



Enhancing Mood, Cognition, and Quality of Life in Pediatric Multiple Sclerosis

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Abstract

Pediatric-onset multiple sclerosis (POMS), representing approximately 5% of all MS cases, affects the central nervous system during its ongoing development. POMS is most commonly diagnosed during adolescence but can occur in younger children as well. For pediatric patients with MS, it is critical to manage the full impact of the disease and monitor for any effects on school and social functioning. Disease management includes not only disease-modifying therapies but also strategies to optimize wellbeing. We review the interventions with the highest evidence of ability to improve the disease course and quality of life in POMS. High levels of vitamin D and a diet low in saturated fat are associated with lower relapse rates. Exercise ameliorates fatigue and sleep. Behavioral strategies for sleep hygiene and mood regulation can also improve fatigue and perceived health. POMS management should be addressed holistically, including assessing overall symptom burden as well as the psychological and functional impact of the disease.

Key Points

Pediatric multiple sclerosis (MS) should be addressed holistically, including its effects on mood and cognition and the functional impact on school performance.

Children with MS should be on disease-modifying therapies, be encouraged to take vitamin D₃, reduce saturated fat intake, exercise, avoid smoking, practice good sleep hygiene, and receive appropriate treatment for any mood disorders.

Behavioral interventions, including targeted cognitive, physical, or occupational therapies, should be warranted in pediatric MS.

1 Introduction

Pediatric-onset multiple sclerosis (POMS) represents a rare subpopulation of the disease, occurring in approximately 3–5% of all cases [1–4]. These patients have a highly inflammatory course with frequent relapses and greater lesion accumulation relative to adults with MS [5, 6]. In contrast to adults, pediatric patients have better relapse recovery with less neurologic impairment [7]. In general, patients with POMS take longer to reach disability milestones but do so at a younger age than their adult counterparts [8, 9]. Controlling inflammation is achievable with disease-modifying therapy (DMT) and is critical for preserving normal brain maturation and development.

In addition to preventing and managing MS relapses, concerns specific to patients with POMS include cognitive issues, mood disturbances, and psychological adjustment to the disease. All are important to address to maintain quality of life (QoL). In this article, we focus on these QoL aspects of POMS and review approaches for intervention.

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2 Management of the Disease Course in Pediatric-Onset Multiple Sclerosis (POMS)

2.1 Disease-Modifying Therapies (DMTs) and Treatment Outcome

As patients with POMS have a high risk of relapse, prompt initiation of DMT is critical. Randomized controlled trials (RCTs) on DMTs in children with MS have specific challenges concerning recruitment, clinical design, and ethical considerations [10]. A large RCT in POMS demonstrated a clear benefit of fingolimod compared with intramuscular injections of interferon (IFN)- β -1a [11], as reviewed elsewhere [12]. Other RCTs are in varying stages of completion, and many open-label and observational studies support the efficacy and safety of DMTs used in adults with MS to treat pediatric patients [13, 14].

2.1.1 Addressing Compliance with DMTs

Adherence to DMTs has been associated with fewer relapses, fewer MS-related emergency room visits and hospitalizations, and better QoL with respect to emotional health, energy, social function, pain, and neurological deficits in patients with MS [15]. Despite the benefits of regularly taking DMTs, 50–70% of the adults [16] and children [17, 18], particularly adolescents, discontinue their DMT at some point.

Barriers to compliance include forgetting the medication, injection-associated anxiety, perceived lack of efficacy, and adverse events. Literature comparing compliance with different DMTs is lacking, but higher adherence rates have been reported with natalizumab as compared with injectable

drugs, likely because of greater physician involvement, less frequent administration, avoiding the discomfort of injections, and higher perceived efficacy [19].

Both family and patient behavioral interventions may help improve adherence to DMTs used for MS. Some strategies include guaranteeing access to care; minimizing side effects, changes in dosing and scheduling; and open physician–patient communication to educate patients on the value of treatment [20]. Unfortunately, not all interventions seem to be successful. For example, a motivation interview and subsequent follow-up through an electronic monitoring device [21] failed to improve adherence to medication among 52 children with POMS. Clinicians need to learn more about the best way to motivate patients and enhance compliance in each age group.

2.2 Vitamin D

As shown in Table 1, there is strong evidence to support vitamin D (25(OH)D) supplementation for disease management. Deficiency in 25(OH)D is a risk factor for developing MS across all age groups [22]. Both children and adults with MS have lower circulating 25(OH)D than expected [23, 24]. Children with higher levels of 25(OH)D at the onset of an acute demyelinating syndrome have a lower risk of developing POMS [13]. Interestingly, maternal [14] and neonatal 25(OH)D levels at birth [25] do not appear to predict the risk of MS in the offspring, but further research on pre- and perinatal 25(OH)D status is warranted.

Once the disease has been established, lower levels of 25(OH)D are associated with a higher relapse rate (RR) in POMS [26, 27]. In a study of POMS, two independent single nucleotide polymorphisms within or near GC and *NADSYN1/DHCR7* genes were strongly associated with 25(OH)D levels. After adjusting for ancestry, sex, DMTs,

Table 1 Level 1 evidence on benefits of vitamin D in pediatric-onset and adult multiple sclerosis

Study	Evidence level	Population	Outcomes studied	Statistical significance
Goldberg et al. [137]	RCT	Adult RRMS	RR	SS
Soilu-Hanninen et al. [29]	RCT	Adult RRMS	MRI activity, RR, EDSS	Fewer T1 lesions—SS The rest—not SS
Aivo et al. [30]	RCT	Adult RRMS	MRI activity, RR, EDSS	Fewer T1 lesions—SS The rest—not SS
Mosayebi et al. [31]	RCT	Adult RRMS	MRI activity, EDSS	Not SS
Shaygannejad et al. [32]	RCT	Adult RRMS	RR, EDSS	Not SS
Kampman et al. [86]	RCT	Adult RRMS	RR, EDSS, functional composite, fatigue	Not SS
Achiron et al. [87]	RCT	Adult RRMS	Fatigue, QoL, RR	SS
Ashtari et al. [88]	RCT	Adult RRMS	QoL	SS
Rolf et al. [89]	RCT	Adult RRMS	Depression	Not SS

EDSS Expanded Disability Status Scale, MRI magnetic resonance imaging, QoL quality of life, RCT randomized controlled trial, RR relapse rate, RRMS relapsing-remitting multiple sclerosis, SS statistically significant

and human leukocyte antigen (HLA)-DRB1*15 carrier status, the highest versus lowest vitamin D genetic risk score was associated with 2.6-fold and twofold higher relapse hazard ratios [28]. The causality of this association is still under investigation, but these studies suggest that aiming to reach a high normal level of circulating 25(OH)D is a reasonable therapeutic approach to lower RRs.

A small study in adults with MS suggested that adding 25(OH)D to DMT reduced magnetic resonance imaging (MRI) activity (fewer T1-enhancing lesions and fewer T2 burden lesions) [29, 30]. Other RCTs did not find significant differences in MRI parameters or disease progression [31, 32].

2.3 Mineral Supplements

The potential benefit of iron and salt supplements has also been investigated, but evidence to date is insufficient for recommendation. Recent experiments in mice have shown that high salt intakes increase interleukin (IL)-17, causing a more severe form of experimental autoimmune encephalomyelitis (EAE) [33]. However, this association has not been confirmed in patients with MS. Farez [34] found that moderate salt consumption increased the MS RR by 2.75 and a high intake increased it by 3.95; however, the cohort was relatively small, and confounding factors could not be excluded. Another recent RCT in women in the Nurses' Health Study found no association between dietary salt and risk of MS [35].

In patients with POMS, Azary et al. [36] did not find a correlation between iron intake and RR. However, other studies found significant decreased iron consumption in patients with POMS [37] and an association between low iron intake and a diagnosis of POMS [37, 38].

Overall, at this time, salt intake does not appear to be associated with POMS diagnosis or time to relapse [39].

2.4 Alternative Therapies: Antioxidants and Cannabis

Patients with MS, like those with other chronic conditions, are willing to incorporate supplements and other alternative remedies into their daily MS care, as it is a popular and easy routine that provides a sense of empowerment over their disease. Several of these antioxidants, vitamins, and dietary supplements have been investigated in animal models, but the evidence in humans is overall small given limitations in the trials. Among them, biotin (B₇) and lipoic acid supplements have the strongest evidence [40].

Vitamin B₇ supplementation is thought to improve remyelination by increasing energy production and fatty acid synthesis. In an open-label pilot study of 23 patients with progressive MS, more than 90% improved clinically

(motor and visual symptoms) after treatment with high-dose B₇ (MD 1003) for an average of 9 months [41]. This study prompted a double-blind, multicenter phase III trial in which 154 adults with primary or secondary progressive MS were randomized to receive either high-dose B₇ or placebo for 12 months. High-dose B₇ significantly improved MS-related disability in 13% compared with none in the placebo group [42]. However, a trial designed to replicate these observations in a larger, international cohort (*n* = 642) failed to show significant improvement in disability or walking speed in patients with progressive MS. Furthermore, adverse effects and laboratory changes were associated with high-dose B₇ therapy [43].

Another multicenter RCT comparing B₇ 300 mg versus placebo showed only modest improvements in motor scores [42]. Further investigation in a larger double-blind, multicenter phase III RCT in adults with progressive MS (NCT02936037) is ongoing.

Lipoic acid (LA) inhibits lymphocyte migration into the central nervous system (CNS), increases regulatory T cells, and downregulates pro-inflammatory cytokines in EAE [44]. In patients with MS, increased LA levels may reduce matrix metalloproteinase-9 and intercellular adhesion molecules inhibiting lymphocyte migration into the CNS [45]. In a small RCT, patients with MS on LA had a significant 68% reduction in brain atrophy and a nonsignificant improvement in walking speed [46]. A larger, phase II RCT is planned to evaluate LA in progressive MS. LA can interact with medications, cause hypoglycemia, and have renal toxic effects.

Research on cannabinoids and medical marijuana in MS is increasing. The recent National Academies of Sciences, Engineering, and Medicine report described the evidence of cannabinoids and derivatives in adults with chronic pain [47], MS-related spasticity [47–49], and chemotherapy-induced nausea and vomiting.

No trials have been undertaken in children with POMS, partly because of concerns regarding the risk of addiction to marijuana in adolescents [50]. Of additional concern are the adverse effects of marijuana use on cognitive function and mood in people with MS. Furthermore, discontinuing cannabis in adults with MS may improve depression [51].

2.5 Managing Diet and Obesity

Obesity and high body mass index (BMI) are risk factors for MS in children and adolescents [22, 52, 53]. Overall, patients with POMS appear to have more relative obesity than their adult counterparts [24] with higher BMIs, even years before onset of symptoms [54].

Table 2 summarizes the highest level of evidence on dietary interventions in MS. Medical subject heading (MeSH) terms used included multiple sclerosis, diet, child,

Table 2 Level 1 evidence on benefits of diet in multiple sclerosis

Study	Diet comparison	Evidence level	Population	Outcomes studied	Statistical significance
Weinstock-Guttman et al. [90]	LSF diet (omega-3 PUFA based) vs. Mediterranean diet	RCT	Adult RRMS	RR, fatigue	SS. Both diets reduced RR; Mediterranean diet reduced fatigue
Riccio et al. [55]	25(OH)D ₃ (placebo) vs. CRD and 25(OH)D ₃ vs. 25(OH)D ₃ and other supplements	RCT	Adult RRMS	Fatigue, EDSS	Not SS
Yadav et al. [56]	LSF diet (vegetarian) vs. control	RCT	Adult RRMS	Fatigue, EDSS, MRI activity	Reduction in fatigue—SS; the rest—not SS
Choi et al. [91]	Control vs. 6 months of ketogenic diet vs. 1 week of MFMD followed by 6 months of Mediterranean diet	RCT	Adult RRMS	EDSS, depression, QoL	SS. Depression and QoL improved in both diets vs. controls
Hempel et al. [57]	PUFA-based diet vs. “hot nature food” vs. Chinese diet vs. very LSF diet supplemented with fish oil, low-saturated fat plant-based diet, vitamin B ₂ supplements	Review (37 RCTs)	Adult RRMS	EDSS	Not SS

25(OH)D₃ 25-hydroxy vitamin D₃, CRD caloric restricted diet, EDSS Expanded Disability Status Scale, LSF low saturated fat, MFMD modified fasting mimicking diet, MRI magnetic resonance imaging, PUFA polyunsaturated fatty acids, QoL quality of life, RCT randomized controlled trial, RR relapse rate, RRMS relapsing-remitting multiple sclerosis, SS statistically significant

recurrence, fatigue, quality of life, depression, and cognition. No RCT on diet and POMS has been published to date.

As shown in Table 2, several POMS and adult MS studies have examined the role of diet and MS relapse. A multicenter prospective cohort study that analyzed the time to relapse in 219 patients with POMS and clinical isolated syndrome (CIS) showed that each 10% of energy intake from fat increased the RR by 56%, and each 10% of energy specifically from saturated fats tripled this hazard. In contrast, each equivalent of a cup of vegetables decreased the RR by 50% [36]. However, in adults, a diet low in saturated fat did not improve Expanded Disability Status Scale (EDSS) score [55, 56], disease progression [57], or MRI activity [56].

2.6 Addressing Smoking and Passive Smoke Exposure

Smoking increases the risk of MS [58, 59], likely because of its underlying proinflammatory [60] and autoimmune effects, risk of respiratory infections, and changes in post-translational processing of immunogenic proteins [61]. Several components of cigarette smoke are particularly toxic to oligodendrocytes and neurons [62]. Interestingly, smokers also tend to have lower 25(OH) D levels [63, 64].

The first major epidemiological study that linked smoking with MS was published in 2001 as part of the Nurses' Health Study [65]. Active smokers have an increased risk

of developing MS [59, 65], and the number of cigarettes and duration of exposure appear to be independent risk factors [66, 67]. Another meta-analysis reported similar rates, with an odds ratio (OR) estimate of 1.46 among ever smokers, 1.57 among current smokers, 1.36 among ex-smokers, and 1.12 among passive smokers. The effect of cigarette pack-year on MS demonstrated an OR estimate of 1.34 for 1–5 cigarette pack-years, 1.56 for 6–10 cigarette pack-years, 1.74 for 11–15 cigarette pack-years, and 1.46 for > 15 cigarette pack-years [68]. This risk only disappeared 10 years after cessation.

Mikaeloff et al. [69] reported an increased risk of developing POMS in the offspring of parents who smoked. This risk was higher in children aged > 10 years, which the authors attributed to a longer period of exposure [69]. Subsequently, the combination of exposure to smoking and HLA-DRB1*15 alleles was found to increase the risk of pediatric MS relative to monophasic demyelination [70]. Thus, parents of children with CIS and POMS should be strongly encouraged to quit smoking.

Once the disease has been established, regular smoking among adults with MS appears to accelerate disease progression [57, 66] and worsen disability [67]. Further studies are needed to confirm these findings in POMS, but adolescent patients should be counseled to avoid smoking and passive cigarette exposure.

2.7 Summary

Disease management is critical for patients with POMS, especially given the risk of frequent relapses and the context of ongoing neurodevelopment. Evidence-based care includes the use of DMTs and vitamin D supplementation. Evidence for mineral supplementation is inadequate. Weight management, lower saturated fat intake, and smoking cessation and prevention are recommended.

3 Management of Cognition, Mood, and Quality of Life (QoL) in POMS

Given the acute period of educational, occupational, and social attainment during development, it is particularly important to identify and address cognitive involvement due to MS in pediatric patients. Cognitive impairment is a common feature of adults with MS and is estimated to affect up to 75% of individuals across their disease course [71]. Pediatric patients are overall less likely to have cognitive involvement but remain at risk. Although early studies of cognitive functioning in POMS suggested relatively high rates of impairment [72], other observational studies showed lower rates [9, 73]. Overall, it is estimated that approximately 25–30% of patients with POMS experience mild cognitive changes [72], mainly involving attention and processing speed [74–77].

Cognitive and mood issues negatively impact children's QoL [78, 79] and place extra burden on social relationships and family and school dynamics. The relation between age of MS onset and cognitive difficulties among those with POMS is unclear, with some studies showing more difficulties in patients with earlier onset [75, 80] and others showing them in older children [81]. Promoting school attendance is critical for academic achievement. Some but not all patients may require individual accommodations such as extra time for tests or reduced workload, depending on school performance.

Other common problems affecting QoL include fatigue and poor sleep and the challenges associated with having a chronic health condition during childhood and adolescence. The risk of missing school and its subsequent challenges are of particular concern. At evaluation, it is important to address the full range of symptoms from the perspectives of both the patient and their family. For example, among a pediatric cohort of 51 individuals, fatigue was noted by parents to be severe in 50%, whereas the self-reported rate was lower at 32% [78, 82].

For some patients with POMS and their families, the diagnosis results in a psychological burden. Education on the disease and its management and expectations for the future are critical, and supportive counseling is recommended for

those with challenges in coping or with associated mood changes. In addition, symptoms such as fatigue, physical impairments (even if transient), cognitive challenges, and dependence on long-term medication reinforce the feeling of being different from peers and can contribute to the psychological burden of disease.

3.1 DMTs

Well-controlled disease may be cognitively protective. The extent to which DMTs preserve cognitive function remains unclear. Presumably, slowing atrophy and lesion accumulation is beneficial for cognition, but the positive effect might require longer-term follow-up than is readily available from RCTs.

The effect of DMT on cognitive function in POMS was examined by performing longitudinal neuropsychological testing during a period of 6–24 months in children treated consistently with an initial DMT ($n = 13$) compared with those switched to a higher-efficacy therapy ($n = 6$). The group that switched remained cognitively stable (despite more relapses), whereas a subset ($n = 9/13$ [69%]) in the lower-efficacy group had some degree of cognitive impairment on follow-up [83]. In line with the hypothesis that more intensive therapy might be beneficial for preserving cognitive function, patients with POMS treated with natalizumab did well when assessed with the EDSS and Symbol Digits Modalities Test (SDMT) in a 2-year follow-up study. Of 20 patients retested, only two declined by ≥ 4 points on the SDMT, whereas the others either improved or remained stable [84].

Little is known regarding the impact on QoL of DMT in pediatric MS. Health-related QoL was an exploratory outcome among the 191 children aged 10–17 years randomized to either intramuscular IFN- β -1a or fingolimod treatment in the PARADIGMS study. In that study, the fingolimod group had a significantly greater reduction in RR, lesion accumulation, and brain volume loss than the group receiving intramuscular IFN- β -1a [11]. Consistent with the primary efficacy results, treatment with fingolimod compared with IFN- β -1a was associated with a greater improvement in all measures of health-related QoL, as reported by the patients, and in Total Scale Score and Physical Health Summary Score as reported by their parents. With respect to clinically meaningful change on the QoL measures, the proportion of patients receiving fingolimod versus IFN treatment with clinical meaningful improvement was higher across all measures. However, the biggest differences between the two treatment arms were noted in psychosocial health by patients (fingolimod vs. intramuscular IFN- β -a1, 52.5 vs. 29.5% improved QoL during the study; $p = 0.001$) and within physical health as reported by parents (fingolimod vs. intramuscular IFN- β -a1, 38.8 vs. 21.5%; $p=0.012$). Presumably,

the lower RR, fewer associated hospitalizations, and possibly fewer IFN-associated side effects contributed to the greater QoL noted by the fingolimod group. These findings further emphasize that parents and patients perceive the impact of the disease process on health outcomes differently [11, 85]

3.2 Vitamin D and Diet

In a low-powered study, Kampman et al. [86] failed to find improvement in functional tests and fatigue severity score in 62 patients with MS taking weekly 20,000 IU 25(OH)D. However, Achiron et al. [87] randomized 158 patients with MS with significant fatigue to receive 25(OH)D or placebo. Those receiving 25(OH)D significantly improved fatigue and QoL scores in the RAYS psychological and social scales and had a decreased RR after 4 months of treatment. Ashtari et al. [88] described similar improvements in patient QoL after 3 months of treatment.

To date, one single randomized pilot study has focused on the relationship between 25(OH)D deficiency and depression in relapsing-remitting MS (RRMS); no statistically significant differences between the treatment and placebo groups were observed [89].

Which low-fat diet provides the highest benefits in MS remains unclear, and further studies comparing different diets are needed. For example, a small RCT in adults with RRMS did not find differences in RR between a low-fat diet with omega-3 poly-unsaturated fatty acids (PUFA) and the Mediterranean diet supplemented with olive oil. However, the “fish oil” group had greater improvement in QoL (physical and mental parameters) at 6 months, whereas fatigue improved exclusively with the Mediterranean diet [90].

Although some studies found that low-fat diets improved fatigue [56], QoL [91], depression, and cognitive health [92] in adults with MS [93], other authors did not reach the same conclusions [55].

3.3 Rehabilitation

There is growing excitement regarding evidence of neuroplasticity as a mechanism to compensate for pathology and cognitive dysfunction in MS. There are no RCTs on neuro-rehabilitation in POMS to date, partly because these interventions in children need to be tailored by each age group according to specific needs, cognitive level, and interests. However, the growing use of telemedicine protocols for enhancing cognitive function, fatigue, and other aspects of well-being shows great promise for application to those with POMS. This methodology facilitates recruitment across wide geographic areas and lessens the toll on the family with respect to participation and compliance with the intervention.

Intensive cognitive rehabilitation with a special emphasis on attention, processing speed, memory, and executive function has shown benefit on improving cognitive deficits and QoL in adults with MS [94–96], with brain changes demonstrated on functional MRI [97, 98].

Different neuro-cognitive interventions have been examined in adults with MS. In a recent review [99], the highest level of evidence supported the “Attention Process Training” [94] and the “RehaCom” computer program [100] to treat attention disorders and the use of images/ context (“modified Story Memory Technique”) [96] and music [101] for memory and learning impairments in adults with MS. Others have demonstrated the benefit of computer-assisted cognitive rehabilitation in the treatment of processing speed and memory issues in MS [102]. A major advantage of this form of cognitive training is that it can be done at home. One study employing telemedicine in adults with MS showed greater improvement in cognitive functioning in the adaptive cognitive remediation program—a supervised computer cognitive training administered at home—over the active control of ordinary computer games [103].

3.4 Exercise

Table 3 summarizes the highest level of evidence on the role of exercise in QoL, fatigue, depression, and cognitive function in patients with MS. No level 1 evidence studies in POMS have been published to date.

Children diagnosed with MS engage in less physical activity than those with monophasic acute disseminated encephalo-myelitis or their healthy counterparts [104, 105]. Grover et al. [104, 105] found that adolescents with less perception of their physical limitations and those scoring higher on the “Physical Activity Self-Efficacy Scale” and the “Exercise Goal-Setting Scale” were more likely to participate in moderate and vigorous exercise. However, the authors did not find a correlation between level of exercise and depression or fatigue, which contrasts with another recent publication that demonstrated less fatigue and depression in those undertaking moderate to vigorous exercise in POMS [106].

A recent exploration of physical activity perceptions in eight adolescents with POMS reported overall positive perceptions of the benefit of physical activity among participants but also a common fear that exercising could worsen their MS symptoms and cause relapses. Participants described the lack of social support, time, and opportunity as hindrances to exercise and asked for better education regarding specific exercises, outcomes, and safety and for opportunities for social engagement with other individuals with POMS [107].

Physical activity helps with sleep issues and fatigue in children with POMS [104, 105, 108]. In adults, exercise and physical therapy improves MS-related fatigue and QoL

Table 3 Level 1 evidence of the benefits of exercise in multiple sclerosis

Study	Evidence level	Population	Outcomes studied	Relevant conclusions/statistical significance
Langeskov-Christensen et al. [109]	Review (234 studies)	Adult RRMS	Pathways of fatigue in MS	Exercise may improve fatigue by directly and indirectly impacting on its biological pathways
Sa [116]	Review (11 RCTs)	Adult RRMS	Effects of exercise in MS	Exercise may improve fatigue
Heine et al. [110]	Meta-analysis (45 RCT)	Adult RRMS	Effects on fatigue in MS	Exercise, particularly endurance, mixed, or 'other' training (e.g., yoga) may improve fatigue
Cruckshank et al. [111]	Meta-analysis (20 RCT and non-RCT)	Adult RRMS	Effects of strength-based exercise in Parkinson and MS in fatigue, QoL, and other domains	Strength training improves fatigue (8.2%), functional capacity (21.5%), and QoL (8.3%) among others
Latimer-Cheung et al. [112]	Meta-analysis (54 RCT and non-RCT)	Adult RRMS	Effects on physical fitness, mobility, fatigue, and QoL in MS	Evidence is inconsistent regarding the effects of exercise on fatigue and QoL
Andreassen et al. [113]	Review (23 RCT and non RCT)	Adult RRMS	Effect on fatigue in MS	Evidence is heterogeneous but with a positive tendency regarding the effects of exercise on fatigue
Motl et al. [114]	Meta-analysis (13 studies including RCT and non RCT)	Adult RRMS	Effects on QoL in MS	Exercise is associated with a small improvement in QoL
Kjohlhede et al. [115]	Review (14 studies including RCT and non RCT)	Adult RRMS	Effects of progressive resistance training in MS	Evidence is heterogeneous but with a positive tendency regarding the effects of exercise on QoL and mood
Ensari et al. [117]	Meta-analysis (13 RCT)	Adult RRMS	Effects on depression	Exercise is associated with a small reduction in depressive symptoms
Morrison et al. [118]	Review (19 studies including RCT and non RCT)	Adult RRMS	Effects on cognition	Evidence is heterogeneous (9/19 studies reported positive effect; 10/19 reported mixed results)
Sandroff et al. [119]	Review (26 studies including RCT and non RCT)	Adult RRMS	Effects on cognition	Evidence is heterogeneous

MS multiple sclerosis, QoL quality of life, RCT randomized controlled trial, RRMS relapsing-remitting MS

[109–116]. A recent meta-analysis also showed a statistically significant benefit of exercise on reducing depressive symptoms [117] and improving cognition [118, 119].

3.5 Sleep and Fatigue Management

Sleep disorders (SDs) are common in adults with MS and include restless legs syndrome, periodic limb movements, and sleep apnea [120].

Several studies in adults with MS have shown that SDs adversely affect QoL [120, 121] by worsening fatigue [120, 122] and depressive symptoms [123, 124]. Treatment of SDs improves MS-related fatigue [125, 126] and QoL [120]. Patients with MS with SD frequently report a decline in self-perceived cognition [127]. However, a study in which participants with MS with altered sleep and those with normal sleep underwent cognitive testing reported no performance differences between the two groups. Interestingly, those with disrupted sleep patterns displayed decreased functional connectivity in thalamic circuits [128].

Few studies have addressed sleep issues in POMS. One author found that patients with POMS were more successful at managing sleep hygiene than matched healthy controls [129]. This may represent a mechanism to adjust for daytime fatigue and/or the consequence of more structured parental-promoted routines in families of children with POMS. Exercise also improves sleep symptoms in children [104, 105]. The specific SDs in children with POMS and their impact on QoL have not yet been described. Further studies are needed to identify the most appropriate interventions to improve sleep in this population.

Children with POMS are prone to mood disorders [7] and fatigue, both of which can negatively influence their QoL. In a cohort of 106 patients with POMS and 210 matched healthy controls, children with MS were significantly more depressed and experienced greater fatigue and loss of QoL than controls [130].

We previously described a cohort of 45 children with POMS with a high incidence of mood disorders (15 with anxiety, 11 with other mood disorders, and 12 with attention deficit and hyperactivity). Although not significant, we found greater cognitive impairment in the group with psychiatric disorders (80 vs. 55%), particularly those with anxiety and mood disorders [79]. Although no studies have addressed the most beneficial interventions in children with POMS and mood disorders, clinicians should be prompt in evaluating and treating these symptoms with counseling and medication when appropriate.

Questions remain as to the most appropriate testing to measure and address cognitive problems, fatigue, and QoL in children and adolescents with POMS [131]. The specific management of SDs is beyond the scope of this review. Regarding the treatment of MS-related fatigue

among adults, pharmacologic interventions do not appear superior to placebo. Hence, it is likely that, for those in the pediatric age group, nonpharmacologic approaches will have the best outcomes.

The nonpharmacologic interventions of cognitive behavioral therapy and rehabilitation can effectively improve fatigue [132, 133], SDs, and depression in adults with MS. Veauthier et al. [134] suggested an algorithm to diagnose and treat MS-related fatigue, depression, nocturia, and SDs. It starts by ruling out comorbid conditions and sedatives and ends with recommendations for therapeutic trials and behavioral interventions. Further research is needed to determine the most beneficial interventions for SDs, fatigue, and mood disorders in children with POMS.

4 Conclusions

MS affects children and adolescents at a critical time in their social and cognitive development.

Parents and children with POMS most often list poor emotional and school functioning as their main concerns [135] and appreciate the resources provided to cope with the diagnosis and a holistic approach in treatment [136].

Most of the studies on functional benefits, including cognition and QoL, in MS have been undertaken in adults. These studies are frequently underpowered and have too many limitations to generalize conclusions. Very few RCTs have addressed these issues in POMS.

Level 1 evidence studies are needed in both children and adults with MS to determine the specific benefits of health interventions that modify factors implicated in the disease course. This is particularly challenging in children given the smaller sample and different levels of functionality and cognitive maturation in each age group. Interventions to enhance cognition in children should be tailored to the specific needs and interests of the age to guarantee adherence and efficacy.

While we wait for a definitive cure for the disease, there is increasing awareness of the importance of treating POMS in a holistic manner, paying attention to functional comorbidities and evaluating and addressing mood and cognition. We can conclude that, in general, promoting healthy coping behaviors and encouraging participation in school sports and extracurricular activities are essential to enhance a sense of well-being in children with MS.

At the time of this review, a large RCT analyzing the benefits of 25(OH)D in MS is ongoing. In the next few years, we expect to see further large studies in the field addressing health interventions to preserve brain reserve and enhance functionality in children with POMS.

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References

- Ghezzi A, Deplano V, Faroni J, Grasso MG, Liguori M, Marrosu G, et al. Multiple sclerosis in childhood: clinical features of 149 cases. *Mult Scler*. 1997;3(1):43–6.
- Boiko A, Vorobeychik G, Paty D, Devonshire V, Sadovnick D, University of British Columbia MSCN. Early onset multiple sclerosis: a longitudinal study. *Neurology*. 2002;59(7):1006–10.
- Chitnis T, Glanz B, Jaffin S, Healy B. Demographics of pediatric-onset multiple sclerosis in an MS center population from the Northeastern United States. *Mult Scler*. 2009;15(5):627–31.
- Harding KE, Liang K, Cossburn MD, Ingram G, Hirst CL, Pickersgill TP, et al. Long-term outcome of paediatric-onset multiple sclerosis: a population-based study. *J Neurol Neurosurg Psychiatry*. 2013;84(2):141–7.
- Benson LA, Healy BC, Gorman MP, Baruch NF, Gholipour T, Musallam A, et al. Elevated relapse rates in pediatric compared

- to adult MS persist for at least 6 years. *Mult Scler Relat Disord*. 2014;3(2):186–93.
- Verhey LH, Shroff M, Banwell B. Pediatric multiple sclerosis: pathobiological, clinical, and magnetic resonance imaging features. *Neuroimaging Clin N Am*. 2013;23(2):227–43.
- Chitnis T, Aaen G, Belman A, Benson L, Gorman M, Goyal MS, et al. Improved relapse recovery in paediatric compared to adult multiple sclerosis. *Brain*. 2020;143(9):2733–41.
- McKay KA, Hillert J, Manouchehrinia A. Long-term disability progression of pediatric-onset multiple sclerosis. *Neurology*. 2019;92(24):e2764–73.
- Charvet LE, O'Donnell EH, Belman AL, Chitnis T, Ness JM, Parrish J, et al. Longitudinal evaluation of cognitive functioning in pediatric multiple sclerosis: report from the US Pediatric Multiple Sclerosis Network. *Mult Scler*. 2014;20(11):1502–10.
- Waubant E, Banwell B, Wassmer E, Sormani MP, Amato MP, Hintzen R, et al. Clinical trials of disease-modifying agents in pediatric MS: opportunities, challenges, and recommendations from the IPMSSG. *Neurology*. 2019;92(22):e2538–49.
- Chitnis T, Arnold DL, Banwell B, Bruck W, Ghezzi A, Giovannoni G, et al. Trial of fingolimod versus interferon beta-1a in pediatric multiple sclerosis. *N Engl J Med*. 2018;379(11):1017–27.
- Deiva K. Pediatric onset multiple sclerosis. *Revue Neurologique*. 2020;176(1–2):30–6.
- Banwell B, Bar-Or A, Arnold DL, Sadovnick D, Narayanan S, McGowan M, et al. Clinical, environmental, and genetic determinants of multiple sclerosis in children with acute demyelination: a prospective national cohort study. *Lancet Neurol*. 2011;10(5):436–45.
- Salzer J, Hallmans G, Nystrom M, Stenlund H, Wadell G, Sundstrom P. Vitamin D as a protective factor in multiple sclerosis. *Neurology*. 2012;79(21):2140–5.
- Steinberg SC, Faris RJ, Chang CF, Chan A, Tankersley MA. Impact of adherence to interferons in the treatment of multiple sclerosis: a non-experimental, retrospective, cohort study. *Clin Drug Investig*. 2010;30(2):89–100.
- Fraser C, Hadjimichael O, Vollmer T. Predictors of adherence to glatiramer acetate therapy in individuals with self-reported progressive forms of multiple sclerosis. *J Neurosci Nurs*. 2003;35(3):163–70.
- Thannhauser JE, Mah JK, Metz LM. Adherence of adolescents to multiple sclerosis disease-modifying therapy. *Pediatr Neurol*. 2009;41(2):119–23.
- Giovannoni G, Southam E, Waubant E. Systematic review of disease-modifying therapies to assess unmet needs in multiple sclerosis: tolerability and adherence. *Mult Scler*. 2012;18(7):932–46.
- Halpern R, Agarwal S, Borton L, Oneacre K, Lopez-Bresnahan MV. Adherence and persistence among multiple sclerosis patients after one immunomodulatory therapy failure: retrospective claims analysis. *Adv Ther*. 2011;28(9):761–75.
- Costello K, Kennedy P, Scanzillo J. Recognizing nonadherence in patients with multiple sclerosis and maintaining treatment adherence in the long term. *Medscape J Med*. 2008;10(9):225.
- Yeh EA, Grover SA, Powell VE, Alper G, Banwell BL, Edwards K, et al. Impact of an electronic monitoring device and behavioral feedback on adherence to multiple sclerosis therapies in youth: results of a randomized trial. *Qual Life Res*. 2017;26(9):2333–49.
- Gianfrancesco MA, Stridh P, Rhead B, Shao X, Xu E, Graves JS, et al. Evidence for a causal relationship between low vitamin D, high BMI, and pediatric-onset MS. *Neurology*. 2017;88(17):1623–9.
- Duan S, Lv Z, Fan X, Wang L, Han F, Wang H, et al. Vitamin D status and the risk of multiple sclerosis: a systematic review and meta-analysis. *Neurosci Lett*. 2014;570:108–13.

24. Brenton JN, Koenig S, Goldman MD. Vitamin D status and age of onset of demyelinating disease. *Mult Scler Relat Disord*. 2014;3(6):684–8.
25. Ueda P, Rafatnia F, Baarnhielm M, Frobom R, Korzunowicz G, Lonnerbro R, et al. Neonatal vitamin D status and risk of multiple sclerosis. *Ann Neurol*. 2014;76(3):338–46.
26. Mowry EM, Krupp LB, Milazzo M, Chabas D, Strober JB, Belman AL, et al. Vitamin D status is associated with relapse rate in pediatric-onset multiple sclerosis. *Ann Neurol*. 2010;67(5):618–24.
27. Graves JS, Barcellos LF, Shao X, Noble J, Mowry EM, Quach H, et al. Genetic predictors of relapse rate in pediatric MS. *Mult Scler*. 2016;22(12):1528–35.
28. Graves JS, Barcellos LF, Krupp L, Belman A, Shao X, Quach H, et al. Vitamin D genes influence MS relapses in children. *Mult Scler*. 2019;26:894–901.
29. Soilu-Hanninen M, Aivo J, Lindstrom BM, Elovaara I, Sumelahti ML, Farkkila M, et al. A randomised, double blind, placebo controlled trial with vitamin D3 as an add on treatment to interferon beta-1b in patients with multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2012;83(5):565–71.
30. Aivo J, Lindstrom BM, Soilu-Hanninen M. A randomised, double-blind, placebo-controlled trial with vitamin D3 in MS: subgroup analysis of patients with baseline disease activity despite interferon treatment. *Mult Scler Int*. 2012;2012:802796.
31. Mosayebi G, Ghazavi A, Ghasami K, Jand Y, Kokhaei P. Therapeutic effect of vitamin D3 in multiple sclerosis patients. *Immunol Invest*. 2011;40(6):627–39.
32. Shaygannejad V, Janghorbani M, Ashtari F, Dehghan H. Effects of adjunct low-dose vitamin d on relapsing-remitting multiple sclerosis progression: preliminary findings of a randomized placebo-controlled trial. *Mult Scler Int*. 2012;2012:452541.
33. Kleinewietfeld M, Manzel A, Titze J, Kvakan H, Yosef N, Linker RA, et al. Sodium chloride drives autoimmune disease by the induction of pathogenic TH17 cells. *Nature*. 2013;496(7446):518–22.
34. Farez MF. Salt intake in multiple sclerosis: friend or foe? *J Neurol Neurosurg Psychiatry*. 2016;87(12):1276.
35. Cortese M, Yuan C, Chitnis T, Ascherio A, Munger KL. No association between dietary sodium intake and the risk of multiple sclerosis. *Neurology*. 2017;89(13):1322–9.
36. Azary S, Schreiner T, Graves J, Waldman A, Belman A, Guttman BW, et al. Contribution of dietary intake to relapse rate in early paediatric multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2018;89(1):28–33.
37. Pakpoor J, Seminatore B, Graves JS, Schreiner T, Waldman AT, Lotze TE, et al. Dietary factors and pediatric multiple sclerosis: a case-control study. *Mult Scler*. 2017;24:1067–76.
38. McDonald J, Graves J, Waldman A, Lotze T, Schreiner T, Belman A, et al. A case-control study of dietary salt intake in pediatric-onset multiple sclerosis. *Mult Scler Relat Disord*. 2016;6:87–92.
39. Nourbakhsh B, Graves J, Casper TC, Lulu S, Waldman A, Belman A, et al. Dietary salt intake and time to relapse in paediatric multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2016;87(12):1350–3.
40. Evans E, Piccio L, Cross AH. Use of vitamins and dietary supplements by patients with multiple sclerosis: a review. *JAMA Neurol*. 2018;75:1013.
41. Sedel F, Papeix C, Bellanger A, Touitou V, Lebrun-Frenay C, Galanaud D, et al. High doses of biotin in chronic progressive multiple sclerosis: a pilot study. *Mult Scler Relat Disord*. 2015;4(2):159–69.
42. Tourbah A, Lebrun-Frenay C, Edan G, Clanet M, Papeix C, Vukusic S, et al. MD1003 (high-dose biotin) for the treatment of progressive multiple sclerosis: a randomised, double-blind, placebo-controlled study. *Mult Scler*. 2016;22(13):1719–31.
43. Cree BAC, Cutter G, Wolinsky JS, Freedman MS, Comi G, Giovannoni G, et al. Safety and efficacy of MD1003 (high-dose biotin) in patients with progressive multiple sclerosis (SPI2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol*. 2020;19(12):988–97.
44. Chaudhary P, Marracci GH, Bourdette DN. Lipoic acid inhibits expression of ICAM-1 and VCAM-1 by CNS endothelial cells and T cell migration into the spinal cord in experimental autoimmune encephalomyelitis. *J Neuroimmunol*. 2006;175(1–2):87–96.
45. Yadav V, Marracci G, Lovera J, Woodward W, Bogardus K, Marquardt W, et al. Lipoic acid in multiple sclerosis: a pilot study. *Mult Scler*. 2005;11(2):159–65.
46. Spain R, Powers K, Murchison C, Heriza E, Wings K, Yadav V, et al. Lipoic acid in secondary progressive MS: a randomized controlled pilot trial. *Neurol Neuroimmunol Neuroinflamm*. 2017;4(5):e374.
47. Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, et al. Cannabinoids for medical use: a systematic review and meta-analysis. *JAMA*. 2015;313(24):2456–73.
48. Leocani L, Nuara A, Houdayer E, Schiavetti I, Del Carro U, Amadio S, et al. Sativex ((R)) and clinical-neurophysiological measures of spasticity in progressive multiple sclerosis. *J Neurol*. 2015;262(11):2520–7.
49. Koppel BS, Brust JC, Fife T, Bronstein J, Youssof S, Gronseth G, et al. Systematic review: efficacy and safety of medical marijuana in selected neurologic disorders: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*. 2014;82(17):1556–63.
50. Brook JS, Lee JY, Brook DW. Trajectories of marijuana use beginning in adolescence predict tobacco dependence in adulthood. *Subst Abus*. 2015;36(4):470–7.
51. Feinstein A, Meza C, Stefan C, Staines WR. Discontinuing cannabis improves depression in people with multiple sclerosis: a short report. *Mult Scler*. 2021;27(4):636–9.
52. Langer-Gould A, Brara SM, Beaver BE, Koebnick C. Childhood obesity and risk of pediatric multiple sclerosis and clinically isolated syndrome. *Neurology*. 2013;80(6):548–52.
53. Chitnis T, Graves J, Weinstock-Guttman B, Belman A, Olsen C, Misra M, et al. Distinct effects of obesity and puberty on risk and age at onset of pediatric MS. *Ann Clin Transl Neurol*. 2016;3(12):897–907.
54. Brenton JN, Woolbright E, Briscoe-Abath C, Qureshi A, Conaway M, Goldman MD. Body mass index trajectories in pediatric multiple sclerosis. *Dev Med Child Neurol*. 2019;61(11):1289–94.
55. Riccio P, Rossano R, Larocca M, Trotta V, Mennella I, Vitaglione P, et al. Anti-inflammatory nutritional intervention in patients with relapsing-remitting and primary-progressive multiple sclerosis: a pilot study. *Exp Biol Med (Maywood)*. 2016;241(6):620–35.
56. Yadav V, Marracci G, Kim E, Spain R, Cameron M, Overs S, et al. Low-fat, plant-based diet in multiple sclerosis: a randomized controlled trial. *Mult Scler Relat Disord*. 2016;9:80–90.
57. Hempel S, Graham GD, Fu N, Estrada E, Chen AY, Miake-Lye I, et al. A systematic review of modifiable risk factors in the progression of multiple sclerosis. *Mult Scler*. 2017;23(4):525–33.
58. Handel AE, Williamson AJ, Disanto G, Dobson R, Giovannoni G, Ramagopalan SV. Smoking and multiple sclerosis: an updated meta-analysis. *PLoS ONE*. 2011;6(1):e16149.
59. Hawkes CH. Smoking is a risk factor for multiple sclerosis: a metanalysis. *Mult Scler*. 2007;13(5):610–5.
60. Holt PG. Immune and inflammatory function in cigarette smokers. *Thorax*. 1987;42(4):241–9.

61. Makrygiannakis D, Hermansson M, Ulfgren AK, Nicholas AP, Zendman AJ, Eklund A, et al. Smoking increases peptidylarginine deiminase 2 enzyme expression in human lungs and increases citrullination in BAL cells. *Ann Rheum Dis*. 2008;67(10):1488–92.
62. O’Gorman C, Lucas R, Taylor B. Environmental risk factors for multiple sclerosis: a review with a focus on molecular mechanisms. *Int J Mol Sci*. 2012;13(9):11718–52.
63. Morabia A, Bernstein MS, Antonini S. Smoking, dietary calcium and vitamin D deficiency in women: a population-based study. *Eur J Clin Nutr*. 2000;54(9):684–9.
64. Schierbeck LL, Rejnmark L, Tofteng CL, Stilgren L, Eiken P, Mosekilde L, et al. Vitamin D deficiency in postmenopausal, healthy women predicts increased cardiovascular events: a 16-year follow-up study. *Eur J Endocrinol*. 2012;167(4):553–60.
65. Hernan MA, Olek MJ, Ascherio A. Cigarette smoking and incidence of multiple sclerosis. *Am J Epidemiol*. 2001;154(1):69–74.
66. Ramanujam R, Hedstrom AK, Manouchehrinia A, Alfredsson L, Olsson T, Bottai M, et al. Effect of smoking cessation on multiple sclerosis prognosis. *JAMA Neurol*. 2015;72(10):1117–23.
67. Manouchehrinia A, Tench CR, Maxted J, Bibani RH, Britton J, Constantinescu CS. Tobacco smoking and disability progression in multiple sclerosis: United Kingdom cohort study. *Brain*. 2013;136(Pt 7):2298–304.
68. Poorolajal J, Bahrami M, Karami M, Hooshmand E. Effect of smoking on multiple sclerosis: a meta-analysis. *J Public Health (Oxf)*. 2017;39(2):312–20.
69. Mikaeloff Y, Caridade G, Tardieu M, Suissa S, group Ks. Parental smoking at home and the risk of childhood-onset multiple sclerosis in children. *Brain*. 2007;130(10):2589–95.
70. Lavery AM, Collins BN, Waldman AT, Hart CN, Bar-Or A, Marrie RA, et al. The contribution of second hand tobacco smoke exposure to pediatric multiple sclerosis risk. *Mult Scler*. 2019;25(4):515–22.
71. Schulz D, Kopp B, Kunkel A, Faiss JH. Cognition in the early stage of multiple sclerosis. *J Neurol*. 2006;253(8):1002–10.
72. Amato MP, Krupp LB, Charvet LE, Penner I, Till C. Pediatric multiple sclerosis: cognition and mood. *Neurology*. 2016;87(9 Suppl 2):S82–7.
73. Julian L, Serafin D, Charvet L, Ackerson J, Benedict R, Braaten E, et al. Cognitive impairment occurs in children and adolescents with multiple sclerosis: results from a United States network. *J Child Neurol*. 2013;28(1):102–7.
74. Wallach AI, Waltz M, Casper TC, Aaen G, Belman A, Benson L, et al. Cognitive processing speed in pediatric-onset multiple sclerosis: baseline characteristics of impairment and prediction of decline. *Mult Scler*. 2019;26:1938–47.
75. Amato MP, Goretti B, Ghezzi A, Lori S, Zipoli V, Moiola L, et al. Cognitive and psychosocial features in childhood and juvenile MS: two-year follow-up. *Neurology*. 2010;75(13):1134–40.
76. Amato MP, Goretti B, Ghezzi A, Hakiki B, Nicolai C, Lori S, et al. Neuropsychological features in childhood and juvenile multiple sclerosis: five-year follow-up. *Neurology*. 2014;83(16):1432–8.
77. Till C, Ghassemi R, Aubert-Broche B, Kerbrat A, Collins DL, Narayanan S, et al. MRI correlates of cognitive impairment in childhood-onset multiple sclerosis. *Neuropsychology*. 2011;25(3):319–32.
78. MacAllister WS, Christodoulou C, Troxell R, Milazzo M, Block P, Preston TE, et al. Fatigue and quality of life in pediatric multiple sclerosis. *Mult Scler*. 2009;15(12):1502–8.
79. Weisbrot D, Charvet L, Serafin D, Milazzo M, Preston T, Cleary R, et al. Psychiatric diagnoses and cognitive impairment in pediatric multiple sclerosis. *Mult Scler*. 2014;20(5):588–93.
80. Aaen G, Waltz M, Vargas W, Makhani N, Ness J, Harris Y, et al. Acquisition of early developmental milestones and need for special education services in pediatric multiple sclerosis. *J Child Neurol*. 2018;34:148–52.
81. Mikaeloff Y, Caridade G, Billard C, Bouyer J, Tardieu M. School performance in a cohort of children with CNS inflammatory demyelination. *Eur J Paediatr Neurol*. 2010;14(5):418–24.
82. Goretti B, Portaccio E, Ghezzi A, Lori S, Moiola L, Falautano M, et al. Fatigue and its relationships with cognitive functioning and depression in paediatric multiple sclerosis. *Mult Scler*. 2012;18(3):329–34.
83. Johnen A, Elpers C, Riepl E, Landmeyer NC, Kramer J, Polzer P, et al. Early effective treatment may protect from cognitive decline in paediatric multiple sclerosis. *Eur J Paediatr Neurol*. 2019;23(6):783–91.
84. Margoni M, Rinaldi F, Riccardi A, Franciotta S, Perini P, Gallo P. No evidence of disease activity including cognition (NEDA-3 plus) in naive pediatric multiple sclerosis patients treated with natalizumab. *J Neurol*. 2019;267:100–5.
85. Krupp BB, Chitnis T, Deiva K, Gärtner J, Ghezzi A, Huppke P, Waubant E, Pearce GL, Stites T, K-Lafamme A, Karan R. Fingolimod treatment improved quality of life in paediatric patients with multiple sclerosis: PARADIGMS study. *Mult Scler*. 2018;24:518.
86. Kampman MT, Steffensen LH, Mellgren SI, Jorgensen L. Effect of vitamin D3 supplementation on relapses, disease progression, and measures of function in persons with multiple sclerosis: exploratory outcomes from a double-blind randomised controlled trial. *Mult Scler*. 2012;18(8):1144–51.
87. Achiron A, Givon U, Magalashvili D, Dolev M, Liraz Zaltzman S, Kalron A, et al. Effect of Alfacalcidol on multiple sclerosis-related fatigue: a randomized, double-blind placebo-controlled study. *Mult Scler*. 2015;21(6):767–75.
88. Ashtari F, Toghianifar N, Zarkesh-Esfahani SH, Mansourian M. High dose Vitamin D intake and quality of life in relapsing-remitting multiple sclerosis: a randomized, double-blind, placebo-controlled clinical trial. *Neurol Res*. 2016;38(10):888–92.
89. Rolf L, Muris AH, Bol Y, Damoiseaux J, Smolders J, Hupperts R. Vitamin D3 supplementation in multiple sclerosis: symptoms and biomarkers of depression. *J Neurol Sci*. 2017;378:30–5.
90. Weinstock-Guttman B, Baier M, Park Y, Feichter J, Lee-Kwen P, Gallagher E, et al. Low fat dietary intervention with omega-3 fatty acid supplementation in multiple sclerosis patients. *Prostaglandins Leukot Essent Fatty Acids*. 2005;73(5):397–404.
91. Choi IY, Piccio L, Childress P, Bollman B, Ghosh A, Brandhorst S, et al. A diet mimicking fasting promotes regeneration and reduces autoimmunity and multiple sclerosis symptoms. *Cell Rep*. 2016;15(10):2136–46.
92. Friedman DB, Becofsky K, Anderson LA, Bryant LL, Hunter RH, Ivey SL, et al. Public perceptions about risk and protective factors for cognitive health and impairment: a review of the literature. *Int Psychogeriatr*. 2015;27(8):1263–75.
93. Fitzgerald KC, Tyry T, Salter A, Cofield SS, Cutter G, Fox R, et al. Diet quality is associated with disability and symptom severity in multiple sclerosis. *Neurology*. 2018;90(1):e1–11.
94. Amato MP, Goretti B, Viterbo RG, Portaccio E, Nicolai C, Hakiki B, et al. Computer-assisted rehabilitation of attention in patients with multiple sclerosis: results of a randomized, double-blind trial. *Mult Scler*. 2014;20(1):91–8.
95. Rosti-Otajarvi EM, Hamalainen PI. Neuropsychological rehabilitation for multiple sclerosis. *Cochrane Database Syst Rev*. 2014;2:CD009131.
96. Chiaravalloti ND, Moore NB, Nickelshpur OM, DeLuca J. An RCT to treat learning impairment in multiple sclerosis: the MEMREHAB trial. *Neurology*. 2013;81(24):2066–72.
97. Filippi M, Riccitelli G, Mattioli F, Capra R, Stampatori C, Pagani E, et al. Multiple sclerosis: effects of cognitive rehabilitation on

- structural and functional MR imaging measures—an explorative study. *Radiology*. 2012;262(3):932–40.
98. Sastre-Garriga J, Alonso J, Renom M, Arevalo MJ, Gonzalez I, Galan I, et al. A functional magnetic resonance proof of concept pilot trial of cognitive rehabilitation in multiple sclerosis. *Mult Scler*. 2011;17(4):457–67.
 99. Goverover Y, Chiaravalloti ND, O'Brien AR, DeLuca J. Evidenced-based cognitive rehabilitation for persons with multiple sclerosis: an updated review of the literature from 2007 to 2016. *Arch Phys Med Rehabil*. 2018;99(2):390–407.
 100. Cerasa A, Gioia MC, Valentino P, Nistico R, Chiriaco C, Pirritano D, et al. Computer-assisted cognitive rehabilitation of attention deficits for multiple sclerosis: a randomized trial with fMRI correlates. *Neurorehabil Neural Repair*. 2013;27(4):284–95.
 101. Thaut MH, Peterson DA, McIntosh GC, Hoemberg V. Music mnemonics aid verbal memory and induce learning—related brain plasticity in multiple sclerosis. *Front Hum Neurosci*. 2014;8:395.
 102. Sigmundsdottir L, Longley WA, Tate RL. Computerised cognitive training in acquired brain injury: a systematic review of outcomes using the International Classification of Functioning (ICF). *Neuropsychol Rehabil*. 2016;26(5–6):673–741.
 103. Charvet LE, Yang J, Shaw MT, Sherman K, Haider L, Xu J, et al. Cognitive function in multiple sclerosis improves with telerehabilitation: results from a randomized controlled trial. *PLoS ONE*. 2017;12(5):e0177177.
 104. Grover SA, Aubert-Broche B, Fetco D, Collins DL, Arnold DL, Finlayson M, et al. Lower physical activity is associated with higher disease burden in pediatric multiple sclerosis. *Neurology*. 2015;85(19):1663–9.
 105. Grover SA, Sawicki CP, Kinnett-Hopkins D, Finlayson M, Schneiderman JE, Banwell B, et al. Physical activity and its correlates in youth with multiple sclerosis. *J Pediatr*. 2016;179:197–203 e2.
 106. Stephens S, Shams S, Lee J, Grover SA, Longoni G, Berenbaum T, et al. Benefits of physical activity for depression and fatigue in multiple sclerosis: a longitudinal analysis. *J Pediatr*. 2019;209:226–32 e2.
 107. Sikes EM, Richardson EV, Motl RW. A qualitative study of exercise and physical activity in adolescents with pediatric-onset multiple sclerosis. *Int J MS Care*. 2019;21(2):81–91.
 108. Rocca MA, Filippi M, Deiva K. Promoting physical activity to control multiple sclerosis from childhood. *Neurology*. 2015;85(19):1644–5.
 109. Langeskov-Christensen M, Bisson EJ, Finlayson ML, Dalgas U. Potential pathophysiological pathways that can explain the positive effects of exercise on fatigue in multiple sclerosis: a scoping review. *J Neurol Sci*. 2017;373:307–20.
 110. Heine M, van de Port I, Rietberg MB, van Wegen EE, Kwakkel G. Exercise therapy for fatigue in multiple sclerosis. *Cochrane Database Syst Rev*. 2015;9:CD009956.
 111. Cruickshank TM, Reyes AR, Ziman MR. A systematic review and meta-analysis of strength training in individuals with multiple sclerosis or Parkinson disease. *Medicine (Baltimore)*. 2015;94(4):e411.
 112. Latimer-Cheung AE, Pilutti LA, Hicks AL, Martin Ginis KA, Fenuta AM, MacKibbin KA, et al. Effects of exercise training on fitness, mobility, fatigue, and health-related quality of life among adults with multiple sclerosis: a systematic review to inform guideline development. *Arch Phys Med Rehabil*. 2013;94(9):1800 e3–1828.
 113. Andreasen AK, Stenager E, Dalgas U. The effect of exercise therapy on fatigue in multiple sclerosis. *Mult Scler*. 2011;17(9):1041–54.
 114. Motl RW, Gosney JL. Effect of exercise training on quality of life in multiple sclerosis: a meta-analysis. *Mult Scler*. 2008;14(1):129–35.
 115. Kjolhede T, Vissing K, Dalgas U. Multiple sclerosis and progressive resistance training: a systematic review. *Mult Scler*. 2012;18(9):1215–28.
 116. Sa MJ. Exercise therapy and multiple sclerosis: a systematic review. *J Neurol*. 2014;261(9):1651–61.
 117. Ensari I, Motl RW, Pilutti LA. Exercise training improves depressive symptoms in people with multiple sclerosis: results of a meta-analysis. *J Psychosom Res*. 2014;76(6):465–71.
 118. Morrison JD, Mayer L. Physical activity and cognitive function in adults with multiple sclerosis: an integrative review. *Disabil Rehabil*. 2017;39(19):1909–20.
 119. Sandroff BM, Motl RW, Scudder MR, DeLuca J. Systematic, evidence-based review of exercise, physical activity, and physical fitness effects on cognition in persons with multiple sclerosis. *Neuropsychol Rev*. 2016;26(3):271–94.
 120. Veauthier C, Gaede G, Radbruch H, Wernecke KD, Paul F. Sleep disorders reduce health-related quality of life in multiple sclerosis (Nottingham health profile data in patients with multiple sclerosis). *Int J Mol Sci*. 2015;16(7):16514–28.
 121. Sarraf P, Azizi S, Moghaddasi AN, Sahraian MA, Tafakhori A, Ghajarzadeh M. Relationship between sleep quality and quality of life in patients with multiple sclerosis. *Int J Prev Med*. 2014;5(12):1582–6.
 122. Veauthier C, Radbruch H, Gaede G, Pfueller CF, Dorr J, Bellmann-Strobl J, et al. Fatigue in multiple sclerosis is closely related to sleep disorders: a polysomnographic cross-sectional study. *Mult Scler*. 2011;17(5):613–22.
 123. Edwards KA, Molton IR, Smith AE, Ehde DM, Bombardier CH, Battalio SL, et al. Relative importance of baseline pain, fatigue, sleep, and physical activity: predicting change in depression in adults with multiple sclerosis. *Arch Phys Med Rehabil*. 2016;97(8):1309–15.
 124. Ghajarzadeh M, Sahraian MA, Fateh R, Daneshmand A. Fatigue, depression and sleep disturbances in Iranian patients with multiple sclerosis. *Acta Med Iran*. 2012;50(4):244–9.
 125. Veauthier C, Gaede G, Radbruch H, Gottschalk S, Wernecke KD, Paul F. Treatment of sleep disorders may improve fatigue in multiple sclerosis. *Clin Neurol Neurosurg*. 2013;115(9):1826–30.
 126. Cote I, Trojan DA, Kaminska M, Cardoso M, Benedetti A, Weiss D, et al. Impact of sleep disorder treatment on fatigue in multiple sclerosis. *Mult Scler*. 2013;19(4):480–9.
 127. Hughes AJ, Turner AP, Alschuler KN, Atkins DC, Beier M, Amtmann D, et al. Association between sleep problems and perceived cognitive dysfunction over 12 months in individuals with multiple sclerosis. *Behav Sleep Med*. 2018;16(1):79–91.
 128. van Geest Q, Westerik B, van der Werf YD, Geurts JJ, Hulst HE. The role of sleep on cognition and functional connectivity in patients with multiple sclerosis. *J Neurol*. 2017;264(1):72–80.
 129. Zafar AB, Ness J, Dowdy S, Avis K, Bashir K. Examining sleep, fatigue, and daytime sleepiness in pediatric multiple sclerosis patients. *Mult Scler*. 2012;18(4):481–8.
 130. Storm Van's Gravesande K, Blaschek A, Calabrese P, Rostasy K, Huppke P, Kessler JJ, et al. Fatigue and depression predict health-related quality of life in patients with pediatric-onset multiple sclerosis. *Mult Scler Relat Disord*. 2019;36:101368.
 131. Storm Van's Gravesande K, Calabrese P, Blaschek A, Rostasy K, Huppke P, Rothe L, et al. The Multiple Sclerosis Inventory of Cognition for Adolescents (MUSICADO): a brief screening instrument to assess cognitive dysfunction, fatigue and loss of health-related quality of life in pediatric-onset multiple sclerosis. *Eur J Paediatr Neurol*. 2019;23(6):792–800.
 132. van Kessel K, Moss-Morris R, Willoughby E, Chalder T, Johnson MH, Robinson E. A randomized controlled trial of cognitive behavior therapy for multiple sclerosis fatigue. *Psychosom Med*. 2008;70(2):205–13.

133. Mohr DC, Hart SL, Goldberg A. Effects of treatment for depression on fatigue in multiple sclerosis. *Psychosom Med.* 2003;65(4):542–7.
134. Veauthier C, Hasselmann H, Gold SM, Paul F. The Berlin Treatment Algorithm: recommendations for tailored innovative therapeutic strategies for multiple sclerosis-related fatigue. *EPMA J.* 2016;7:25.
135. Florea A, Maurey H, Le Sauter M, Bellesme C, Sevin C, Deiva K. Fatigue, depression, and quality of life in children with multiple sclerosis: a comparative study with other demyelinating diseases. *Dev Med Child Neurol.* 2019;62:241–4.
136. Hebert D, Geisthardt C, Hoffman H. Insights and recommendations from parents receiving a diagnosis of pediatric multiple sclerosis for their child. *J Child Neurol.* 2019;34(8):464–71.
137. Goldberg P, Fleming MC, Picard EH. Multiple sclerosis: decreased relapse rate through dietary supplementation with calcium, magnesium and vitamin D. *Med Hypotheses.* 1986;21(2):193–200.