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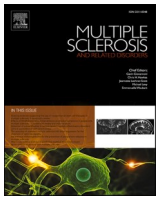

Original article

Low serum 25-hydroxy-vitamin D levels are associated with cognitive impairment in multiple sclerosis

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ABSTRACT

Background: Cognitive impairment frequently affects people with multiple sclerosis (MS). Low vitamin D has been associated with cognitive dysfunction in different neurodegenerative diseases, and, in MS, with motor disability and disease activity. We aim to investigate associations between vitamin D and cognitive status in MS.
Methods: In this cross-sectional study, we included 181 MS patients, recruited consecutively at the MS Unit of the Policlinico Federico II University Hospital of Naples, Italy, between January and April 2022, with serum 25-hydroxy (25-OH) vitamin D measurements using Chemiluminescence-ImmunoAssay, and cognitive assessment using the Brief International Cognitive Assessment for MS (BICAMS), which includes Symbol Digit Modalities Test (SDMT), California Verbal Learning Test-II (CVLT-II) and Brief Visuospatial Memory Test-Revised (BVMT-R). We collected demographics (age, sex, education), and clinical variables (disease duration, disease subtype, expanded disability status scale (EDSS), disease modifying treatment, relapses in previous 12 months, vitamin D supplementation, comorbidities). For a subset of patients (n = 41, 23.2% of the total sample), we collected Beck Depression Inventory-II, Beck Anxiety Inventory, and Modified Fatigue Impact Scale.
Results: At univariable linear regression models, serum 25-OH-vitamin D levels were 0.9 ng/mL higher for each unit increase of SDMT adjusted scores (Coeff=0.93; 95%CI=0.81, 1.04; p<0.01), 0.7 ng/mL higher for each unit increase of CVLT-II adjusted scores (Coeff=0.68; 95%CI=0.53, 0.83; p<0. 01), 0.6 ng/mL higher for each unit increase of BVMT-R adjusted scores (Coeff=0.58; 95%CI=0.43, 0.73; p<0.01), -9.63 ng/mL lower for each impaired BICAMS test (Coeff=-9.63; 95%CI=-11.48, -7.79; p<0.01), and -2.2 ng/mL lower for each unit increase of EDSS (Coeff=-2.16; 95%CI=-3.57, -0.75; p<0.01). At multivariable linear regression models, we confirmed associations between 25-OH-vitamin D and EDSS (Coeff=-2.09; 95%CI=-4.45, -0.43; p<0.01), SDMT (Coeff=0.75; 95%CI=0.60, 0.90; p<0.01), and CVLT-II (Coeff=0.14; 95%CI=0.01, 0.28; p = 0. 04). Results remained unchanged when including depression, anxiety and fatigue scores.
Conclusions: Lower serum 25-OH-vitamin D was associated with worse cognitive function in MS. Future studies should consider longitudinal variations in cognitive function in relation to vitamin D supplementation.

1. Introduction

Cognitive impairment (CI) is a disabling clinical feature of multiple sclerosis (MS), with prevalence ranging from 40% to 70% (Chiaravalloti and DeLuca, 2008). Attention, information processing speed, and visuospatial memory are the most commonly affected domains in MS. Other frequently affected domains are working and verbal memory, and executive function (McNicholas et al., 2018).

CI in MS is associated with neurodegenerative aspects, including progressive motor symptoms and prominent cortical and subcortical atrophy (Chiaravalloti and DeLuca, 2008; Moccia et al., 2016; Kuhlmann et al., 2023). By contrast, vitamin D can mediate neurotrophic and

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neuroprotective mechanisms of the central nervous system, and its deficiency is associated with worse cognitive performance in older adults, (Annweiler et al., 2015) and with risk and severity of purely neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD) (Evatt et al., 2008). Low levels of vitamin D and its metabolites increase the risk of MS, (Tiller et al., 2022) and correlate with worse motor disability and higher relapse rate (Ascherio et al., 2010; Huang et al., 2022; Miele et al., 2022; Akhtar et al., 2022; Vandebergh et al., 2022; Galus et al., 2022). However, emerging evidence suggests possible association between vitamin D and cognitive dysfunction in MS as well, but the extent of this association and involved cognitive domains remain poorly explored (Koven et al., 2013; Cortese et al., 2020; Darwish et al., 2020).

Thus, our aim is to evaluate the association between serum vitamin D levels and cognitive function using the Brief International Cognitive Assessment for MS (BICAMS), a widely used battery that explores the cognitive domains most commonly affected in MS.

2. Methods

2.1. Study design and population

This is a cross-sectional study, aiming to evaluate the possible associations between serum 25-hydroxy(OH)-vitamin D levels and neuropsychological performances in MS. The study was approved by the Policlinico Federico II University Hospital Ethics Committee (355/19). All patients signed informed consent authorizing the use of anonymized data collected routinely as part of the clinical practice, in line with data protection regulation (GDPR EU2016/679). The study was performed in accordance with good clinical practice and Declaration of Helsinki. Patients were recruited consecutively at the MS Unit of the Policlinico Federico II University Hospital of Naples, Italy, between January and April 2022.

Inclusion criteria were: (1) MS diagnosis based on McDonald 2017 dissemination in space and time criteria using clinical, CSF and/or MRI data, as necessary; (Thompson et al., 2018) (2) consent to neuropsychological assessment and collection of blood samples for 25-OH-vitamin D measurements. Exclusion criteria were: (1) age <18 years; (2) concomitant diseases or treatments potentially affecting cognitive performance (e.g., diagnosis of dementia and/or prescription of memantine, rivastigmine, donepezil, and/or antipsychotics).

2.2. Vitamin D measurement

Fasting blood samples were obtained on the same day of the neuropsychological assessment, and were analysed using fully-automated chemiluminescence immunoassay (CLIA) to quantify serum 25-OH-vitamin D (measured in nanograms per milliliter, ng/mL). We used the LIAISON® 25OH Vitamin D total assay (DiaSorin Inc., 1951 Northwestern Ave—Stillwater, MN 55,082—USA). According to the Italian Endocrinologist Guidelines, (Cesareo et al., 2018) we defined vitamin-D deficiency for serum 25-OH-vitamin D below or equal to 20 ng/mL, insufficiency if between 20 and 30 ng/mL, and sufficiency if above 30 ng/mL .

2.3. Clinical and cognitive variables

We collected age, sex, education, disease duration (time between MS onset and the neuropsychological evaluation), disease subtype (relapsing vs progressive MS, Kuhlmann et al., 2023) disease modifying treatment (DMT), relapses in previous 12 months (yes/no), steroid treatment in previous 12 months (yes/no), and comorbidities (Charlson Comorbidity Index, then dichotomised to yes/no due to small number of observations). MS disability was scored with the Expanded Disability Status Scale (EDSS) by certified physicians on the same day of vitamin D measurement. For statistical purposes, we classified DMTs into platform (dimethyl-fumarate, interferon-beta, teriflunomide) and high-efficacy DMTs (alemtuzumab, cladribine, ocrelizumab, S1P inhibitors). We also collected concomitant vitamin D supplementation (yes/no), which was included as a covariate in the statistical models; indeed, our main variable of interest is blood level of 25-OH-vitamin D, not necessarily reflecting the use of vitamin D supplements (i.e., underdosing, short interval of treatment, etc.).

All patients underwent the Brief International Cognitive Assessment for MS (BICAMS) neuropsychological battery, which includes the following tests: the Symbol Digit Modalities Test (SDMT), evaluating attention and information processing speed; the California Verbal Learning Test-II (CVLT-II), evaluating memory and verbal learning; and the Brief Visuospatial Memory Test-Revised (BVMTR), evaluating visuospatial learning. Results were adjusted for age, sex, and education, according to the Italian normative values. (Goretti et al., 2014).

For a subset of patients ($n = 41$, 23.2% of the total sample), we also collected Beck Depression Inventory-II (BDI-II) for depression, Beck Anxiety Inventory (BAI) for anxiety, (Sica and Ghisi, 2007) and Modified Fatigue Impact Scale (MFIS) for fatigue (Kos et al., 2005).

2.4. Statistics

Mean (and standard deviation) (25-OH-vitamin D, age, disease duration, SDMT, CVLT-II, BVMT-R, BDI-II, BAI and MFIS), median (and range) (EDSS), and number (and percent) (25-OH-vitamin D classification, sex, disease subtype, DMTs, relapses, steroid treatment, vitamin D supplementation, patients with comorbidities, patients with impaired BICAMS tests) were calculated for different study variables.

We used different univariable linear regression models for associations between 25-OH-vitamin D, as dependent variable, and, in turn, each demographic (age, sex), clinical (disease duration, disease subtype, EDSS, DMT, relapses in previous 12 months, steroid treatment in previous 12 months, concomitant vitamin D supplementation, comorbidities) and cognitive variables (adjusted scores of SDMT, CVLT-II and BVMT-R, number of impaired BICAMS tests, BDI-II, BAI, MFIS), as independent variables. Using these models, we identified demographic, clinical, and cognitive variables reflecting vitamin D status, that were then included as independent variables in the same multivariable linear regression model, using 25-OH-vitamin D as dependent variable, to explore the strongest clinical and cognitive correlates; additional covariates were age and sex.

Results were reported as coefficients (Coeff), 95% confidence interval (95%CI), and p-values, as appropriate. Distribution of variables and residuals was checked using both graphical and statistical methods. Statistical analyses were performed using Stata 15.0 (StataCorp, College Station, TX, USA). Results were considered statistically significant if $p<0.05$.

3. Results

We included 181 MS patients with availability of 25-OH-vitamin D measurements, along with clinical and cognitive variables. Demographic, clinical, and cognitive variables are reported in Table 1. BDI-II, BAI, and MFIS were available for 41 patients (23.2%).

On univariable linear regression models, serum 25-OH-vitamin D levels were 0.9 ng/mL higher for each unit increase of SDMT adjusted scores (Coeff=0.93; 95%CI=0.81, 1.04; $p<0.01$), 0.7 ng/mL higher for each unit increase of CVLT-II adjusted scores (Coeff=0.68; 95%CI=0.53, 0.83; $p<0.01$), 0.6 ng/mL higher for each unit increase of BVMT-R adjusted scores (Coeff=0.58; 95%CI=0.43, 0.73; $p<0.01$), −9.63 ng/mL lower for each impaired BICAMS test (Coeff=−9.63; 95% CI=−11.48, −7.79; $p<0.01$), and −2.2 ng/mL lower for each unit increase of EDSS (Coeff=−2.16; 95%CI=−3.57, −0.75; $p<0.01$) (Table 2). No statistically significant associations were found for age (Coeff=0.11; 95%CI=−0.08, 0.30; $p = 0.25$), sex (Coeff=−0.97; 95%CI=−5.50, 3.55; $p = 0.67$), disease duration (Coeff=0.09; 95%CI=−0.06, 0.25; $p = 0.24$),

Table 1
Demographic, clinical, and cognitive variables.

		MS patients	
Age, *years, mean±SD*		$n = 181$	46.8 ± 11.4
Sex, *females, number (%)*		$n = 181$	111 (61.3%)
25-OH-vitamin D, *ng/mL, mean±SD*		$n = 181$	24.2 ± 15.0
Vitamin D deficient patients (< 20 ng/mL), *number (%)*		$n = 181$	71 (39.3%)
Vitamin D insufficient patients (20–30 ng/mL), *number (%)*		$n = 181$	64 (35.3%)
Vitamin D sufficient patients (>30 ng/mL), *number (%)*		$n = 181$	46 (25,4%)
Disease duration, *years, mean±SD*		$n = 181$	14.9 ± 13.9
Disease subtype, *number (%)*	*Relapsing*	$n = 181$	133 (73.5%)
Primary progressive			15 (8.3%)
Secondary progressive			33 (18.2%)
EDSS, *median (range)*		$n = 181$	3.5 (1.5 – 7.5)
DMTs, *number (%)*	*Alemtuzumab*	$n = 181$	2 (1.1%)
	Cladribine		27 (14.9%)
	Dimethyl fumarate		16 (8.8%)
	Interferon beta		6 (3.3%)
	Ocrelizumab		41 (22.6%)
	S1P inhibitors		85 (52.0%)
	Teriflunomide		4 (2.2%)
Relapses in previous 12 months, yes, *number (%)*		$n = 181$	11 (6.1%)
Steroid treatment in previous 12 months, *number (%)*		$n = 181$	4 (2.2%)
Concomitant vitamin D supplementation, *number (%)*		$n = 181$	14 (7.7%)
Patients with comorbidities, *number (%)*		$n = 181$	69 (38.1%)
SDMT, *adjusted score, mean±SD*		$n = 181$	45.1 ± 12.3
SDMT, *patients with impaired score, number (%)*		$n = 181$	42 (23.2%)
CVLT-II, *adjusted score, mean±SD*		$n = 181$	41.1 ± 13.1
CVLT-II, *patients with impaired score, number (%)*		$n = 181$	61 (33.7%)
BVMT-R, *adjusted score, mean±SD*		$n = 181$	47.7 ± 12.2
BVMT-R, *patients with impaired score, number (%)*		$n = 181$	27 (14.9%)
Number of impaired BICAMS tests, *number (%)*	*0*	$n = 181$	99 (54.7%)
1			49 (27.1%)
2			18 (9.9%)
3			15 (8.3%)
BDI-II, *score, mean±SD*		$n = 41$	5.0 ± 9.4
BAI, *score, mean±SD*		$n = 41$	5.6 ± 10.7
MFIS, *score, mean±SD*		$n = 41$	17.6 ± 22.4

disease subtype (Coeff=−3.07; 95%CI=−8.05, 1.90; $p = 0.22$), DMT (Coeff=2.08; 95%CI=−4.20, 8.37; $p = 0.51$), relapses in previous 12 months (Coeff=0.36; 95%CI=−8.78, 9.60; $p = 0.93$), steroid treatment in previous 12 months (Coeff=1.08; 95%CI=−13.93, 16.10; $p = 0.88$), vitamin D supplementation (Coeff=3.13; 95%CI=−5.11, 11.38; $p = 0.45$), and comorbidities (Coeff=1.73; 95%CI=−2.80, 6.27; $p = 0.45$) (Table 2).

When evaluating the subset of patients with specific testing (23.2% of the initial sample), on univariable linear regression models, no statistically significant associations were found between 25-OH-vitamin D levels and BDI-II (Coeff=−0.13; 95%CI=−0.47, 0.20; $p = 0.42$), BAI (Coeff=−0.02; 95%CI=−0.32, 0.27; $p = 0.86$), and MFIS (Coeff=−0.09; 95%CI=−0.23, 0.04; $p = 0.16$).

When including all statistically significant variables in the same multivariable linear regression model, serum 25-OH-vitamin D levels were −2.0 ng/mL lower for each unit increase of EDSS (Coeff=−2.09; 95%CI=−4.45, −0.43; $p<0.01$) (Fig. 1a), 0.7 ng/mL higher for each unit increase of SDMT adjusted scores (Coeff=0.75; 95%CI=0.60, 0.90; $p<0.01$) (Fig. 1b) and 0.1 ng/mL higher for each unit increase CVLT-II adjusted scores (Coeff=0.14; 95%CI=0.01, 0.28; $p = 0.04$) (Fig. 1c), while we found no statistically significant association for BVMT-R (Coeff=0.10; 95%CI=−0.05, 0.26; $p = 0.19$) (Fig. 1d) (Table 2). When adding BDI-II, BAI, and MFIS to the previous model (only including 23.2% of the initial sample), separately, we confirmed associations for EDSS, SDMT adjusted scores, and CVLT-II adjusted scores.

4. Discussion

Our study showed that 25-OH-vitamin D levels are associated with cognitive function in MS, as already well demonstrated in the general population and in neurodegenerative diseases of the central nervous system (Annweiler et al., 2015; Evatt et al., 2008). In particular, we demonstrated that, in MS, vitamin D levels are associated with attention/information processing speed (i.e., SDMT), and with working and verbal memory (i.e., CVLT-II), suggesting an interplay with vitamin D pathology mechanisms. On the contrary, performance on the visuospatial memory test (i.e., BVMT-R) showed no significant association after adjusting for other clinical and demographic variables.

Previous studies evaluating associations between CI and vitamin D have focused on a single cognitive domain using one neuropsychological test (i.e., PASAT or BVMTR, Darwish et al., 2020, Virgilio et al., 2021) while we applied a more comprehensive cognitive battery, namely the BICAMS. The BICAMS is the most frequently used battery for cognitive assessment in MS, due to well established validation studies and ease of administration (Saccà et al., 2017). In our study, we confirmed previous associations between attention/information processing speed on SDMT and vitamin D levels, (Darwish et al., 2020; Virgilio et al., 2021) and also found an association with verbal memory (CVLT-II) (Koven et al., 2013). Intriguingly, a previous longitudinal study found improvement in SDMT

Table 2
Results of linear regression models.

	Univariable				Multivariable			
	Coeff	*95%CI*		*p-value*	*Coeff*	*95%CI*		*p-value*
		Upper	*Lower*			*Upper*	*Lower*	
Age	0.11	−0.08	0.30	0.25	−0.01	−0.12	0.11	0.91
Sex (females vs males)	−0.97	−5.50	3.55	0.67	1.35	−1.45	4.16	0.34
Disease duration	0.09	−0.06	0.25	0.24				
Disease subtype (relapsing vs progressive)	−3.07	−8.05	1.90	0.22				
DMT (platform vs high efficacy)	2.08	−4.20	8.37	0.51				
Relapses in previous 12 months (no vs yes)	0.36	−8.78	9.60	0.93				
Steroid treatment in previous 12 months (no vs yes)	−1.08	−13.93	16.10	0.88				
Vitamin D supplementation (no vs yes)	3.13	−5.11	11.38	0.45				
Comorbidities (no vs yes)	1.73	−2.80	6.27	0.45				
EDSS	−2.16	−3.57	−0.75	<0.01	−2.09	−4.45	−0.43	<0.01
BVMT-R adjusted score	0.58	0.43	0.73	<0.01	0.10	−0.05	0.26	0.19
CVLT-II adjusted score	0.68	0.53	0.83	<0.01	0.14	0.01	0.28	0.04
SDMT adjusted score	0.93	0.81	1.04	<0.01	0.75	0.60	0.90	<0.01
Number of impaired BICAMS tests	−9.63	−11.48	−7.79	<0.01	−1.63	−3.94	0.66	0.16

Table shows coefficients (Coeff), 95% confidence intervals (95%CI), and p-values from linear regression models. First, we run different univariable linear regression models for associations between 25-OH-vitamin D, as dependent variable, and, in turn, each demographic, clinical and cognitive variables, as independent variables. Using these models, we identified demographic, clinical, and cognitive variables reflecting vitamin D status, that were then included, as independent variables, in the same multivariable linear regression model, using 25-OH-vitamin D as dependent variable; additional covariates were age and sex.

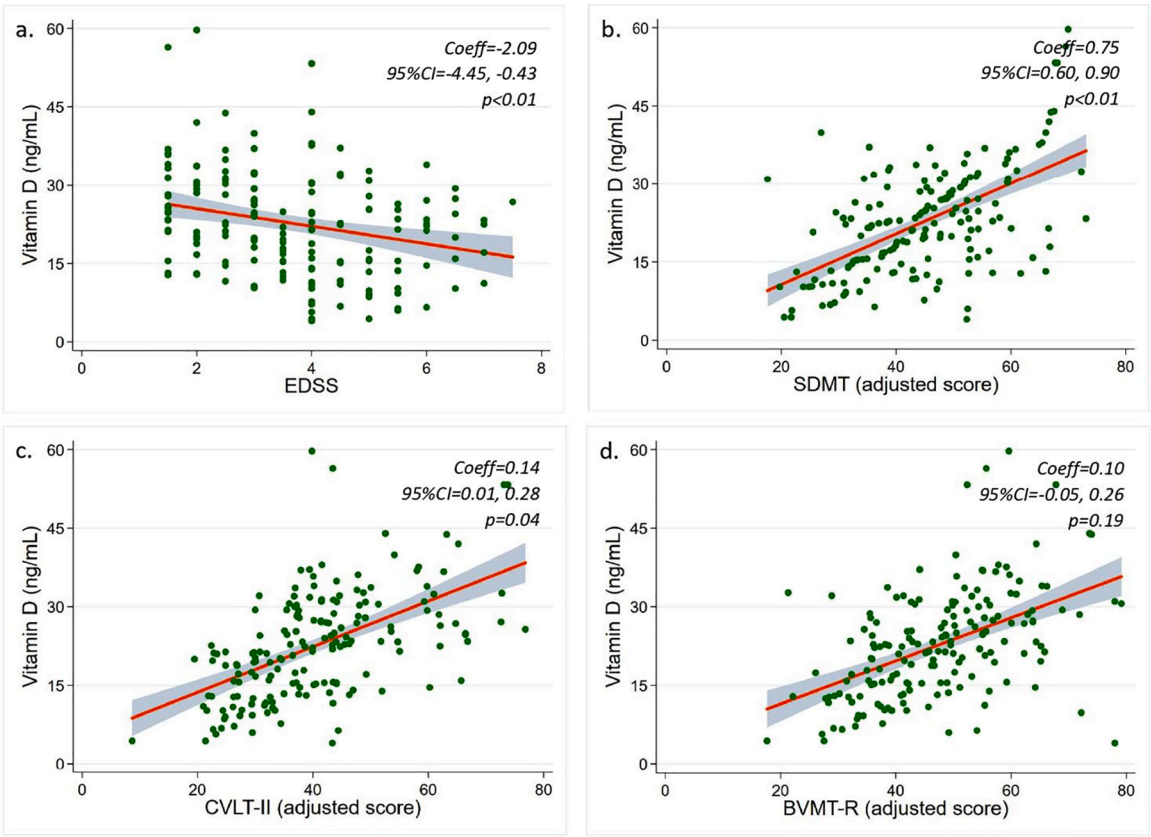

Fig. 1. Scatter plots for vitamin D associations.
Scatter plots show associations between 25-OH-vitamin D and EDSS (a), SDMT (b), CVLT-II (c), and BVMT-R (d). Coefficients (Coeff), 95% confidence intervals (95% CI, represented as gray shadow), and p-values are reported from multivariable linear regression models.

performance in people with MS who became vitamin D sufficient at follow-up, starting from deficiency, thus suggesting direct relationship (Darwish et al., 2020). However, there are potential confounding in the association between vitamin D and cognition, that need to be addressed in future studies to support a causality argument. Our association between visuospatial memory on BVMT-R and vitamin D on the univariate model was not confirmed in the multivariable model. Indeed, working memory is related to performance on visuospatial learning and memory tests, by sharing similar features, (Poirier et al., 2019) and thus could have affected significance of results in the multivariable model. While the understanding of relationships between cognitive domains is out of the scope of the present work, previous studies suggesting an association between vitamin D and BVMT-R could have been limited by the lack of adjustment for possible correlations between cognitive tests (Darwish et al., 2017). Considering that depression, anxiety and fatigue can affect cognitive performance in patients with MS, (Chiaravalloti and DeLuca, 2008) we also evaluated their impact in a subset of patients (only 23.2% of the initial sample), but the associations between vitamin D and cognitive performance remained unchanged, suggesting independent relationship.

CI in MS is possibly the result of a network disconnection syndrome due to the combination of inflammatory (e.g., demyelinating lesions) and neurodegenerative mechanisms (e.g., neuro-axonal loss) (Petracca et al., 2021). Vitamin D might be implicated in immune-mediated biological mechanisms of long-term neuroprotection and could be a prognostic marker of long-term cognition and neuroaxonal integrity. In particular, higher vitamin D levels at MS onset demonstrated to maintain immune homeostasis, (Muris et al., 2016) and to predict lower neurofilaments, thus indicating less neuroaxonal loss (Cortese et al., 2020; Holmøy et al., 2019). Vitamin D contributes to neuroprotection by modulating the production of nerve growth factor, neurotrophin, glial cell derived neurotrophic factor, nitric oxide synthase, and choline acetyl transferase. Not least, vitamin D insufficiency was associated with other neurodegenerative diseases, such as PD and AD (Evatt et al., 2008). Lower vitamin D concentrations are associated with poorer cognitive function in otherwise healthy individuals, and with higher risk of developing AD (Balion et al., 2012). Interestingly, hippocampal neurons express vitamin D receptors, thus suggesting a direct effect on memory (Eyles et al., 2005). Vitamin D deficiency is common in PD, and may be responsible for metabolic dysfunction and/or cell death. From a clinical standpoint, there is some evidence that vitamin D is associated with motor symptoms' severity, and non-motor features of PD, including executive function (e.g., verbal fluency) and verbal memory (Fullard and Duda, 2020). Overall, our associations with motor and cognitive disability in MS confirms the interplay between vitamin D and neurodegenerative aspects of MS, as already well established in other diseases of the central nervous system. However, all mechanisms listed remain speculative, and longitudinal studies are needed to better identify the basis of vitamin D pathology in MS.

This study has some limitations, including its cross-sectional design, not allowing any causal inference. In particular, low levels of vitamin D have been associated with multiple negative outcomes in MS and other neurological diseases, (Evatt et al., 2008; Ascherio et al., 2010) with possible reverse causation. However, we have defined parameters for future longitudinal studies; for instance, based on our point estimates, increasing vitamin D levels of 10 ng/mL, would correspond to a clinically meaningful improvement of 14 points on SDMT (40% improvement for an impaired score $\leq$35). We used the BICAMS battery, but larger number of neuropsychological tests will be warranted in the future to improve specificity. Moreover, in our study, we did not consider the effect of specific DMTs due to small sample size, nor did evaluate further descriptors of MS progression (e.g., primary and

secondary progressive MS) (Kuhlmann et al., 2023). Finally, we used CLIA assay for 25-OH-vitamin D, which measures the sum of 25-OH-vitamin D2 and D3, not allowing to discriminate between different metabolites of vitamin D, unlike other more accurate techniques (e.g., chromatographic assays) (Snellman et al., 2010).

In conclusion, our study highlights that vitamin D is associated with both motor and cognitive disability in MS, thus suggesting its relationship with neurodegenerative aspects of the disease. Future longitudinal studies are warranted.

5. Disclosures

Marcello Moccia has received research grants from ECTRIMS-MAGNIMS, UK MS Society, and Merck; honoraria from Biogen, BMS Celgene, Janssen, Merck, Roche, and Sanofi-Genzyme.Maria Petracca has received travel/meeting expenses from Novartis, Janssen, Roche and Merck; speaking honoraria from HEALTH&LIFE S.r.l., AIM Education S.r.l. and FARECOMUNICAZIONE E20; honoraria from Biogen; and research grants from Italian MS Foundation and Baroni Foundation. Antonio Carotenuto has received research grants from ECTRIMS-MAGNIMS and Almirall; and has received honoraria from Merk, Novartis, Biogen, Mylan, Roche and Almirall. Vincenzo Brescia Morra has received research grants from Italian MS Federation and Roche; and honoraria from Almirall, Biogen, BMS Celgene, Janssen, Merck, Novartis, Roche, Sanofi-Genzyme, and Viatris.

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CRediT authorship contribution statement

Antonio Luca Spiezia: Conceptualization, Formal analysis, Investigation, Project administration, Software, Supervision, Writing – original draft, Writing – review & editing. **Fabrizia Falco:** Conceptualization, Formal analysis, Investigation, Project administration, Software, Supervision, Writing – original draft, Writing – review & editing. **Andrea Manganelli:** Conceptualization, Formal analysis, Investigation, Project administration, Software, Supervision, Writing – original draft, Writing – review & editing. **Antonio Carotenuto:** Conceptualization, Formal analysis, Investigation, Project administration, Software, Supervision, Writing – original draft, Writing – review & editing. **Maria Petracca:** Conceptualization, Formal analysis, Investigation, Project administration, Software, Supervision, Writing – original draft, Writing – review & editing. **Federica Novarella:** Conceptualization, Formal analysis, Investigation, Project administration, Software, Supervision, Writing – original draft, Writing – review & editing. **Carmine Iacovazzo:** Conceptualization, Formal analysis, Investigation, Project administration, Software, Supervision, Writing – original draft, Writing – review & editing. **Giuseppe Servillo:** Conceptualization, Formal analysis, Investigation, Project administration, Software, Supervision, Writing – original draft, Writing – review & editing. **Roberta Lanzillo:** Conceptualization, Formal analysis, Investigation, Project administration, Software, Supervision, Writing – original draft, Writing – review & editing. **Vincenzo Brescia Morra:** Conceptualization, Formal analysis, Investigation, Project administration, Software, Supervision, Writing – original draft, Writing – review & editing. **Marcello Moccia:** Conceptualization, Formal analysis, Investigation, Project administration, Software, Supervision, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

Marcello Moccia has received research grants from ECTRIMS-MAGNIMS, UK MS Society, and Merck; honoraria from Biogen, BMS Celgene, Janssen, Merck, Roche, and Sanofi-Genzyme.Maria Petracca has received travel/meeting expenses from Novartis, Janssen, Roche and Merck; speaking honoraria from HEALTH&LIFE S.r.l., AIM Education S.r.l. and FARECOMUNICAZIONE E20; honoraria from Biogen; and research grants from Italian MS Foundation and Baroni Foundation. Antonio Carotenuto has received research grants from ECTRIMS-MAGNIMS and Almirall; and has received honoraria from Merk, Novartis, Biogen, Mylan, Roche and Almirall. Vincenzo Brescia Morra has received research grants from Italian MS Federation and Roche; and honoraria from Almirall, Biogen, BMS Celgene, Janssen, Merck, Novartis, Roche, Sanofi-Genzyme, and Viatris.

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