

## Research Article

# The effect of combined training (core stability, resistance and balance) on serum BDNF and GDNF levels in individuals with multiple sclerosis

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## Abstract

Multiple sclerosis (MS) is a chronic neurological disease associated with neurodegeneration and impaired neurotrophic support. Neuromuscular training, through integrated activation of the nervous and muscular systems, may positively influence these neurotrophic factors. Therefore, this study investigated the effect of combined training on serum BDNF and GDNF levels in individuals with multiple sclerosis. Thirty women with multiple sclerosis (mean age: 36.2±5.8 years; BMI: 22.1±4.2 kg/m<sup>2</sup>) were purposively selected and randomly assigned to an experimental group (n=15) or a control group (n=15). The experimental group completed an eight-week combined training program (three sessions per week), consisting of core stability, resistance, balance, and agility exercises with progressive overload, while exercise intensity was controlled using the Borg perceived exertion scale., while the control group continued their usual daily activities. Blood samples were collected 24 hours before and 48 hours after the final training session, and the obtained serum was used to measure BDNF and GDNF levels. Data were analyzed using repeated-measures analysis of variance with a significance level of 0.05, employing SPSS software (version 27). The results demonstrated that neuromuscular training induced significant increases in serum BDNF ( $p=0.001$ ,  $\eta^2=0.80$ ) and GDNF ( $p=0.001$ ,  $\eta^2=0.79$ ) levels in the experimental group compared with the control group. Overall, the results of this study demonstrate that eight weeks of neuromuscular training elicit significant increases in serum BDNF and GDNF levels in women with multiple sclerosis. These findings indicate an enhanced neurotrophic environment that may support neural plasticity and neuroprotective mechanisms. Accordingly, neuromuscular training appears to be a safe and effective non-pharmacological strategy for improving neural health and potentially attenuating neurological dysfunctions associated with multiple sclerosis.

**Key Words:** Combined training, BDNF, GDNF, Multiple sclerosis

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## Introduction

Multiple sclerosis (MS) is a chronic, inflammatory, and autoimmune disorder of the central nervous system characterized by demyelination, axonal damage, and progressive impairment of neurological functions (Marzoli et al., 2026). The disease predominantly affects young and middle-aged adults and is considered one of the leading causes of non-traumatic neurological disability worldwide. In addition to immune dysfunction, growing evidence suggests that reduced neurotrophic support and impaired neuroprotective mechanisms play a significant role in the progression of motor and neurological symptoms in patients with MS (Karimimoghadem et al., 2023). In recent years, physical exercise has been increasingly recognized as a safe and effective non-pharmacological strategy for managing symptoms in patients with multiple (Marzoli et al., 2026). Regular physical training can help mitigate functional limitations in these individuals by improving motor coordination, enhancing neuromuscular control, and increasing the efficiency of neural pathways (Prosperini & Di Filippo, 2019). Unlike traditional resistance or aerobic exercise, neuromuscular training emphasizes the integration of the nervous and muscular systems, stimulation of proprioceptive receptors, and refinement of movement patterns, thereby providing a distinct and targeted stimulus to the nervous system (Yucekaya et al., 2025). Neuromuscular training involves the simultaneous activation of sensory, motor, and balance systems, which may promote adaptive responses within both central and peripheral neural networks (Taube et al., 2008). This form of training not only contributes to improved postural stability and reduced risk of falls in patients with multiple sclerosis (Zhang & Huang, 2025). But also enhances the efficiency of neural signal transmission by reducing excessive neural load Furthermore, emerging evidence suggests that neuromuscular training may exert neuroprotective effects through modulation of inflammatory responses and activation of neurotrophic signaling pathways (Andreu-Caravaca et al., 2025). Brain-derived neurotrophic factor (BDNF) is one of the most im-

-portant proteins involved in the regulation of neuronal survival, growth, and synaptic plasticity and plays a fundamental role in maintaining central nervous system function (Luo et al., 2025). Evidence suggests that in patients with multiple sclerosis, BDNF levels are reduced as a result of chronic inflammation, demyelination, and impaired neural signaling, which may contribute to the progression of motor and cognitive disabilities (Diechmann et al., 2021). Decreased BDNF expression in individuals with MS has therefore been considered a key indicator of impaired neuroplasticity and reduced capacity for neural repair (Farajnia et al., 2025). Previous studies have shown that regular physical activity can increase BDNF gene expression through enhanced neuronal activity, improved cerebral blood flow, and activation of CREB-dependent molecular signaling pathways (Lee et al., 2025; Oyowwi et al., 2025). In particular, neuromuscular training, due to its multidimensional nature and simultaneous engagement of sensory, motor, and balance systems, may provide a stronger stimulus for activating neurotrophic mechanisms in patients with multiple sclerosis (Landers et al., 2025). Therefore, this study was designed to test the hypothesis that an 8-week HIIT program and multi-strain probiotic supplementation, individually and in combination, would upregulate intestinal FXR and PPAR- $\gamma$  expression in a rat model of T2DM. We further hypothesized that the combined intervention would produce synergistic effects, reflecting enhanced restoration of intestinal metabolic signaling.

Glial cell line-derived neurotrophic factor (GDNF) is another critical neurotrophic factor involved in neuronal protection, particularly for motor and dopaminergic neurons (Soke et al., 2021). GDNF plays an essential role in neuronal survival, axonal regeneration, and synaptic regulation, and reductions in its levels have been associated with the progression of neurological dysfunction and deterioration of motor performance (Massah & Taghian, 2026). In patients with multiple sclerosis, decreased GDNF levels may reflect weakened neuroprotective mechanisms and a diminished capacity for neural regeneration (Soke et al., 2021). Neuromuscular training, by promoting dynamic interactions between skeletal muscle and the nervous system, may play a significant role in stimulating GDNF gene expression. By reducing neural stress, improving motor coordination, and modulating inflammatory responses, this form of training may create a favorable environment for the activation of neurotrophic signaling pathways (Tang et al., 2025). Although accumulating evidence highlights the beneficial effects of physical activity on neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF), most existing studies have primarily focused on aerobic or resistance exercise, while the specific role of neuromuscular training remains insufficiently explored. In particular, direct evidence regarding the effects of neuromuscular training on BDNF and GDNF gene expression in patients with MS is limited.

Furthermore, it is not yet fully understood to what extent improvements in sensorimotor integration and neuromuscular coordination induced by neuromuscular training may activate neurotrophic signaling pathways through the reduction of neural stress and modulation of inflammatory responses. Therefore, examining the effects of neuromuscular training on BDNF and GDNF gene expression may address an important gap in the literature and provide novel insights for the development of targeted exercise-based interventions aimed at enhancing neuromuscular and neural health in individuals with MS. Accordingly, in light of the existing gaps in the literature, the present study aimed to investigate the effects of eight weeks of combined training on serum levels of BDNF and GDNF in patients with multiple sclerosis.

## Materials and methods

### Experimental design

This study was a quasi-experimental and applied research conducted to investigate the effects of eight weeks of neuromuscular training on BDNF and GDNF levels in women with multiple sclerosis. The statistical population consisted of all women with relapsing–remitting multiple sclerosis (RRMS) aged 30 to 50 years residing in Isfahan, Iran. Following initial screening, 30 participants were selected using convenience sampling and then randomly assigned to two groups. The neuromuscular training group included 15 women with multiple sclerosis whose blood samples were collected 48 hours before the start of the training period, and body composition indices were also assessed (Taghizadeh et al., 2021). Participants in this group then performed neuromuscular training for eight weeks, and blood samples were collected again 48 hours after the final training session to evaluate the effects of the intervention on the study variables. The control group consisted of 15 women with multiple sclerosis who did not participate in any regular exercise program and continued their usual daily activities. Blood samples were collected at the same time points as in the training group during the pre-test and post-test stages, and body composition indices were also measured. Blood samples were collected 48 hours after the final training session to minimize acute exercise effects and to assess resting levels reflecting chronic training adaptation. The sample size was estimated using G\*Power software, considering a significance level of 0.05, a statistical power of 80%, and an effect size of 0.3. The inclusion criteria included a confirmed diagnosis of RRMS based on the revised McDonald criteria, the ability to perform physical activity and participate in exercise training, absence of pregnancy, no bone fractures within the previous six months, and no severe neurological disorders prior to the start of the study. Participants were also required to be within the 30–50-year age range. The mean Expanded Disability Status Scale (EDSS) score of the participants was 2, with a range of 1 to 4.5.

## Combined training

Each training session lasted approximately 60 minutes and was conducted three times per week for eight weeks. Sessions began with a 10-minute preparatory phase consisting of stretching and functional movements, followed by a 45-minute main exercise phase, and concluded with a 5-minute cool-down period. The training program was designed according to the principle of progressive overload, such that the number of repetitions, duration of exercises, resistance levels (TheraBands), and types of exercises were gradually increased throughout the intervention period. The neuromuscular training program included exercises emphasizing core stability, muscular strengthening, balance, and agility. During the final two weeks of the intervention, plyometric exercises with varying intensities were incorporated. Exercises were performed in a circuit-based format, in which each participant completed 8 to 15 repetitions of a specific movement at each station before rotating to the next station. All exercises were performed in three sets with one-minute rest intervals, and proper movement technique as well as maintenance of a neutral spinal posture were emphasized throughout the sessions. Exercise intensity was monitored using the Borg perceived exertion scale. The exercises were performed at very low intensity during weeks one and two, low intensity during weeks three to five, and moderate intensity during weeks six to eight (perceived exertion rating of 9–13). All participants in the experimental group followed an identical training program, which was developed based on established guidelines aimed at improving muscular strength, proprioceptive function, and balance in individuals with multiple sclerosis and osteoarthritis. All training sessions were supervised and conducted by a qualified exercise science professional.

## Sampling and measuring biochemical variables

Blood samples were collected from participants in both groups 48

hours before the first training session and 48 hours after the final training session by a laboratory technician. The samples were centrifuged at 3000 rpm for 10 minutes, and plasma was separated from other blood components. The obtained plasma was transferred into 1-mL microtubes and stored at  $-80^{\circ}\text{C}$  until further analysis. Blood sampling was performed after a 12-hour overnight fast and in a resting condition. At each stage, 5 mL of blood was drawn from the antecubital vein of the left arm while participants were in a seated position. Blood samples were collected into sterile tubes. Following post-test sampling, all blood samples were removed from the freezer on the same day and analyzed according to standard protocols. Plasma levels of BDNF and GDNF were measured using commercially available human ELISA kits (Abcam,US) with picogram-per-milliliter sensitivity. Given that the present study was conducted on human participants and involved a relatively long-term exercise intervention, all ethical principles of research were fully observed. Ethical approval was obtained from the Ethics Committee of Islamic Azad University, Isfahan (Khorasgan) Branch (Approval Code: IR.IAU.KHUISF.REC.1404.525).

## Statistical analysis

In the present study, data were described using mean  $\pm$  standard deviation. In addition, repeated-measures analysis of variance (ANOVA) was used to compare variables between the two groups. Data analysis was performed using SPSS software (version 27) at a significance level of 0.05.

## Results

Thirty patients with multiple sclerosis aged 30–50 years were enrolled in the study and randomly assigned to two groups: a control group ( $n=15$ ) and an experimental group (neuromuscular training,  $n=15$ ). The participants' demographic characteristics, including age, height, weight, and body mass index (BMI), are presented in Table 2. After confirming the normal distribution of

**Table 1.** Combined training protocol

Exercise Category	Content of Training	Training Weeks	Sets $\times$ Repetitions
Core Stability	Supine abdominal draw-in, pelvic tilt, Abdominal draw in with knee to chest, Supine butt lift with arms at side, Quadruped with leg lift, Quadruped opposite arm/leg	Weeks 1–6	3 $\times$ 8–12
Strength	Shoulder and hip flexion with theraband (red, green, blue, and black) Abduction of shoulder and hip with theraband (red, green, blue, and black) Extension of shoulder and hip joint with theraband (red, green, blue, and black) Flexion of hip with theraband (red, green, blue, and black) Flexion of knee with theraband (red, green, blue, and black)	Weeks 1–8	3 $\times$ 8–15
Balance	Static lunge with support Tandem stance Static lunge without support Tandem stance on the foam with support Tandem stance on the foam without help	1 3 8 1-2 3 8 and 10 2 3 8 and 12 3-4 3 8 and 12 and 15	Weeks 1–7 3 $\times$ 8–15
Agility	Sit-to-stand, Walking between two cone obstacles, Walk diagonally between two obstacles, Zigzag walking between obstacles, Fast walking between two cone obstacle, Fast walking between two obstacles diagonally, Zigzag running between obstacles	Weeks 1–7	3 $\times$ 3–15
Plyometric	Dynamic lunge with return, Side step up (low height), Vertical jump, Pair jump at specified locations, Hopping (jumping from one leg to the same leg) at specified locations	Weeks 6–8	3 $\times$ 3–12

**Table 2.** Distribution of age, height, weight and BMI of the subjects in the two group.4

Group	N	age (year)	height (cm)	weight (kg)	BMI(kg/m <sup>2</sup> )
Neuromuscular training	15	36.2 ± 5.8	161.5 ± 6.1	57.3 ± 10.8	22.1 ± 4.2
Control	15	37.1 ± 5.5	160 ± 5.2	58.2 ± 9.7	22.4 ± 3.1

**Table 3.** Results of the repeated-measures analysis of variance in the studied groups

Variable	Time	Mean ± S. D		Time	Groups	Interaction
		Control	Training			
BDNF	pre	227.77±26.30	228.78±60.46	P=0.0001	P=0.0001	P=0.0001
	post	223.07±10.85	450.43±24.31			
				( <sup>2</sup> η=0.79)	( <sup>2</sup> η=0.99)	( <sup>2</sup> η=0.8)
GDNF	pre	103.51±19.07	101.78±17.01	P=0.0001	P=0.0001	P=0.0001
	post	94.60±11.50	188.05±9.32			
				( <sup>2</sup> η=0.83)	( <sup>2</sup> η=0.88)	( <sup>2</sup> η=0.79)

the demographic variables in both groups, an independent samples t-test was used to compare the group means. The results of the independent t-test indicated no significant differences between the two groups in terms of age (p=0.81), height (p=0.96), weight (p=0.87), or body mass index (p=0.56). The results of the measurements of BDNF and GDNF parameters in the control and experimental groups are presented in Table 3. Given the study design, a 2×2 repeated-measures analysis of variance (ANOVA) was used for data analysis. The underlying assumptions of the model were examined, and the results are reported as follows. According to the Shapiro–Wilk test, the assumption of normality of the error distribution was not violated for BDNF at the pretest (p=0.576) and posttest (p=0.231), nor for GDNF at the pretest (p=0.953) and posttest (p=0.828). In addition, based on Levene’s test, the assumption of homogeneity of error variances between the two groups was not violated for BDNF at the pretest (p=0.953) and posttest (p=0.150), nor for GDNF at the pretest (p=0.795) and posttest (p=0.483).

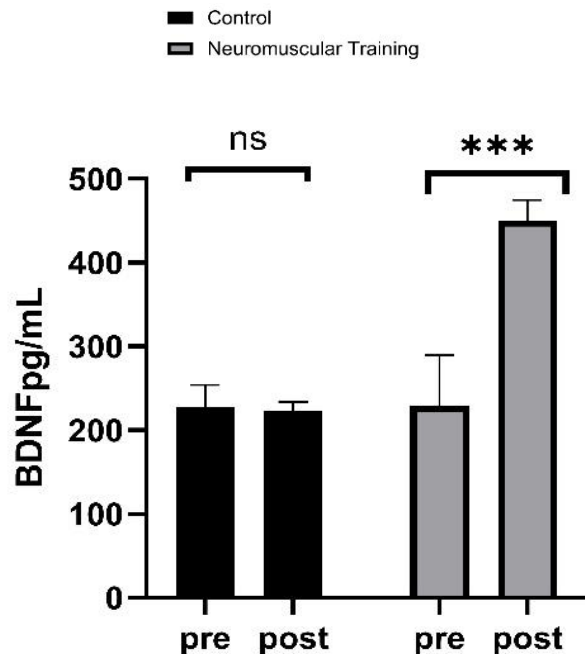
Regarding BDNF, the results of the repeated-measures ANOVA presented in Table 3 indicated that the main effect of time (F(1,28)=107.861, p=0.0001, η<sup>2</sup>=0.79), the main effect of group (F(1,28)=5369.17, p=0.0001, η<sup>2</sup>=0.99), and the group×time interaction effect (F(1,28)=117.42, p=0.0001, η<sup>2</sup> =0.80) were all statistically significant at the 0.05 level (Figure 1).

Similarly, for GDNF, a significant main effect of time (F (1, 28)= 146.07, p=0.0001, η<sup>2</sup>=0.83), a significant main effect of group (F(1,28)=111.60, p=0.001, η<sup>2</sup>=0.88), and a significant group× time interaction effect (F(1,28)=221.14, p=0.001, η<sup>2</sup>=0.79) were observed (Figure 2).

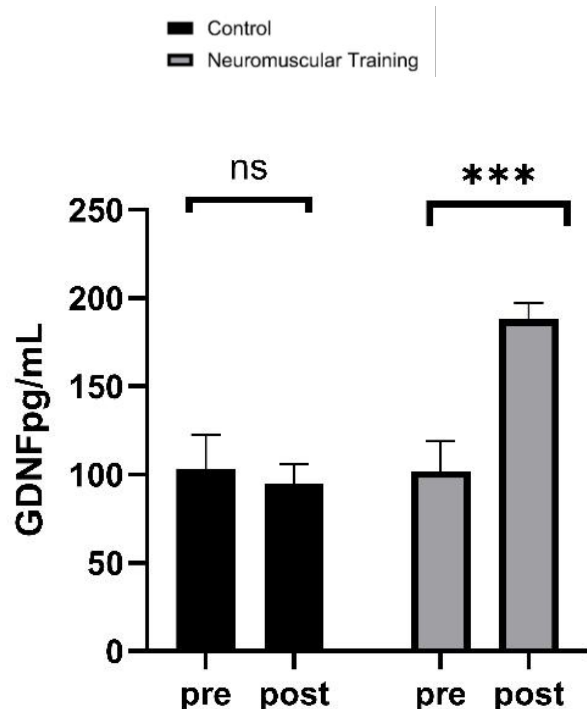
### Discussion

Studies show that in patients with multiple sclerosis, eight weeks of neuromuscular training can significantly increase neurotrophic factors such as BDNF and GDNF; this rise helps improve neuronal function, reduce myelin damage, and enhance cognitive

and motor abilities. Therefore, planning neuromuscular training is recommended as an effective complementary approach in managing MS (Luo et al., 2025). Schultz and colleagues showed that eight weeks of dual-cycle cycling exercise did not produce a significant change in BDNF levels in MS patients (Schulz et al., 2010). Also, Gold et al showed that a 30-minute cycling session at 60 % of VO<sub>2</sub>max did not change BDNF (Gold SM, 2003). On the other hand, Bansi et al showed that BDNF levels in MS patients increased significantly after 3 weeks of aerobic exercise at 60 % of VO<sub>2</sub>max (Bansi et al., 2013) Wens et al. reported increased BDNF concentrations after 24 weeks of aerobic-resistance training(Wens C, 2016.). Brecken et al found that a single 30-minute cycling session significantly raised BDNF



**Figure 1.** Pre- and post-test means (±SD) of serum BDNF levels in the control and neuromuscular training groups based on the results of repeated-measures analysis of variance. \* indicates significant between- and within-group differences at p < 0.05.



**Figure 2.** Pre- and post-test means ( $\pm$ SD) of serum GDNF levels in the control and neuromuscular training groups based on the results of repeated-measures analysis of variance. \* indicates significant between- and within-group differences at  $p < 0.05$ .

in progressive MS patients, but no change was observed after 24 training sessions. The present study found that eight weeks of neuromuscular training increased BDNF levels in patients with multiple sclerosis. Differences in the type and duration of training protocols, variations in the characteristics of the subjects, and discrepancies in laboratory methods may account for the differences observed in the results obtained. Physical activity leads to the activation of CREB (cAMP Response Element-Binding Protein) and the MAPK (Mitogen-Activated Protein Kinase) pathway in the hippocampus (Lee et al., 2025). The MAPK signaling cascade results in the phosphorylation of CREB and synapsin I. CREB plays a crucial role in synaptic plasticity and memory, and its phosphorylation induces the expression of the BDNF gene. In addition, physical activity regulates Trk receptors in the brain, which ultimately leads to an increase in BDNF levels in the brain. In addition, this type of training reduces neuroinflammation and modulates inflammatory cytokines, thereby providing a favorable environment for the enhanced action of BDNF, which overall can contribute to improvements in motor and cognitive function in individuals with multiple sclerosis (Oyovwi et al., 2025). The results of the present study also showed that eight weeks of neuromuscular training led to an increase in GDNF levels in patients with multiple sclerosis. Rho et al, in a study, examined the effects of an eight-week aerobic training program (three sessions per week, 40 minutes per sess-

-ion, treadmill exercise at 70% of maximal heart rate) on the levels of neurotrophic factors in obese and non-obese individuals. The results showed that although serum levels of BDNF and NGF increased in both groups after the training intervention, no significant difference was observed between the two groups (Roh & So, 2017). McCoy et al. investigated the effects of two weeks of forced wheel running exercise on GDNF levels in skeletal muscle of rats. The results demonstrated that increased physical activity led to an elevation in the protein content of GDNF in muscle tissue. Accordingly, the positive effects of physical activity on GDNF may provide a beneficial explanation for its role in protein production and the recovery of the nervous system (McCullough MJ & JM, 2011). Moreover, the findings of the present study are not consistent with those reported by Bansi et al. Bansi et al. investigated the effects of three weeks of regular endurance training performed in water and on land on cytokines and neurotrophic factors in middle-aged patients with multiple sclerosis. Their results indicated that changes in cytokines and neurotrophins did not differ significantly between the two exercise groups following the endurance training programs, and no significant differences were observed in NGF levels (Bansi J, 2013).

Neuromuscular training, by engaging neural coordination, motor control, and repeated activation of motor units, leads to increased activity of motor neurons. Evidence from animal studies indicates that motor neuron activation and forced limb use result in increased expression and protein content of GDNF in skeletal muscle and motor-related brain regions (Soke et al., 2021). In multiple sclerosis, this mechanism may contribute to enhanced survival and functional maintenance of motor neurons. Multiple sclerosis is associated with chronic inflammation and oxidative stress, both of which contribute to reduced expression of neurotrophic factors. Regular exercise, particularly neuromuscular training performed at controlled intensities, leads to a reduction in pro-inflammatory cytokines such as TNF- $\alpha$  and inflammatory IL-6, along with an increase in anti-inflammatory cytokines including IL-10. This anti-inflammatory environment may provide more favorable conditions for the synthesis and secretion of GDNF in skeletal muscle and the central nervous system (Schulz et al., 2010). The observed improvements may be partly attributed to neurobiological adaptations induced by neuromuscular training. In the present study, significant changes were observed in serum levels of BDNF and GDNF, indicating enhanced neuroplasticity and neural adaptation in individuals with multiple sclerosis. BDNF plays a key role in synaptic plasticity, neuronal survival, and motor learning, whereas GDNF is involved in the protection and regeneration of motor neurons. Therefore, improvements in functional outcomes in individuals with multiple sclerosis may, at least in part, be mediated by increased serum levels of these neurotrophic factors in response to neuromuscular training.

The simultaneous increase in BDNF and GDNF observed in the present study may indicate a synergistic neuroprotective adaptation to exercise in individuals with multiple sclerosis. BDNF exerts its biological effects primarily through activation of the TrkB receptor, leading to stimulation of downstream signaling cascades such as PI3K/Akt and MAPK/ERK pathways, which promote neuronal survival, synaptic plasticity, and remyelination (Huang & Reichardt, 2001). In parallel, GDNF supports motor neuron survival and modulates neuroinflammatory responses via GFR $\alpha$ 1 and RET receptor signaling (Airaksinen & Saarna, 2002). The concurrent elevation of these neurotrophic factors may therefore reflect a coordinated mechanism enhancing neuroprotection and neural repair processes in MS. From a mechanistic perspective, the proposed “muscle–brain cross-talk” may underlie these adaptations. Exercise-induced skeletal muscle contractions stimulate the release of myokines and metabolic mediators that influence central nervous system function, either directly or indirectly, and contribute to increased neurotrophic factor expression (Wrann et al., 2013). Such activity-dependent signaling may enhance neuroplasticity and resilience in demyelinating conditions. Therefore, the observed increases in BDNF and GDNF may represent an integrated peripheral-to-central adaptive response to the applied exercise protocol in the present study, although efforts were made to control participants’ dietary programs, certain limitations remained, including the lack of complete supervision over dietary intake throughout the entire intervention period. Additionally, non-exercise physical activities were not fully controlled, which may have influenced the outcomes. Another important limitation of this study is the relatively small sample size ( $n = 15$  per group). Although the sample size was determined a priori using G\*Power to ensure adequate statistical power, small samples may limit the stability of parameter estimates and reduce the generalizability of the findings. Furthermore, the large effect sizes observed ( $\eta^2 \approx 0.80$ ) should be interpreted with caution, as effect size estimates derived from small samples are more susceptible to inflation. Therefore, replication of these findings in studies with larger and more diverse samples is recommended to confirm the robustness and external validity of the results. Finally, to better elucidate the underlying mechanisms of the observed effects, future studies with larger cohorts and more rigorous methodological controls are warranted.

## Conclusion

The results of the present study indicate that combined training, as an effective non-pharmacological intervention, leads to a significant increase in serum levels of BDNF and GDNF in individuals with multiple sclerosis. These changes are likely mediated through improved neuromuscular–neural interactions, increased motor neuron activity, and modulation of inflammatory

responses. Accordingly, neuromuscular training may be considered a safe and complementary strategy in rehabilitation programs for individuals with multiple sclerosis.

## What is already known on this subject?

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system characterized by demyelination and impaired neural signal transmission. This condition can lead to a wide range of symptoms, including muscle weakness, motor dysfunction, impaired balance, chronic fatigue, and cognitive deficits, ultimately affecting patients’ quality of life. Immune, genetic, and environmental factors play important roles in the onset and progression of MS, and evidence suggests that chronic inflammation and alterations in neurotrophic factors are key mechanisms involved in its pathophysiology.

## What this study adds?

Combined training, by simultaneously engaging the nervous and muscular systems, can play an effective role in modulating neurotrophic factors. Evidence suggests that this type of training, through increased targeted motor activity, improved neuromuscular coordination, and reduced neural stress, leads to enhanced expression and secretion of key neurotrophic factors such as BDNF and GDNF. Elevated levels of these factors may contribute to improved neuronal survival and plasticity, facilitation of neural repair, and strengthening of synaptic connections, ultimately resulting in improved neural and motor function, particularly in individuals with neurological disorders such as multiple sclerosis.

### Organ Cross-Talk Tips:

- Neuromuscular training generates targeted motor signals from skeletal muscle to the central nervous system, stimulating the release of key neurotrophic factors such as BDNF and GDNF, which play essential roles in neuronal survival and plasticity.
- The exercise-induced elevation of BDNF and GDNF suggests that improvements in muscular function and neuromuscular coordination can positively influence brain and spinal cord health through neural and circulating pathways, thereby strengthening muscle–brain cross-talk.

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None.

## Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Compliance with ethical standards

**Conflict of interest** the authors declare that there is no conflict of interest in the present research.

**Ethical approval** Given that the present study was conducted on human samples with exercise intervention over a relatively long period of time, in full compliance with the ethical principles of research, approval was received from the ethics committee with the ID number IR.IAU.KHUISF.REC.1404.525 from the Islamic Azad University, Isfahan (Khorasgan) Branch.

**Informed consent** Participants signed an informed consent form prior to participation in the study.

## Author contributions

**Conceptualization:** A.S.H., K.J.; **Methodology:** A.S.H., K.J.,F.T.; **Software:** A.S.H., K.J.; **Validation:** A.S.H., K.J.,F.T.AA.A; **Formal analysis:** K.J.; **Investigation:** A.S.H., K.J.,F.T.; **Resources:** A.S.H., K.J.,F.T.AA.A.; **Data curation** A.S.H., K.J.,F.T.; **Writing - original draft:** Z A.S.H., K.J.; **Writing–review & editing:** A.S.H., K.J.,F.T.; **Visualization:** A.S.H., K.J.,F.T.AA.A.; **Supervision:** K.J.; **Project administration:** A.S.H., K.J.; **Funding acquisition:** A.S.H.

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