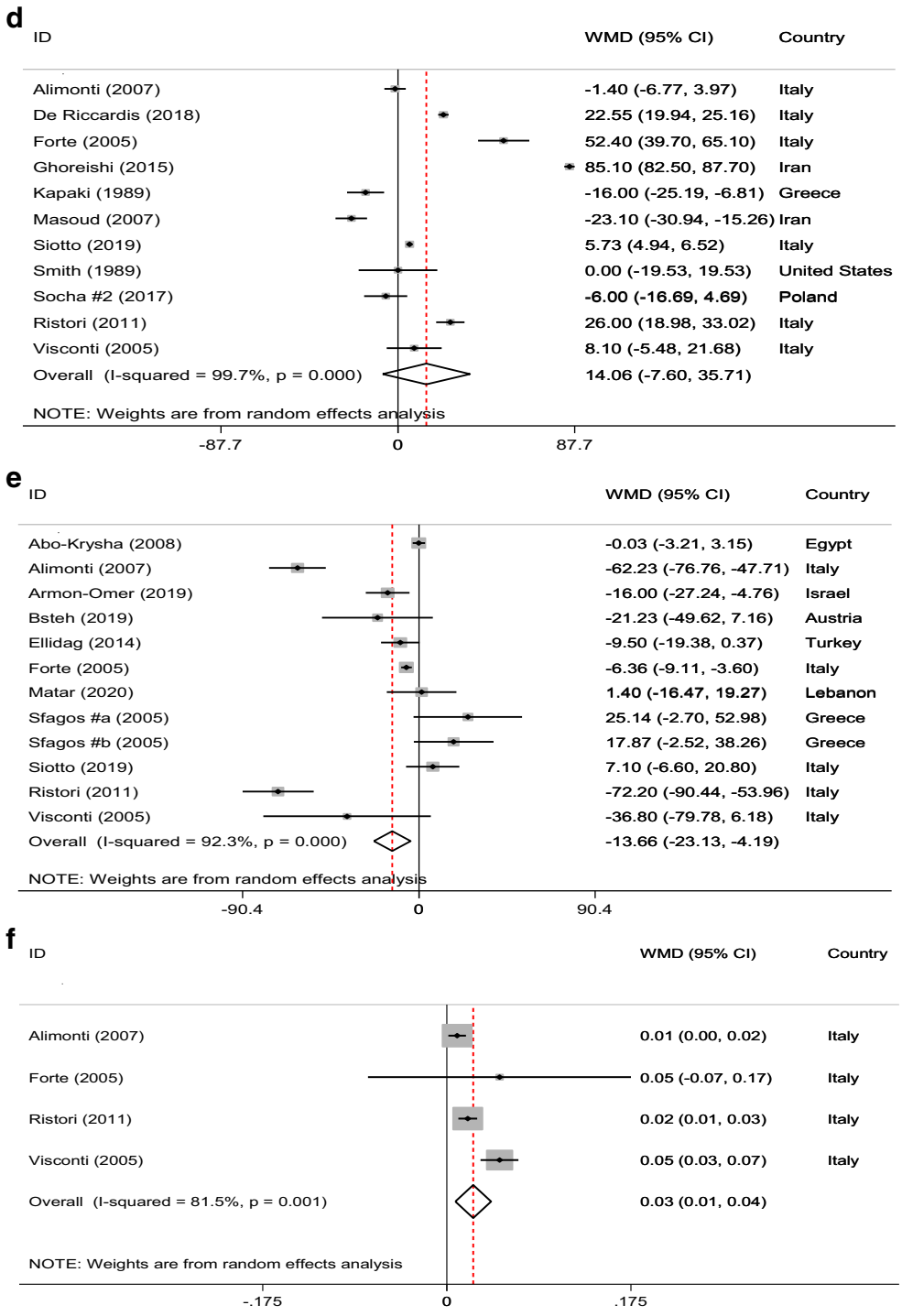

Fig. 2 (continued)

deceased in some strata. Based on the results obtained from meta-regression analyses, the studied continuous factors did not have any statistically significant effects on Se concentrations (Table 3). Moreover, the pooled findings remained constant in sensitivity analyses (Supplementary Fig. S2). The results of Egger's test ($P = 0.155$) and Begg's test ($P = 0.188$) showed that there was no publication bias.

Cu Among MS Patients and Controls

Eleven studies comprised of 507 MS patients and 540 controls have investigated Cu levels. According to their pooled results, Cu concentrations were not significantly different between the two groups (MS patients/controls) (WMD = 14.06 mcg/dl, 95% CI = − 7.60 to 35.71). However, it was shown that there

Table 2 Findings of subgroup analyses

Outcomes			Number of studies	WMD (95% CI)	I^2 and P-value
Zn (mcg/dl)	Total		17	− 7.83 (− 12.78, − 2.87)	99.0%, $P < 0.001$
	Study design	Case-control	14	− 6.52 (− 11.80, − 1.25)	99.1%, $P < 0.001$
		Cohort	3	− 13.52 (− 25.02, − 2.01)	92.1%, $P < 0.001$
		Cross-sectional	-	-	-
	Region	Europe	7	− 11.09 (− 15.85, − 6.34)	79.9%, $P < 0.001$
		Asia	3	0.43 (− 35.87, 36.72)	99.5%, $P < 0.001$
		America	5	− 5.34 (− 10.08, − 0.60)	98.5%, $P < 0.001$
		Africa	2	− 15.44 (− 22.97, − 7.91)	0.0%, $P = 0.728$
	Type of MS	Non-specific MS	13	− 5.25 (− 10.67, 0.17)	99.1%, $P < 0.001$
		RR-MS	1	− 21.60 (− 30.00, − 13.20)	-
		Other	3	− 14.91 (− 18.03, − 11.79)	0.0%, $P = 0.931$
	Blood sampling	Serum	13	-10.52 (-20.26, -0.78)	99.2%, $P < 0.001$
		Plasma	4	0.06 (− 6.80, 6.91)	89.8%, $P < 0.001$
Fe (mcg/dl)	Total		12	− 13.66 (− 23.13, − 4.19)	92.3%, $P < 0.001$
	Study design	Case-control	11	− 13.21 (− 23.00, − 3.43)	92.9%, $P < 0.001$
		Cohort	-	-	-
		Cross-sectional	1	− 21.23 (− 49.62, 7.16)	-
	Region	Europe	8	− 18.48 (− 40.36, 3.41)	94.2%, $P < 0.001$
		Asia	3	− 9.98 (− 18.12, − 1.84)	24.8%, $P = 0.265$
		America	-	-	-
		Africa	1	− 0.03 (− 3.21, 3.15)	-
	Type of MS	Non-specific MS	6	− 23.61 (− 42.42, − 4.79)	90.8%, $P = 0.016$
		RR-MS	4	0.72 (− 7.75, 9.18)	61.0%, $P = 0.053$
		Other	2	− 22.51 (− 101.01, 55.98)	97.5%, $P < 0.001$
	Blood sampling	Serum	11	− 14.77 (− 29.45, − 0.08)	92.9%, $P < 0.001$
		Plasma	1	− 6.36 (− 9.11, − 3.60)	-
Mg (mcg/dl)	Total		9	− 182.91 (− 419.81, 53.99)	97.7%, $P < 0.001$
	Study design	Case-control	8	− 160.83 (− 415.13, 93.48)	97.9%, $P < 0.001$
		Cohort	1	− 350.00 (− 496.11, 203.89)	-
		Cross-sectional	-	-	-
	Region	Europe	6	− 3.01 (− 120.07, 114.04)	75.0%, $P = 0.001$
		Asia	3	− 498.17 (− 1305.42, 309.08)	99.4%, $P < 0.001$
		America	-	-	-
		Africa	-	-	-
	Type of MS	No specific MS	6	− 75.75 (− 272.78, 121.28)	90.1%, $P < 0.001$
		RR-MS	-	-	-
		Other	3	− 382.81 (− 1051.10, 285.47)	99.3%, $P < 0.001$
	Blood sampling	Serum	7	7.70 (− 91.87, 107.27)	83.8%, $P < 0.001$
		Plasma	2	− 808.55 (− 1679.93, 62.83)	97.9%, $P < 0.001$
Se (mcg/dl)	Total		6	− 0.19 (− 1.69, 1.31)	92.5%, $P < 0.001$
	Study design	Case-control	3	− 0.37 (− 3.12, 2.38)	96.7%, $P < 0.001$
		Cohort	3	− 0.29 (− 0.96, 0.38)	0.0%, $P = 0.469$
		Cross-sectional	-	-	-
	Region	Europe	5	− 0.09 (− 2.06, 1.88)	93.9%, $P < 0.001$
		Asia	-	-	-
		America	1	− 0.55 (− 1.34, 0.24)	-
		Africa	-	-	-
	Type of MS	No specific MS	3	0.25 (− 1.81, 2.31)	93.1%, $P < 0.001$
		RR-MS	1	− 2.40 (− 3.00, − 1.80)	-

Table 2 (continued)

Outcomes			Number of studies	WMD (95% CI)	I^2 and *P*-value
		Other	2	0.38 (− 0.89, 1.65)	0.0%, $P = 0.879$
	Blood sampling	Serum	4	− 0.92 (− 2.26, 0.43)	82.0%, $P < 0.001$
		Plasma	2	0.99 (− 2.08, 4.06)	95.1%, $P < 0.001$
Cu (mcg/dl)	Total		11	14.06 (− 7.60, 35.71)	99.7%, $P < 0.001$
	Study design	Case-control	9	19.66 (− 4.48, 43.81)	99.8%, $P < 0.001$
		Cohort	2	− 13.35 (− 35.71, 9.01)	78.4%, $P = 0.031$
		Cross-sectional	-	-	-
	Region	Europe	8	11.09 (1.92, 20.26)	97.3%, $P < 0.001$
		Asia	2	31.07 (− 74.97, 137.10)	99.8%, $P < 0.001$
		America	1	0.00 (− 19.53, 19.53)	-
		Africa			
	Type of MS	No specific MS	7	19.03 (− 22.60, 60.66)	99.5%, $P < 0.001$
		RR-MS	3	8.21 (− 5.48, 21.90)	98.7%, $P < 0.001$
		Other	1	− 1.40 (− 6.77, 3.97)	-
	Blood sampling	Serum	9	11.35 (− 12.63, 35.33)	99.8%, $P < 0.001$
		Plasma	2	26.75 (− 24.59, 78.09)	94.9%, $P < 0.001$

was significant inter-heterogeneity across the included studies ($I^2 = 99.7\%$, $P < 0.001$). Moreover, subgroups' findings on the association between MS disease and Cu levels remained insignificant in different strata of study testing, type of MS, and blood sampling (Table 2). However, the stratification of studies based on the region wherein they were performed revealed significant increases in Cu levels among patients in Europe ($n = 8$, WMD = 11.09 mcg/dl, 95% CI = 1.92 to 20.26; $I^2 = 97.3\%$, $P < 0.001$). In addition, the meta-regression analysis showed that the studied continuous factors had no significant effect on the association between MS and Cu levels (Table 3).

Yet, the pooled WMD in sensitivity analysis remained constant after each study, which addressed the association between the two groups, was excluded (Supplementary Fig. S4). There was no statistically potential publication bias using Begg's test ($P = 0.578$) and Egger's test ($P = 0.938$).

Discussion

MS is the most frequent chronic inflammatory demyelinating disease of the CNS. It is characterized by autoimmunity and

Table 3 Findings of meta-regression analyses

Outcomes	Continues factors	Coefficient	95% CI	*P*-value	tau2	Adj *R*-squared
Zn (mcg/dl)	Publication year	− 0.46	− 1.03, 0.12	0.114	219.8	10.20%
	Total sample size	− 0.11	− 0.20, − 0.01	0.026	184	24.82%
	Quality scores	− 3.90	− 12.51, 4.72	0.350	244	0.31%
Fe (mcg/dl)	Publication year	0.15	− 3.15, 3.45	0.922	866	− 11.16%
	Total sample size	− 0.32	− 0.67, 0.02	0.064	548.5	29.60%
	Quality scores	− 1.65	− 23.52, 20.22	0.870	870.7	− 11.75%
Mg (mcg/dl)	Publication year	12.58	− 32.10, 57.27	0.527	214753	− 7.97%
	Total sample size	3.17	− 3.29, 9.62	0.284	189228	4.87%
	Quality scores	295.85	− 214.84, 806.55	0.213	174672	12.18%
Se (mcg/dl)	Publication year	− 0.09	− 0.24, 0.07	0.193	2.08	24.94%
	Total sample size	− 0.02	− 0.05, 0.01	0.168	1.94	30.07%
	Quality scores	− 1.27	− 2.81, 0.28	0.085	1.39	50.32%
Cu (mcg/dl)	Publication year	1.05	− 1.12, 3.21	0.301	969	2.29%
	Total sample size	0.07	− 0.42, 0.56	0.760	1091	− 9.98%
	Quality scores	− 3.77	− 32.54, 24.99	0.773	1089	− 9.82%

neurodegeneration, leading to irreversible and severe clinical disability [18, 21]. Among the environmental factors, abnormalities of trace elements have been hypothesized to be involved in the pathogenesis of various neurologic diseases, including MS [2, 49]. This systematic review and meta-analysis aimed to ascertain if the blood concentrations of patients with MS and healthy adults are different in terms of Zn, Fe, Mn, Mg, Se, and Cu. Findings obtained from the present meta-analysis revealed significantly lower circulating levels of Fe and Zn among patients with MS in comparison with the healthy controls. However, trace elements of Cu and Se were not significantly different between MS patients and controls. With respect to Mg, there was no significant difference between the two groups.

Zinc is an essential trace element in the brain and a cofactor of more than 300 enzymes including matrix metalloproteinases (MMPs). It is a component of many proteins such as myelin basic protein. Thus, it plays a significant role in MS pathophysiology [5, 45, 60]. Our findings of considerably lower serum Zn levels in MS patients compared to controls are in line with some previous studies. A previous meta-analysis reported a significant reduction in overall serum/plasma Zn levels in patients with MS compared to the controls [6]. Moreover, in a cohort study, it was revealed that MS diagnosis is associated with lower serum zinc concentrations compared to the controls, but without marked zinc deficiency. This cohort study also declared that lower zinc levels in MS patients could be a result of enhanced upregulation of zinc-dependent MMPs, with higher levels during the active disease stage. Likewise, this upregulation might explain the reported lower zinc levels in RR-MS patients compared to patients with chronic disease [45]. Subsequent to the subgroup analyses, the observed heterogeneity decreased within some of the subgroups, including European and RR-MS ones. It should be noted that Europeans showed lower Zn levels in MS patients compared to controls, implying the need for further investigations to explore the reason behind Zn deficiency in patients suffering from MS in this region. Moreover, zinc levels were demonstrated to be significantly lower in RR-MS subgroups compared with other types. It is highly recommended that more cohort and clinical trial studies be conducted to assess Zn therapy in RR-MS patients, as a more common type of MS.

Fe is a cofactor of various enzymes for normal brain metabolisms [30, 31]. Abnormal Fe homeostasis may contribute to neurodegeneration which is relevant to the pathology of MS. Findings obtained from the present study are consistent with recent works as they revealed that the MS group had considerably lower Fe values in comparison with healthy controls [4]. Iron is considered a key factor in MS pathogenesis, as it may lead to neuronal damage through triggering oxidative stress [35]. Fe subgroup analyses showed lower heterogeneity within different geographical subgroups. In this regard, Asians showed significantly lower circulating levels of Fe in comparison with other regions. Therefore, studies that are more comprehensive are needed to clarify the observed iron deficiency in Asian patients with MS.

Mn serves as a cofactor for maintaining the function and regulation of many biochemical and cellular reactions, including multiple enzymes, which are critical for synthesis and metabolism of neurotransmitters and neuronal and glial function [16, 25]. It is also recognized as a neurotoxicant through the formation of hydroxyl radicals that decreases cellular antioxidants and offers crucial implications for MS [56]. Our meta-analysis results indicated, based on four qualified studies, that Mn levels were significantly higher in MS patients than in controls with high heterogeneity. Therefore, further studies with a larger sample size are required to explain the exact implication of Mn in patients with MS.

Mg has a key role in the nervous system by reducing the excitability of nerve cells [32]. Mg activates about 320 enzymes and interacts with other minerals, such as calcium, zinc, and aluminum, affecting the immune system and the content of these elements in the central nervous system [64]. Mg deficiency impairs antioxidant defense through decreased activity of Cu/Zn superoxide dismutase and reduced glutathione synthesis. It also increases synthesis or activity of injurious mediators, e.g., tumor necrosis factor (TNF), interleukin 6 (IL-6), IL-1, oxygen-free radicals, and endothelin, thereby being possibly implicated in the etiology of MS [29]. With respect to Mg, no significant difference was found between the two groups in the present meta-analysis. In a previous study on RR-MS patients, the average serum level of Mg was normal, but certain abnormalities were observed, due to a high number of MS patients represented a dysregulated serum Mg. As patients with a deficiency and an excess of serum Mg levels had a worse clinical condition, Mg supplementation should be taken after the concentration of this element in the serum is evaluated [29]. Moreover, more studies with a larger sample size are required to explain the exact role played by Mg in the pathophysiology of MS.

Se is another important trace element that is well known for its key role in the glutathione peroxidase enzyme and its anti-inflammatory effect [3]. Because of its potent antioxidant and anti-inflammatory properties, Se may have a protective effect on the course of MS. Therefore, it is frequently claimed that Se deficiency is a common and important issue in MS [51]. In this study, no statistically significant difference was shown between MS patients and controls in terms of their circulating levels of Se, though MS patients demonstrated a lower Se level compared to the control group.

Cu is involved in the structure and function of several brain enzymes, oxidative defense, iron metabolism, regulating neurotransmitters, and myelin synthesis [10]. Cu is also crucial for the normal development of the nervous system [59]. The role of Cu in MS pathology is shown to be through its excessive

concentrations and subsequent oxidative damage. Therefore, Cu levels should be precisely adjusted for essential enzyme activity and prevention of oxidative stress [54]. Based on the present study, no statistically significant difference was found between MS patients and controls in terms of Cu trace element. However, given higher Cu levels in MS patients, the assumption that higher circulating levels of Cu may contribute to MS development is unclear. A recent meta-analysis also showed a higher concentration of Cu in MS patients compared to the healthy controls [50]. The differences between the results of these meta-analyses may be due to the method used to determine pooled effect size. These findings confirm the possible function of Cu in MS etiology and could stimulate future studies with longitudinal designs and larger sample sizes.

It should be noted that this meta-analysis had several limitations that should be taken into account. First, given the high heterogeneity of the selected studies, the obtained results should be interpreted with caution. Next, it is likely that the associations reported in the present meta-analysis are affected by participants' gender, age, and/or expanded disability status scale (EDSS) scores that are not addressed in this meta-analysis. This is because the included articles lacked detailed respective information. Furthermore, most of the included studies of this meta-analysis did not take account of the confounding factors including smoking, alcohol, lifestyle habits, and dietary intake of trace elements. Accordingly, the aforementioned factors are to be addressed in subsequent studies assessing the association between the level of trace elements and MS. A strength of this meta-analysis would be the pooled result of the minerals that permits a precise assessment of the relationship between the circulating levels of the trace elements and MS. To identify the possible sources of heterogeneity in our study, a subgroup analysis was conducted. Likewise, since no publication bias was detected, it is likely that the obtained results are not biased. Notably, iodine (I) was considered as a trace element in our search, although no article was found to report the role of this element in MS.

Conclusion

This meta-analysis revealed that patients with MS had lower Zn and Fe as compared with the controls. Mn levels were significantly higher in MS patients than in the controls. In addition, Fe and Zn levels were influenced by the region and disease subtypes. However, it was also shown that MS patients were not significantly associated in terms of Se, Mg, and Cu. It is suggested that additional, larger, and well-designed clinical studies, especially on iodine and other trace elements with lower available evidence, could produce invaluable results in the context of MS. Given the substantial heterogeneity among the included studies, the results should be treated with caution. Finally, the identification of potential nutritional supplements such as trace elements may provide valuable insights into the treatment options for MS, especially for patients in whom disease-modifying drugs do not prevent disease progression or nutritional deficiencies are prevalent.

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Data Availability Data will be made available on reasonable request.

Declarations

Ethics Approval and Consent to Participate This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Conflict of Interest The authors declare no conflict of interest.

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