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Review

Risk Factors for Cognitive Impairment in Multiple Sclerosis Patients

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Abstract: Cognitive impairment is one of the most significant burdens among the many neurological complaints in multiple sclerosis patients. Cognitive deficits negatively impact these patients' quality of life, leading to partial or total loss of several mental functions, such as learning, memory, perception, or problem-solving. While the precise mechanisms involved in the onset and evolution of cognitive decline remain unknown, several risk factors have been associated with intellectual disability. With increasing data on this topic in recent years, the main aim of this review is to summarize the most relevant risk factors correlated with cognitive impairment in multiple sclerosis patients. Firstly, the authors demonstrate the importance of mental disability based on epidemiological data from multiple sclerosis patient cohorts. Subsequently, the intensely debated major risk factors for cognitive decline are discussed, with brief insights into the pathophysiology and possible underlying mechanisms. Finally, the authors describe the impact of medication on cognitive impairment in multiple sclerosis patients, highlighting the main research directions for future studies.

Keywords: multiple sclerosis; cognitive impairment; neurodegeneration; smoking; vitamin D; depression

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1. Introduction

Multiple sclerosis (MS) remains the most common demyelinating disorder of the central nervous system (CNS) in young adults worldwide [1]. According to recent epidemiological data, the incidence and prevalence of this disease have continued to rise steadily during the last decade [2,3]. Moreover, MS poses a significant burden on the young adult population, being a major factor that negatively impacts the patient's quality of life [4]. Also, from the socioeconomic point of view, MS generates high direct and indirect costs that pressure healthcare systems in most European countries [5].

The MS-related burden may be caused by the very diverse spectrum of neurological complaints that result from the many possible locations of demyelinating plaques in the CNS: periventricular, cortical-juxtacortical, infratentorial, and even in the spinal cord [6]. On the one hand, vision and balance problems, motor and sensory deficits, and bowel and bladder dysfunction are frequently encountered, starting from the early stages of the disease [7]. On the other hand, non-specific symptoms such as dizziness, fatigue, depression, and cognitive impairment are also found in MS patients in different stages of the disorder [8]. In particular, cognitive impairment has become a topic of interest among researchers, according to the many published studies in recent years.

Typically involving several mental functions, such as complex attention, memory, information processing speed, or executive functions, cognitive impairment is a constant complaint in CNS disorders, as well as in autoimmune diseases such as MS [9,10]. The exact prevalence of cognitive decline differs upon study and depends on the number of patients included, their age, and the disease duration. Even so, cognitive problems remain a significant complaint in MS patients, with the majority of clinical trials showing a prevalence

between 30% and up to 70% [11,12]. While cognitive decline was initially considered a marker for progressive MS, increasing evidence suggests that mental disability might be a relevant symptom even in the early stages of MS [13]. Several studies were conducted to determine the prevalence of cognitive impairment in clinically isolated syndrome (CIS), resulting in very heterogeneous data. While one study found a higher rate (57%), mainly because it focused on a group of MS patients with more widespread brain lesions who were tested using a more extensive test battery [14], another trial had much lower rates (12.3%) as a result of the use of a simpler cognitive assessment tool [15]. Other studies found frequencies of cognitive impairment between 18 and 34%, with the highest figures in trials including patients with longer disease duration [16]. Based on these data and the rising interest in improving the quality of life of MS patients, neurologists should diagnose as soon as possible cognitive impairment and promote adequate treatment [17].

Considering the lack of curative treatment for cognitive decline, one promising method to delay its onset and moderate its evolution is based on the strict control of the risk factors. According to research published during the last decade, several modifiable factors such as diet, smoking, lack of physical exercise, and vitamin D deficiency increase the risk of MS patients developing cognitive impairment besides the other classical symptoms of MS. In the context of epidemiological data and the expanding literature on this topic, the main aim of this review is to summarize the most relevant risk factors correlated with cognitive impairment in MS patients. The possible underlying pathophysiological mechanisms and the impact of MS-related medication on cognitive decline are subsequently discussed. Finally, the authors offer promising new research directions in both the diagnosis and the therapeutic management of cognitive decline in MS patients.

2. Epidemiological Data Explaining the Burden of Cognitive Impairment in MS Patients

According to recent data, cognitive impairment seems to be a frequent complaint in MS patients, affecting up to 65% of patients during the disease course [18]. The classical opinion was that cognitive decline is more related to the later stages of MS when the neurodegenerative process replaces the periodic neuroinflammatory phenomenon [19]. The progressive forms of MS are linked to a more pronounced and frequent cognitive deficit compared to relapsing-remitting multiple sclerosis (RRMS) [20]. However, mental disability was also observed in the early stages of the disorder, even in clinically and radiologically isolated syndromes (RISs) [21]. The definition of early-stage MS remains intensely discussed within the literature, as definitions vary among studies. While the early phase of MS represents the short period after a clinically isolated syndrome (CIS) [22], other authors consider early MS the duration up to five years after the diagnosis or when the Expanded Disability Status Scale (EDSS) score remains below 3–3.5 [23].

In MS patients, cognitive impairment is associated with a worse prognosis. One study showed that cognitive decline in CIS and RIS patients increases their risk of conversion to clinically definite MS [24]. Another interesting bidirectional relationship is observed between mental impairment and the patient's general disability measured via the EDSS score. Early cognitive impairment was associated with more significant disability in the long term in MS patients [25]. On the other hand, a high EDSS score might also be a risk factor for developing and worsening cognitive impairment, as described further on. Finally, cognitive decline is an additional mortality risk factor, especially in MS patients with multiple comorbidities [26].

Regarding the exact cognitive domain that is affected, several phenotypes were observed. The most frequently detected deficits were related to learning, episodic memory, visuospatial abilities, processing speed, and executive functions [27]. When studied in larger cohorts, MS patients suffering from cognitive impairment could be categorized into the following groups: mild monodomain impairment (most frequently language impairment), mild multidomain involvement, severe monodomain impairment (most often executive dysfunction or attention deficit), and severe multidomain involvement [28].

Lastly, there is an individual variable cognitive impairment profile, with all cognitive domains possibly to be affected in some MS patients.

Both older and more recent data highlight the significant burden posed by cognitive impairment in many aspects related to the course of MS. Many clinical trials were conducted in the direction of earlier and more precise diagnosis, with several specific tests such as the Symbol Digit Modalities Test (SDMT) currently available [29]. Despite neurologists' intense concern for this issue, there is no particular treatment for cognitive impairment in MS patients. In this context, finding modifiable risk factors linked to cognitive decline could be a good strategy for delaying the onset and evolution of cognitive impairment and its associated negative impact.

3. Major Risk Factors for Cognitive Impairment in MS Patients

Several risk factors have been considered during the last decade regarding the cognitive impairment affecting MS patients. A complete overview of all factors highlighted in the literature would be too broad to be included in a single article. Thus, the authors offered a practically oriented review of the most frequent and relevant risk factors in MS patients with cognitive decline. To maintain a didactic approach, risk factors can be divided into two large categories: non-modifiable and modifiable factors. The modifiable risk factors can, in turn, be divided into clinical and lifestyle factors. Age and cognitive reserve are the most constant among non-modifiable factors for cognitive deficit in MS patients, with gender or family history still inconclusive, as further demonstrated. On the other hand, the strong correlation between smoking, diet, physical exercise, vitamin D deficiency (considered lifestyle factors), EDSS score, psychiatric comorbidities (considered clinical factors), and MS-related cognitive decline opens an exciting list of potential areas where non-pharmacological and pharmacological therapies could provide benefits. Table 1 summarizes the major risk factors associated with cognitive impairment in MS, highlighting possible underlying pathophysiological and relevant references published in the last ten years.

Table 1. Major risk factors associated with cognitive impairment in multiple sclerosis patients.

		Pathophysiological Mechanisms/Related Factors	Relevant References
Non-modifiable risk factors	Age	Physiological aging mechanisms Neurodegeneration	[30–33]
	Cognitive reserve	Formal education Informal cognitive enrichment Personality traits	[34–36]
Modifiable risk factors (clinical risk factors)	Anxiety Depression	Systemic and neuroinflammation Adverse treatment effects	[37,38]
	EDSS score	Increased lesion load	[39,40]
Modifiable risk factors (lifestyle risk factors)	Diet	Gut–brain axis Renin–angiotensin–aldosterone system	[41–44]
	Lack of physical exercise	To be determined	[45,46]
	Smoking	Increased plaque load Reduced gray matter fraction	[47–50]
	Vitamin D deficiency	Gene transcription modulation T cells, B cells, and macrophages inhibition Regulation of Ca^{2+} intake in neurons Astrocyte activation, Oligodendrocyte maturation	[51–55]

3.1. Non-Modifiable Risk Factors

The effect of age on cognitive impairment in MS patients is an intensely studied topic, with many clinical trials having found a direct correlation between aging and cognitive decline [30–32]. According to one study, the impact of aging in MS patients was observed as decreased attentional, executive, and information processing speed perfor-

mance [30]. At the same time, other research found links between disease duration and cognitive deficit [31]. Not all cognitive domains are affected in a similar way; one recent Iranian study showed no correlation between non-modifiable variables such as age or gender and decreased performance, in particular, perception, visual learning, and processing speed [33].

While aging is constantly correlated with reduced cognitive function, the duration of the disease was considered a risk factor in only some studies. This raises questions regarding the exact mechanism that could explain the onset of cognitive impairment in MS patients. It seems that neuroinflammation is not the primary process responsible for MS-related mental disability. However, neurodegeneration is a well-known condition that associates cognitive decline through various incompletely explained mechanisms, as research on Alzheimer's disease and other dementias demonstrated [56,57]. This also applies to MS, as cognitive impairment is more frequent and severe in progressive forms of MS than in RRMS [58].

According to the cognitive reserve hypothesis, the brain has reserve accounts for susceptible age-related or pathologically related changes that are individually different [59]. Cognitive reserve depends on many measurable variables, such as education, occupational attainment, cognitively stimulating behaviors and environment, and personality traits [60]. Much research was conducted on the impact of cognitive reserve in dementia patients, with a recent meta-analysis showing the protective feature of increased cognitive reserve for mild and moderate Alzheimer's disease [61]. Similarly, fresh data from MS patients show that higher levels of cognitive reserve correlate with better cognitive performance despite long disease duration [34]. However, the moderate protective effect of higher cognitive reserve was found only concerning specific cognitive domains, such as information processing, verbal memory, and visuospatial learning and memory [35]. Both formal education and informal cognitive enrichment are closely related to increased cognitive reserve, helping MS patients to better cope with the mental impairment resulting from MS cerebral lesions [36].

3.2. Clinical Risk Factors

Anxiety and depression are the two most frequent psychiatric comorbidities found in MS, with a negative impact on the patient's general condition. Much research was conducted in this direction, frequently studying anxiety and depression correlated with other parameters such as treatment adherence or EDSS score. According to most studies, symptoms of anxiety and depression were associated with reduced cognitive functioning [37]. One recent longitudinal study confirmed the association between depression and lower cognitive status [38]. The results are similar to the ones found in cohorts of patients suffering from other systemic inflammatory disorders, such as inflammatory bowel disease and rheumatoid arthritis. This suggests that the underlying pathophysiological mechanisms explaining this link are more complex than the direct impact of the structural lesions. Systemic and localized inflammation, adverse treatment effects, and other comorbidities could play important roles in the MS–psychiatric symptoms continuum [37].

Another relevant observation results from the correlation between MS clinical burden and cognitive impairment. The EDSS score is used to assess the general degree of disability in MS patients; however, it does not include any evaluation of cognition. Many clinical trials studied the association between cognitive deficit and the degree of disability in MS. It can be concluded that there is a direct correlation between increased disability, namely an increased EDSS score, and a more important cognitive impairment [39,40]. However, the results should be received critically, as the main limitation of this research derives from the imperfect test batteries used to assess cognition. There is a mandatory need to improve currently existing cognitive testing by making it more reliable and comprehensive to the patient's clinical condition and individual impairments.

3.3. Lifestyle Risk Factors

Despite the general interest in personalized nutrition in neurological disorders, evidence of dietary intervention in MS remains scarce in humans. While healthy diet and lifestyle were correlated before with lesser disability and symptom burden in MS patients [41], clear directions are not suggested. We mention an interesting result of a study conducted on a frequently used animal model for MS, which showed that the exogenous administration of sodium chloride improved the clinical status and decreased oxidative stress and inflammation, most likely via the inhibition of the renin–angiotensin–aldosterone system [42]. In MS patients, intermittent fasting and the Mediterranean diet only lowered neuroinflammatory biomarkers, such as T and B cells, without any reported impact on cognition [43]. This could be explained by the complex mechanisms encountered in MS-related cognitive impairment. The chronic neuroinflammatory state is only one of the many possible mechanisms explaining the cognitive impairment in MS patients, with the multifaceted neurodegenerative process still to be understood entirely. There is currently no dietary intervention capable of stopping or reversing neurodegeneration. Oxidative stress, impaired clearance with subsequent accumulation of neurotoxic molecules in the CNS, and disturbed microglial functioning are some directions worth studying from the nutritional perspective. Before searching for a specific diet to improve cognitive impairment in MS patients, researchers should focus on understanding the MS-relevant molecular pathways that nutrients could modulate. In this regard, the gut–brain axis was explored in greater detail, with indirect research suggesting that dietary intervention at that level might benefit the cognitive deficit of MS [44]. Depending on the type of diet, the macro and micronutrients included alter the gut microbiome, which has a relevant impact on the local and systemic inflammatory status and consequences at the CNS level. With limited evidence up to the present, other processes and extracerebral structures linked to MS pathogenesis that could be modulated by diet should be further studied.

Besides diet, lack of physical exercise, smoking, and vitamin D deficiency are other easily modifiable lifestyle risk factors correlated with cognitive decline in MS patients. One pilot study showed the beneficial impact of exercise interventions on cognition, particularly on improving memory [45]. Another study showed that moderate-to-vigorous physical activity positively impacts cognitive decline, particularly processing speed, but not memory [46]. This is in line with research conducted on mild cognitive impairment (MCI) and dementia patients, where aerobic exercises up to moderate intensity were found beneficial for reducing global cognitive decline and lessening behavioral problems [62]. However, the low evidence quality of currently existing clinical trials should be noted as the main limitation in making strong evidence recommendations. Therefore, there is a high need for more research regarding different physical therapy protocols in larger MS patient cohorts and more precise primary endpoints [63].

Tobacco, under the form of passive exposure, active smoking, or even oral (smokeless) administration, is associated with a faster MS progression and negatively impacts secondary outcomes [47]. Regarding the smoking–cognitive impairment association, even older studies assess this negative link [48]. MRI studies in MS smokers showed a correlation between smoking, MS, and an increased plaque load, together with reduced brain parenchyma and gray matter fractions [49]. Moreover, smoking cessation showed significant improvement in the evolution of MS, slowing the rate of motor disability deterioration, equivalent to the natural MS progression in non-smokers [50]. Whether discontinuing smoking has a positive impact on cognitive decline remains to be further studied.

Lastly, there is considerable interest in the role of micronutrients in MS, particularly vitamin D. Low serum vitamin D levels were considered for a long time a significant risk factor for the onset and progression of MS [51]; however, only recently was vitamin D deficiency associated with impaired cognition in MS patients [52,53]. Among the most affected cognitive domains, low vitamin D was demonstrated to be a marker of poor information processing speed [54]. On the other hand, vitamin D supplementation was associated with a lower relapse rate, a lower rate of new (active) lesions, and decreased

disability progression [55]. There are many proposed mechanisms explaining the role of vitamin D as a protective factor in MS. For example, vitamin D is thought to bind to specific DNA sequences, thus modulating gene transcription and subsequently inhibiting T cells, B cells, and macrophages. Vitamin D regulates Ca^{2+} intake in neurons and modulates astrocyte activation and oligodendrocyte maturation [54]. While the exact pathway is to be determined, the ease of exogenous supplementation with vitamin D makes this method desirable for the adjunctive treatment of cognitive disorders in MS.

4. The Impact of Medication and Cognitive Rehabilitation on Cognitive Impairment in MS Patients

MS treatment includes at least three main directions: treatment of the relapse represented by short-acting immunosuppressive therapy (intravenous or oral corticosteroids), long-term disease-modifying therapies (DMTs), and symptomatic and rehabilitative treatment.

Regarding corticoid treatment, the current therapeutic guidelines support the use of intravenous pulses of methylprednisolone for acute relapses [64]. Despite the high amounts (up to 5 g per cure), the administration is limited to a short three-to-five-day period. Still, several short-term adverse effects were observed, such as psychosis with suicidal ideation [65], hepatotoxicity [66], or hypokalemia with cardiac complications [67], but no cognitive impairment. In the long term, repetitive intravenous pulses of methylprednisolone may be associated with an increased risk of osteoporosis [68], but again, there is no proof of a negative impact on cognition. Oral high-dose steroids may be considered instead of intravenous treatment. However, this approach is not recommended anymore because of the risks associated with the overconsumption of steroids for fractional or vague symptoms [69].

The DMTs' adverse effects, including their impact on cognition, are of great interest, considering the new medication that emerged on the market in recent years. However, more thorough literature research on this topic quickly reveals many shortcomings. Cognitive decline was not directly studied in earlier clinical trials of DMTs; all data were indirectly extracted as secondary or even tertiary outcomes. In more recent trials, follow-up was only 1–2 years short, and thus insufficient to study long-term effects. Limitations regarding the cognitive tests and the small cohorts are also frequently reported [70]. Despite the previously mentioned impediments, a very recent review showed that most DMTs correlate with improved cognitive function [70]. The only two DMTs that showed inconsistent results were glatiramer acetate and fingolimod [71], but extensive real-world studies should be conducted. Further studies are needed to clearly identify whether DMTs' positive effect on cognition is a direct implication related to their mechanisms of action or just a by-standing finding correlated to the no evidence of disease activity (NEDA) goal.

Symptomatic treatment in MS patients is limited to pharmacological and non-pharmacological approaches toward better control of spasticity, incontinence, fatigue, psychiatric symptoms, and pain. We mention the increasing interest related to the effects of fampridine on cognitive function, with the results of the IGNITE study showing a beneficial impact on information processing speed in MS patients treated up to 12 months [72]. This type of research is still in the beginning, with more extensive large cohort studies urgently needed.

Finally, an encouraging non-pharmacological approach targeting MS-related cognitive decline is cognitive rehabilitation. This therapy aims to reduce cognitive impairment and improve awareness of cognitive difficulties encountered in daily living, thus having a positive impact on the quality of life of MS patients [73]. The underlying mechanisms explaining these beneficial effects correlate with the enhancement of functional and structural neuroplasticity, dependent on the trained cognitive tasks [74]. In addition, cognitive rehabilitation may induce beneficial neurobiological changes in the hypothalamic–pituitary–adrenal axis, improving the regulation of serotonin precursors and neurogenesis via direct mechanisms and also as an indirect effect that occurs with the decrease in the stress and depression level [75]. Once a personalized neuropsychological assessment is completed,

the therapy can be tailored according to the individual needs of each MS patient. A broad range of cognitive rehabilitation methods are currently available and can be classified into two categories: compensatory approaches and restorative interventions. Both therapists and patients have preferred practical compensatory approaches, as they show usefulness in the activities of daily living [75]. The use of reminder devices and workplace adjustments was demonstrated to be particularly effective in MS patients with mild to moderate memory and attention problems. Still, ongoing support is necessary until new routines become habits in these persons. Newer approaches, such as the modified Story Memory Technique, self-generation, and visual imagery, target memory skills directly and, despite requiring more time to be learned, are more effective for specific goals [76]. Restorative approaches may also be effective when aimed at improving specific cognitive domains, such as attention, information processing speed, and memory in MS patients [77]. These interventions are based on computerized cognitive training programs, and the possibility of accessing them online makes them accessible for MS patients living in rural or remote areas [78]. Having a relatively low cost of implementation and associating low-risk adverse effects, cognitive rehabilitation remains the central pillar in treating cognitive impairment, considering the lack of efficient pharmacological approaches.

5. Conclusions and Future Research Directions

The interest in studying cognitive impairment in MS patients has grown steadily in the last decade, with an increasing number of studies addressing multiple aspects of cognitive decline in neuroinflammatory disorders. According to currently available data, epidemiological studies confirm the huge burden cognitive impairment poses in young adults suffering from MS. Although the exact pathophysiological mechanisms are incompletely known, non-modifiable risk factors such as age and cognitive reserve, clinical risk factors such as anxiety, depression, and EDSS score, and lifestyle factors such as smoking, diet, and vitamin D deficiency were confirmed. Age, psychiatric symptoms, EDSS score, and smoking have a particularly negative impact on cognition in MS patients. On the other hand, intervention in diet, physical exercises, and vitamin D levels were shown to be beneficial, at least for some particular cognitive domains.

Besides the abovementioned risk factors, the impact of the pharmacological approach on MS patients and its correlation to cognitive decline remains a critical aspect to be studied. While the effect of DMTs on cognition has been increasingly addressed in recent years, the impact of short-term high doses of corticosteroids and the potential benefits of symptomatic treatment need more attention. Currently, only cognitive rehabilitation seems to be effective in coping with MS-related cognitive impairment.

With no curative treatment for MS and related cognitive impairment, interventions minimizing risk factors could be a successful approach. Particularly, the strict control of lifestyle risk factors, such as dietary changes, physical activity, smoking cessation, and vitamin D supplementation, could be interesting therapeutic strategies. However, clinical trials on this topic still have significant limitations, such as a reduced number of patients, heterogeneous protocols, and unclear endpoints, making it difficult to systematize the final results in the form of guidelines. Future research should include randomized clinical trials with clear interventional protocols while also focusing on a better understanding of the underlying pathophysiological mechanisms. In conclusion, it is mandatory to continue conducting studies on larger MS patient cohorts and directly address the cognitive deficit as a primary outcome concerning the modulation of modifiable risk factors.

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Abbreviations

CIS	clinically isolated syndrome
CNS	central nervous system
DMT	disease-modifying therapy
MS	multiple sclerosis
NEDA	no evidence of disease activity
RIS	radiologically isolated syndromes
RRMS	relapsing-remitting multiple sclerosis
SDMT	Symbol Digit Modalities Test

References

1. Wang, M.; Liu, C.; Zou, M.; Niu, Z.; Zhu, J.; Jin, T. Recent Progress in Epidemiology, Clinical Features, and Therapy of Multiple Sclerosis in China. *Ther. Adv. Neurol. Disord.* **2023**, *16*, 17562864231193816. [CrossRef]
2. Qian, Z.; Li, Y.; Guan, Z.; Guo, P.; Zheng, K.; Du, Y.; Yin, S.; Chen, B.; Wang, H.; Jiang, J.; et al. Global, Regional, and National Burden of Multiple Sclerosis from 1990 to 2019: Findings of Global Burden of Disease Study 2019. *Front. Public Health* **2023**, *11*, 1073278. [CrossRef] [PubMed]
3. Lane, J.; Ng, H.S.; Poyser, C.; Lucas, R.M.; Tremlett, H. Multiple Sclerosis Incidence: A Systematic Review of Change over Time by Geographical Region. *Mult. Scler. Relat. Disord.* **2022**, *63*, 103932. [CrossRef] [PubMed]
4. Faraclas, E. Interventions to Improve Quality of Life in Multiple Sclerosis: New Opportunities and Key Talking Points. *Degener. Neurol. Neuromuscul. Dis.* **2023**, *13*, 55–68. [CrossRef] [PubMed]
5. Battaglia, M.A.; Bezzini, D.; Cecchini, I.; Cordioli, C.; Fiorentino, F.; Manacorda, T.; Nica, M.; Ponzio, M.; Ritrovato, D.; Vassallo, C.; et al. Patients with Multiple Sclerosis: A Burden and Cost of Illness Study. *J. Neurol.* **2022**, *269*, 5127–5135. [CrossRef] [PubMed]
6. Wattjes, M.P.; Ciccarelli, O.; Reich, D.S.; Banwell, B.; de Stefano, N.; Enzinger, C.; Fazekas, F.; Filippi, M.; Frederiksen, J.; Gasperini, C.; et al. 2021 MAGNIMS-CMSC-NAIMS Consensus Recommendations on the Use of MRI in Patients with Multiple Sclerosis. *Lancet Neurol.* **2021**, *20*, 653–670. [CrossRef]
7. Ford, H. Clinical presentation and diagnosis of multiple sclerosis. *Clin. Med.* **2020**, *20*, 380–383. [CrossRef]
8. Heitmann, H.; Andlauer, T.F.M.; Korn, T.; Mühlau, M.; Henningsen, P.; Hemmer, B.; Ploner, M. Fatigue, Depression, and Pain in Multiple Sclerosis: How Neuroinflammation Translates into Dysfunctional Reward Processing and Anhedonic Symptoms. *Mult. Scler.* **2022**, *28*, 1020–1027. [CrossRef]
9. Maiese, K. Cognitive Impairment in Multiple Sclerosis. *Bioengineering* **2023**, *10*, 871. [CrossRef]
10. Piacentini, C.; Argento, O.; Nocentini, U. Cognitive impairment in multiple sclerosis: "classic" knowledge and recent acquisitions. Deficiência cognitiva na esclerose múltipla: Conhecimentos "clássicos" e aquisições recentes. *Arq. Neuropsiquiatr.* **2023**, *81*, 585–596.
11. Amato, M.P.; Prestipino, E.; Bellinvia, A.; Niccolai, C.; Razzolini, L.; Pastò, L.; Fratangelo, R.; Tudisco, L.; Fonderico, M.; Mattiolo, P.L.; et al. Cognitive impairment in multiple sclerosis: An exploratory analysis of environmental and lifestyle risk factors. *PLoS ONE* **2019**, *14*, e0222929. [CrossRef]
12. Ozakbas, S.; Turkoglu, R.; Tamam, Y.; Terzi, M.; Taskapilioglu, O.; Yucesan, C.; Baser, H.L.; Gencer, M.; Akil, E.; Sen, S.; et al. Prevalence of and risk factors for cognitive impairment in patients with relapsing-remitting multiple sclerosis: Multi-center, controlled trial. *Mult. Scler. Relat. Disord.* **2018**, *22*, 70–76. [CrossRef]
13. Oset, M.; Stasiolek, M.; Matysiak, M. Cognitive Dysfunction in the Early Stages of Multiple Sclerosis-How Much and How Important? *Curr. Neurol. Neurosci. Rep.* **2020**, *20*, 22. [CrossRef]
14. Feuillet, L.; Reuter, F.; Audoin, B.; Malikova, I.; Barrau, K.; Cherif, A.A.; Pelletier, J. Early cognitive impairment in patients with clinically isolated syndrome suggestive of multiple sclerosis. *Mult. Scler.* **2007**, *13*, 124–127. [CrossRef]
15. Uher, T.; Blahova-Dusankova, J.; Horakova, D.; Bergsland, N.; Tyblova, M.; Benedict, R.H.; Kalincik, T.; Ramasamy, D.P.; Seidl, Z.; Hagermeier, J.; et al. Longitudinal MRI and neuropsychological assessment of patients with clinically isolated syndrome. *J. Neurol.* **2014**, *261*, 1735–1744. [CrossRef]
16. Brochet, B.; Ruet, A. Cognitive Impairment in Multiple Sclerosis with Regards to Disease Duration and Clinical Phenotypes. *Front. Neurol.* **2019**, *10*, 261. [CrossRef]
17. Giorelli, M. Current and Future Perspectives of an Early Diagnosis of Cognitive Impairment. *Front. Neurol.* **2023**, *14*, 1171681. [CrossRef]
18. Portaccio, E.; Amato, M.P. Cognitive Impairment in Multiple Sclerosis: An Update on Assessment and Management. *NeuroSci* **2022**, *3*, 667–676. [CrossRef]
19. DeLuca, J.; Chiaravalloti, N.D.; Sandroff, B.M. Treatment and Management of Cognitive Dysfunction in Patients with Multiple Sclerosis. *Nat. Rev. Neurol.* **2020**, *16*, 319–332. [CrossRef]
20. Benedict, R.H.B.; Amato, M.P.; DeLuca, J.; Geurts, J.J.G. Cognitive Impairment in Multiple Sclerosis: Clinical Management, MRI, and Therapeutic Avenues. *Lancet Neurol.* **2020**, *19*, 860–871. [CrossRef]

21. Anhoque, C.F.; Biccas Neto, L.; Domingues, S.C.A.; Teixeira, A.L.; Domingues, R.B. Cognitive impairment in patients with clinically isolated syndrome. *Dement. Neuropsychol.* **2012**, *6*, 266–269. [CrossRef]
22. Kolčava, J.; Kočica, J.; Hulová, M.; Dušek, L.; Horáková, M.; Keřkovský, M.; Stulík, J.; Dostál, M.; Kuhn, M.; Vlčková, E.; et al. Conversion of Clinically Isolated Syndrome to Multiple Sclerosis: A Prospective Study. *Mult. Scler. Relat. Disord.* **2020**, *44*, 102262. [CrossRef]
23. Amato, M.P.; Portaccio, E.; Goretti, B.; Zipoli, V.; Iudice, A.; Della Pina, D.; Malentacchi, G.; Sabatini, S.; Annunziata, P.; Falcini, M.; et al. Relevance of Cognitive Deterioration in Early Relapsing-Remitting MS: A 3-Year Follow-Up Study. *Mult. Scler.* **2010**, *16*, 1474–1482. [CrossRef]
24. Domingo-Santos, Á.; Labiano-Fontcuberta, A.; Aladro-Benito, Y.; Martínez-Ginés, M.L.; Ayuso-Peralta, L.; Puertas-Martín, V.; Cerezo-García, M.; Higueras-Hernández, Y.; Mato-Abad, V.; Álvarez-Linera, J.; et al. Predicting Conversion to Multiple Sclerosis by Assessing Cognitive Impairment in Radiologically Isolated Syndrome. *Mult. Scler. Relat. Disord.* **2021**, *49*, 102749. [CrossRef]
25. Kavaliunas, A.; Tinghög, P.; Friberg, E.; Olsson, T.; Alexanderson, K.; Hillert, J.; Karrenbauer, V.D. Cognitive Function Predicts Work Disability Among Multiple Sclerosis Patients. *Mult. Scler. J. Exp. Transl. Clin.* **2019**, *5*, 2055217318822134. [CrossRef]
26. Cavaco, S.; Ferreira, I.; Moreira, I.; Santos, E.; Samões, R.; Sousa, A.P.; Pinheiro, J.; Teixeira-Pinto, A.; da Silva, A.M. Cognitive Dysfunction and Mortality in Multiple Sclerosis: Long-Term Retrospective Review. *Mult. Scler.* **2022**, *28*, 1382–1391. [CrossRef]
27. Macías Islas, M.Á.; Ciampi, E. Assessment and Impact of Cognitive Impairment in Multiple Sclerosis: An Overview. *Biomedicines* **2019**, *7*, 22. [CrossRef]
28. De Meo, E.; Portaccio, E.; Giorgio, A.; Ruano, L.; Goretti, B.; Niccolai, C.; Patti, F.; Chisari, C.G.; Gallo, P.; Grossi, P.; et al. Identifying the Distinct Cognitive Phenotypes in Multiple Sclerosis. *JAMA Neurol.* **2021**, *78*, 414–425. [CrossRef]
29. Strober, L.; DeLuca, J.; Benedict, R.H.; Jacobs, A.; Cohen, J.A.; Chiaravalloti, N.; Hudson, L.D.; Rudick, R.A.; LaRocca, N.G. Multiple Sclerosis Outcome Assessments Consortium (MSOAC). Symbol Digit Modalities Test: A valid clinical trial endpoint for measuring cognition in multiple sclerosis. *Mult. Scler.* **2019**, *25*, 1781–1790. [CrossRef]
30. Tremblay, A.; Charest, K.; Brando, E.; Roger, E.; Duquette, P.; Rouleau, I. The Effects of Aging and Disease Duration on Cognition in Multiple Sclerosis. *Brain Cogn.* **2020**, *146*, 105650. [CrossRef]
31. Javadi, A.H.S.; Shafikhani, A.A.; Beizapour, N. Evaluation of the Determinants of Cognitive Dysfunction in Patients with Multiple Sclerosis. *Middle East. Curr. Psychiatry* **2022**, *29*, 97. [CrossRef]
32. Baird, J.F.; Cederberg, K.L.J.; Sikes, E.M.; Jeng, B.; Sasaki, J.E.; Sandroff, B.M.; Motl, R.W. Changes in Cognitive Performance with Age in Adults with Multiple Sclerosis. *Cogn. Behav. Neurol.* **2019**, *32*, 201–207. [CrossRef]
33. Hassanshahi, E.; Asadollahi, Z.; Azin, H.; Hassanshahi, J.; Hassanshahi, A.; Azin, M. Cognitive Function in Multiple Sclerosis Patients Based on Age, Gender, and Education Level. *Acta Med. Iran.* **2020**, *58*, 500–507. [CrossRef]
34. Maffezzini, S.; Pucci, V.; Riccardi, A.; Montemurro, S.; Puthenparampil, M.; Perini, P.; Rinaldi, F.; Gallo, P.; Arcara, G.; Mondini, S. Clinical Profiles in Multiple Sclerosis: Cognitive Reserve and Motor Impairment along Disease Duration. *Behav. Sci.* **2023**, *13*, 708. [CrossRef]
35. Alexandra, T.; Kim, C.; Estefania, B.; Elaine, R.; Pierre, D.; Isabelle, R. Cognitive Reserve as a Moderating Factor between EDSS and Cognition in Multiple Sclerosis. *Mult. Scler. Relat. Disord.* **2023**, *70*, 104482.
36. Grant, J.G.; Rapport, L.J.; Darling, R.; Waldron-Perrine, B.; Lumley, M.A.; Whitfield, K.E.; Bernitsas, E. Cognitive Enrichment and Education Quality Moderate Cognitive Dysfunction in Black and White Adults with Multiple Sclerosis. *Mult. Scler. Relat. Disord.* **2023**, *78*, 104916. [CrossRef]
37. Whitehouse, C.E.; Fisk, J.D.; Bernstein, C.N.; Berrigan, L.I.; Bolton, J.M.; Graff, L.A.; Hitchon, C.A.; Marriott, J.J.; Peschken, C.A.; Sareen, J.; et al. Comorbid Anxiety, Depression, and Cognition in MS and Other Immune-Mediated Disorders. *Neurology* **2019**, *92*, e406–e417. [CrossRef]
38. van Ballegooijen, H.; van der Hiele, K.; Enzinger, C.; de Voer, G.; Visser, L.H.; CONFIDENCE Study Group. The Longitudinal Relationship between Fatigue, Depression, Anxiety, Disability, and Adherence with Cognitive Status in Patients with Early Multiple Sclerosis Treated with Interferon Beta-1a. *eNeurologicalSci* **2022**, *28*, 100409. [CrossRef]
39. Elshebawy, H.; Fahmy, E.M.; Elfayoumy, N.M.; Abdelalim, A.M.; Ismail, R.S. Clinical Predictors to Cognitive Impairment in Multiple Sclerosis Patients. *Egypt J. Neurol. Psychiatry Neurosurg.* **2021**, *57*, 38. [CrossRef]
40. Al-Falaki, T.A.; Hamdan, F.B.; Sheaheed, N.M. Assessment of Cognitive Functions in Patients with Multiple Sclerosis. *Egypt J. Neurol. Psychiatry Neurosurg.* **2021**, *57*, 127. [CrossRef]
41. Fitzgerald, K.C.; Tyry, T.; Salter, A.; Cofield, S.S.; Cutter, G.; Fox, R.; Marrie, R.A. Diet Quality Is Associated with Disability and Symptom Severity in Multiple Sclerosis. *Neurology* **2018**, *90*, e1–e11. [CrossRef]
42. Martín-Hersog, F.A.; Muñoz-Jurado, A.; Escribano, B.M.; Luque, E.; Galván, A.; LaTorre, M.; Giraldo, A.I.; Caballero-Villarraso, J.; Agüera, E.; Santamaría, A.; et al. Sodium Chloride-Induced Changes in Oxidative Stress, Inflammation, and Dysbiosis in Experimental Multiple Sclerosis. *Nutr. Neurosci.* **2022**, *27*, 74–86. [CrossRef]
43. Fitzgerald, K.C.; Bhargava, P.; Smith, M.D.; Vizthum, D.; Henry-Barron, B.; Kornberg, M.D.; Cassard, S.D.; Kapogiannis, D.; Sullivan, P.; Baer, D.J.; et al. Intermittent Calorie Restriction Alters T Cell Subsets and Metabolic Markers in People with Multiple Sclerosis. *EBioMedicine* **2022**, *82*, 104124. [CrossRef]
44. Ghadiri, F.; Ebadi, Z.; Asadollahzadeh, E.; Naser Moghadasi, A. Gut Microbiome in Multiple Sclerosis-Related Cognitive Impairment. *Mult. Scler. Relat. Disord.* **2022**, *67*, 104165. [CrossRef] [PubMed]

45. Mayo, C.D.; Harrison, L.; Attwell-Pope, K.; Stuart-Hill, L.; Gawryluk, J.R. A Pilot Study of the Impact of an Exercise Intervention on Brain Structure, Cognition, and Psychosocial Symptoms in Individuals with Relapsing-Remitting Multiple Sclerosis. *Pilot. Feasibility Stud.* **2021**, *7*, 65. [CrossRef] [PubMed]
46. Motl, R.W.; Sandroff, B.M.; Benedict, R.H.B. Moderate-to-Vigorous Physical Activity Is Associated with Processing Speed, but Not Learning and Memory, in Cognitively Impaired Persons with Multiple Sclerosis. *Mult. Scler. Relat. Disord.* **2022**, *63*, 103833. [CrossRef] [PubMed]
47. Wu, J.; Olsson, T.; Hillert, J.; Alfredsson, L.; Hedström, A.K. Influence of Oral Tobacco versus Smoking on Multiple Sclerosis Disease Activity and Progression. *J. Neurol. Neurosurg. Psychiatry* **2023**, *94*, 589–596. [CrossRef] [PubMed]
48. Özcan, M.E.; İnce, B.; Bingöl, A.; Erturk, S.; Altinoz, M.A.; Karadeli, H.H.; Koçer, A. Association between Smoking and Cognitive Impairment in Multiple Sclerosis. *Neuropsychiatr. Dis. Treat.* **2014**, *10*, 1715–1719. [CrossRef] [PubMed]
49. Alshehri, E.; Cohen, J.A.; Ontaneda, D.; Nakamura, K.; Husak, S.; Love, T.E.; Fox, R.J.; Briggs, F.B.; Conway, D.S. The Impact of Cigarette Smoking on Cognitive Processing Speed and Brain Atrophy in Multiple Sclerosis. *Mult. Scler.* **2023**, *29*, 846–855. [CrossRef]
50. Rodgers, J.; Friede, T.; Vonberg, F.W.; Constantinescu, C.S.; Coles, A.; Chataway, J.; Duddy, M.; Emsley, H.; Ford, H.; Fisniku, L.; et al. The Impact of Smoking Cessation on Multiple Sclerosis Disease Progression. *Brain* **2022**, *145*, 1368–1378. [CrossRef]
51. Sangha, A.; Quon, M.; Pfeffer, G.; Orton, S.M. The Role of Vitamin D in Neuroprotection in Multiple Sclerosis: An Update. *Nutrients* **2023**, *15*, 2978. [CrossRef]
52. Alhussain, F.; Alomar, M.; Alenazi, A.; Aldraihem, M.; Alshiha, L.; Bashir, S. The Relationship between Vitamin D Levels and Cognitive Impairment in Patients with Multiple Sclerosis. *Eur. Rev. Med. Pharmacol. Sci.* **2021**, *25*, 2021–2030.
53. Spiezia, A.L.; Falco, F.; Manganelli, A.; Carotenuto, A.; Petracca, M.; Novarella, F.; Iacovazzo, C.; Servillo, G.; Lanzillo, R.; Morra, V.B.; et al. Low Serum 25 Hydroxy-Vitamin D Levels Are Associated with Cognitive Impairment in Multiple Sclerosis. *Mult. Scler. Relat. Disord.* **2023**, *79*, 105044. [CrossRef]
54. Virgilio, E.; Vecchio, D.; Crespi, I.; Barbero, P.; Caloni, B.; Naldi, P.; Cantello, R.; Dianzani, U.; Comi, C. Serum Vitamin D as a Marker of Impaired Information Processing Speed and Early Disability in Multiple Sclerosis Patients. *Brain Sci.* **2021**, *11*, 1521. [CrossRef] [PubMed]
55. Miclea, A.; Bagnoud, M.; Chan, A.; Hoepner, R. A Brief Review of the Effects of Vitamin D on Multiple Sclerosis. *Front. Immunol.* **2020**, *11*, 781. [CrossRef]
56. Rao, R.V.; Subramaniam, K.G.; Gregory, J.; Bredesen, A.L.; Coward, C.; Okada, S.; Kelly, L.; Bredesen, D.E. Rationale for a Multi-Factorial Approach for the Reversal of Cognitive Decline in Alzheimer's Disease and MCI: A Review. *Int. J. Mol. Sci.* **2023**, *24*, 1659. [CrossRef] [PubMed]
57. Murdaca, G.; Banchero, S.; Casciaro, M.; Tonacci, A.; Billeci, L.; Nencioni, A.; Pioggia, G.; Genovese, S.; Monacelli, F.; Gangemi, S. Potential Predictors for Cognitive Decline in Vascular Dementia: A Machine Learning Analysis. *Processes* **2022**, *10*, 2088. [CrossRef]
58. Brochet, B.; Clavelou, P.; Defer, G.; De Seze, J.; Louapre, C.; Magnin, E.; Ruet, A.; Thomas-Anterion, C.; Vermersch, P. Cognitive Impairment in Secondary Progressive Multiple Sclerosis: Effect of Disease Duration, Age, and Progressive Phenotype. *Brain Sci.* **2022**, *12*, 183. [CrossRef]
59. Zemach, M.; Vakil, E.; Lifshitz, H. Brain Reserve Theory: Are Adults with Intellectual Disability More Vulnerable to Age than Peers with Typical Development? *J. Appl. Res. Intellect. Disabil.* **2023**, *36*, 796–811. [CrossRef]
60. Stern, Y. Cognitive Reserve in Ageing and Alzheimer's Disease. *Lancet Neurol.* **2012**, *11*, 1006–1012. [CrossRef]
61. Nelson, M.E.; Jester, D.J.; Petkus, A.J.; Andel, R. Cognitive Reserve, Alzheimer's Neuropathology, and Risk of Dementia: A Systematic Review and Meta-Analysis. *Neuropsychol. Rev.* **2021**, *31*, 233–250. [CrossRef] [PubMed]
62. Law, C.K.; Lam, F.M.; Chung, R.C.; Pang, M.Y. Physical Exercise Attenuates Cognitive Decline and Reduces Behavioural Problems in People with Mild Cognitive Impairment and Dementia: A Systematic Review. *J. Physiother.* **2020**, *66*, 9–18. [CrossRef] [PubMed]
63. Proschinger, S.; Kuhwand, P.; Rademacher, A.; Walzik, D.; Warnke, C.; Zimmer, P.; Joisten, N. Fitness, Physical Activity, and Exercise in Multiple Sclerosis: A Systematic Review on Current Evidence for Interactions with Disease Activity and Progression. *J. Neurol.* **2022**, *269*, 2922–2940. [CrossRef] [PubMed]
64. Ramo-Tello, C.; Blanco, Y.; Brieva, L.; Casanova, B.; Martínez-Cáceres, E.; Ontaneda, D.; Ramió-Torrentá, L.; Rovira, À. Recommendations for the Diagnosis and Treatment of Multiple Sclerosis Relapses. *J. Pers. Med.* **2021**, *12*, 6. [CrossRef] [PubMed]
65. Carle, G.; Abgrall-Barbry, G. Conduites suicidaires et corticothérapie: À propos d'un cas [Corticotherapy and suicidal behavior: A case report]. *Encephale* **2016**, *42*, 272–276. [CrossRef]
66. Björnsson, E.S.; Vucic, V.; Stirnimann, G.; Robles-Díaz, M. Role of Corticosteroids in Drug-Induced Liver Injury. A Systematic Review. *Front. Pharmacol.* **2022**, *13*, 820724. [CrossRef]
67. Sodero, A.; Squitieri, M.; Mazzeo, S.; Pasca, M.; Matà, S.; Pieri, F.; Bessi, V.; Sorbi, S. Acute Symptomatic Sinus Bradycardia in High-Dose Methylprednisolone Therapy in a Woman with Inflammatory Myelitis: A Case Report and Review of the Literature. *Clin. Med. Insights Case Rep.* **2019**, *12*, 1179547619831026. [CrossRef]
68. Kobza, A.O.; Herman, D.; Papaioannou, A.; Lau, A.N.; Adachi, J.D. Understanding and Managing Corticosteroid-Induced Osteoporosis. *Open Access Rheumatol.* **2021**, *13*, 177–190. [CrossRef]
69. Smets, I.; Van Deun, L.; Bohyn, C.; van Pesch, V.; Vanopdenbosch, L.; Dive, D.; Bissay, V.; Dubois, B. Corticosteroids in the management of acute multiple sclerosis exacerbations. *Acta Neurol. Belg.* **2017**, *117*, 623–633. [CrossRef]

70. Kania, K.; Ambrosius, W.; Kozubski, W.; Kalinowska-Łyszczarz, A. The Impact of Disease Modifying Therapies on Cognitive Functions Typically Impaired in Multiple Sclerosis Patients: A Clinician's Review. *Front. Neurol.* **2023**, *14*, 1222574. [CrossRef]
71. Kasindi, A.; Fuchs, D.T.; Koronyo, Y.; Rentsendorj, A.; Black, K.L.; Koronyo-Hamaoui, M. Glatiramer Acetate Immunomodulation: Evidence of Neuroprotection and Cognitive Preservation. *Cells* **2022**, *11*, 1578. [CrossRef]
72. Bakirtzis, C.; Konstantinopoulou, E.; Langdon, D.W.; Grigoriadou, E.; Minti, F.; Nikolaidis, I.; Boziki, M.K.; Tatsi, T.; Ioannidis, P.; Karapanayiotides, T.; et al. Long-Term Effects of Prolonged-Release Fampridine on Cognitive Function, Fatigue, Mood and Quality of Life of MS Patients: The IGNITE Study. *J. Neurol. Sci.* **2018**, *395*, 106–112. [CrossRef]
73. Chen, M.H.; Chiaravalloti, N.D.; DeLuca, J. Neurological update: Cognitive rehabilitation in multiple sclerosis. *J. Neurol.* **2021**, *268*, 4908–4914. [CrossRef]
74. Kumar, J.; Patel, T.; Sugandh, F.; Dev, J.; Kumar, U.; Adeeb, M.; Kachhadia, M.P.; Puri, P.; Prachi, F.; Zaman, M.U.; et al. Innovative Approaches and Therapies to Enhance Neuroplasticity and Promote Recovery in Patients with Neurological Disorders: A Narrative Review. *Cureus* **2023**, *15*, e41914. [CrossRef]
75. Longley, W.A. Cognitive rehabilitation in multiple sclerosis. *Aust. J. Gen. Pract.* **2022**, *51*, 233–237. [CrossRef]
76. Chiaravalloti, N.D.; Moore, N.B.; DeLuca, J. The efficacy of the modified Story Memory Technique in progressive MS. *Mult. Scler.* **2020**, *26*, 354–362. [CrossRef]
77. Nauta, I.M.; Bertens, D.; Fasotti, L.; Fieldhouse, J.; Uitdehaag, B.M.; Kessels, R.P.; Speckens, A.E.; de Jong, B.A. Cognitive rehabilitation and mindfulness reduce cognitive complaints in multiple sclerosis (REMIND-MS): A randomized controlled trial. *Mult. Scler. Relat. Disord.* **2023**, *71*, 104529. [CrossRef]
78. Ghadiri, F.; Naser Moghadasi, A.; Sahraian, M.A. Telemedicine as a strategic intervention for cognitive rehabilitation in MS patients during COVID-19. *Acta Neurol. Belg.* **2022**, *122*, 23–29. [CrossRef]