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Immediate and short-term effect of physical exercise on BDNF in multiple sclerosis patients: a systematic review and meta-analysis

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Low brain-derived neurotrophic factor (BDNF) concentrations have been found in individuals with multiple sclerosis (MS). Physical exercise is an effective strategy for acutely increasing the levels of this neurotrophin in various populations; nevertheless, definitive results are still required for individuals with MS. Thus, this systematic review with meta-analysis aimed to analyze the acute and short-term effects of physical exercise on BDNF concentrations in MS patients. In this pre-registered systematic review (PROSPERO; ID: CRD42024505920), six electronic databases (PubMed-Medline, Scopus, Web of Science, SportDiscus, EbscoHost, and Cochrane) were searched by two independent researchers to identify eligible studies investigating the acute or short-term effects (≤ 3 weeks) of physical exercise sessions on blood concentration of BDNF in MS. Studies that used a sample population with other pathologies or did not provide or specify numerical data on the specified variables were excluded. After applying the inclusion and exclusion criteria, nine studies were included. A total sample of 259 people with MS were analyzed. Effect sizes of outcomes were presented as standardized mean difference (SMD) and 95% confidence intervals (95%CI). The effect estimation was computed using the inverse variance random effects method. Immediately after a session, a significant increase in BDNF was observed (large standardized mean difference (SMD) = 1.52, $p = 0.001$, I2 = 95). A significant effect (SMD = 0.27, $p = 0.05$; I^2=0%) was found after three weeks of physical training on the BDNF. Our study indicates that physical exercise is an appropriate stimulus to increase BDNF release in MS patients. The acute and short-term increases in this neurotrophin reflect physical exercise's potential and interesting neuroprotective character in populations with neurodegenerative diseases.

Trial registration: This study was preregistered in the International Prospective Register of Systematic Review (PROSPERO) with the following registration number: CRD42024505920.

Keywords Acute exercise, Brain-derived neurotrophic factor, Neurotrophin, Strength training, Neurological disease

The brain-derived neurotrophic factor (BDNF), discovered in the 1980s[1], is a protein belonging to the neurotrophin growth factor family[2]. This neurotrophin binds to a tyrosine kinase receptor, triggering the phosphorylation of tyrosine TrkB and activating its cytoplasmic segments and the BDNF–brain TrkB kinase. The kinase segment recruits and activates specific proteins in the cytoplasm to initiate signaling pathways that control various brain functions, including cognition, plasticity, memory, and learning[3]. BDNF has been attributed to the

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capacity to enhance synaptic plasticity, brain circuits, neural connectivity, and angiogenesis[4,5]. In this context, concentrations of BDNF have been associated with functional changes in the brain, such as neurogenesis and increased hippocampal volume or survival of *de novo* hippocampal neurons[4]. BDNF release is not exclusive to neurons; other cells, including skeletal muscle, fibroblasts, or glial cells, also release this neurotrophin[6]. It has been demonstrated that peripheral BDNF (released, for example, by skeletal muscles) can cross the blood-brain barrier[7], which could lead to an improvement in the aforementioned neural improvements. Consequently, previous research has identified high concentrations of BDNF in organs such as the lungs, liver, heart, and spleen, as well as in the brain itself[6].

Low concentrations of BDNF have been found in individuals with dementia[8], depression[9], amyotrophic lateral sclerosis (ALS)[10], Alzheimer's disease[11], or multiple sclerosis (MS)[12]. Particularly in MS, a partially unknown etiology progressive neurological disease-causing axonal degeneration, some studies have established that plasma and serum levels of BDNF decrease during relapses[12], while other studies have found slight increases in BDNF after a disease relapse, suggesting a role for this neurotrophin during the recovery of acute demyelinating inflammatory lesion[13,14]. Additionally, BDNF values have been shown to decrease as the years of the disease progress[12]. However, research conducted by Nociti and Romozzi[15] demonstrated that BDNF levels increase during the demyelination process, presumably to compensate for glial and neuronal damage.

Substantial evidence supports the effectiveness of physical exercise in reducing the risk of metabolic, musculoskeletal[16], and mental illnesses[17]. Randomized controlled trials (RCTs) and systematic reviews with meta-analyses indicate that acute and chronic physical exercise induces the release of BDNF[18–21], with this neurotrophin being one of the factors underlying the mechanisms explaining the relationship between exercise and neural improvements. The acute increase in BDNF release following a single session of physical exercise is particularly relevant due to its association with transient synaptic plasticity and immediate neuroprotective mechanisms, including enhanced neurotransmission, facilitation of long-term potentiation, and modulation of inflammatory responses[18,19]. These short-term neurobiological effects may be especially important in individuals with MS, where neuronal damage and repair processes coexist dynamically. On the other hand, short-term exercise interventions (up to three weeks) allow for the evaluation of early neuroadaptive responses—such as cumulative BDNF release, receptor sensitivity modulation, and preliminary improvements in functional outcomes—without the interference of structural or systemic changes induced by long-term training[22]. This temporal distinction is physiologically meaningful, as acute responses primarily reflect immediate neuromodulatory effects, while short-term interventions may reveal the onset of adaptive processes. Evaluating both timeframes separately provide a more nuanced understanding of how exercise influences neuroplasticity and neuroprotection in MS and may inform the timing and design of therapeutic interventions targeting early phases of rehabilitation.

Physical exercise is a recognized non-pharmacological tool that enhances the quality of life and functionality in individuals with MS[23,24]. Furthermore, previous studies indicate increases in BDNF concentration after physical training programs, which are associated with improvements in cognition, motor control, or autonomy in this population[25,26]. However, the acute and short-term effect of exercise on BDNF levels in MS patients is unclear, with studies presenting conflicting results[27–29]. Therefore, considering that previous systematic reviews did not focus on the acute and short-term effects of physical exercise on this neurotrophin, along with the publication of a large number of recent scientific studies not included in previous reviews, it is necessary to review and meta-analyze the existing literature to understand the acute and short-term impact of exercise on BDNF levels in this population. Hence, this systematic review with meta-analysis aimed to analyze the acute and short-term effects of physical exercise on BDNF concentrations in MS patients.

Materials and methods

Design

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement[30] was adhered to for this systematic review and meta-analysis. The study was registered in the International Prospective Register of Systematic Review (PROSPERO; CRD42024505920). The review methods were established prior to the systematic review.

Data sources and searches

PubMed-Medline, Scopus, Web of Science, SportDiscus, EbscoHost, and Cochrane databases were used to search for articles from inception through 01 April 2025. Two authors (LAC and DJRC) independently reviewed the titles and abstracts, identified and read full-text articles, extracted relevant information from the included articles, and assessed the methodological quality of the included studies. In the event of disagreement between the two reviewers, a third author was invited to reach an agreement (JARA). The following keyword strategy was used: ("Multiple Sclerosis" OR MS OR sclerosis) AND (exercise OR training OR "physical activity" OR "physical therapy" OR fitness) AND (BDNF OR "brain-derived neurotrophic factor" OR "neurotrophic factor" OR "growth factor" OR neuroplasticity OR plasticity). Specific search strategy for each database can be consulted in Supplementary Table 1.

Selection criteria

The inclusion and exclusion criteria for studies, structured according to PICOS, were as follows: Population: Adults diagnosed with MS according to the McDonald criteria[31]. Studies were excluded if the population included pediatric MS or individuals with other pathologies. Intervention: Physical training or exercise interventions of acute (single session) or short-term duration (≤ 3 weeks). Studies must have assessed blood BDNF concentrations at specific time points following exercise: (a) Time point 1: immediately to 30 min post-exercise; (b) Time point 2: 30–60 min post-exercise; (c) Time point 3: 60–120 min post-exercise; (d) Time point 4: more than 120 min

post-exercise. Comparison: Resting or baseline BDNF measurements taken before the intervention served as the comparator. Studies that did not provide or specify pre- and post-exercise BDNF levels were excluded[32]. Outcomes: Quantitative measurement of BDNF in serum, plasma, or whole blood. Eligible assays included enzyme-linked immunoassays (ELISA) or other validated quantitative methods. Study design: Randomized controlled RCTs or non-RCT. The following were excluded: case reports, case series, abstracts, protocols, letters, commentaries, review articles, and animal or in vitro studies. In addition, only studies published in English or Spanish were included.

Outcome variable

The primary outcome was the change in peripheral BDNF concentrations before and after exercise training sessions. The research question was based on the PICO strategy[33] (**P**articipants: individuals with MS, **I**ntervention: post-exercise physical activity values of BDNF in MS patients, **C**omparison: pre-exercise physical activity values of BDNF in MS patients, and **O**utcome: blood concentrations of BDNF).

Study selection and data extraction

Two authors (LAC and DJRC) identified pertinent articles, and in case of discrepancy, deliberations ensued with a third author (JARA) for resolution. Additionally, the bibliographies of the included articles underwent scrutiny to uncover additional relevant studies, and the corresponding authors of some articles were contacted for unreported information. Two authors (LAC and DJRC) individually extracted data from the articles included. The following information was coded: site and country of the study, sex, age (years), weight (kg), height (cm), body mass index (BMI, $kg{\cdot}m^{-2}$) Expanded Disability Status Scale (EDSS) score (a.u.), time since diagnosis of MS (years), and phenotype of MS (relapsing-remitting MS, [RRMS], primary-progressive MS [PPMS] or secondary-progressive MS [SPMS]). The characteristics of physical exercise sessions included exercise type (aerobic training, resistance training, or others), exercise modality (continuous or interval), program duration (weeks), session length (min), frequency (days/week), and intensity (% of peak heart rate, % of peak or maximal oxygen consumption [i.e., VO_2 peak or VO_2 max]). Database search was done manually to find eligible studies. After a thorough assessment, the selected studies were stored and exported to the Endnote 9X software.

Risk of bias assessment (study quality)

The risk of bias assessment for randomized trials was conducted using the Cochrane Risk-of-Bias tool (RoB 2.0)[34]. This tool evaluated various domains, including the randomization process (allocation sequence and concealment), deviations from intended interventions (occurrence of non-protocol interventions and failures in implementing the protocol interventions that could affect the outcomes, or non-adherence to the assigned intervention by participants), missing outcome data (evidence regarding the result was not biased by missing outcome data), measurement of the outcome (measurement error for continuous outcomes differential or non-differential in relation to intervention assignment), and selection of the reported results. Each domain was categorized as "low risk of bias", "some concerns" or "high risk of bias"[35]. The overall risk of bias for each study was then classified as (1) "low risk of bias" if all domains had a low risk, (2) "some concerns" if at least one domain raised concerns but none had a high risk, or (3) "high risk of bias" if there was a high risk in at least one domain or some concerns in multiple domains[34].

For non-randomized controlled trials (non-RCTs) and quasi-experimental studies, the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I)[36] was employed. Seven domains were assessed, including (1) cofounding, (2) selection of participants into the study, (3) classification of the interventions, (4) biases due to deviations from intended interventions, (5) missing data, (6) measurement of outcomes, and (7) selection of the reported results. Each domain was rated as having low, moderate, serious, or critical risk of bias. Studies were categorized as (1) "low risk of bias" when all domains had a low risk; (2) "moderate risk of bias" when all domains had low or moderate risk; (3) "serious risk of bias" when at least one domain had a serious risk but none had a critical risk, and (4) "critical risk of bias" when at least one domain had a critical risk[36]. Two independent reviewers (LAC and DJRC) assessed the risk of bias, with a third reviewer (JARA) consulted for resolution in case of disagreements.

Data synthesis and statistical analysis

We conducted the meta-analysis and statistical analysis utilizing Review Manager Software (RevMan 5.2). Effect sizes of outcomes were presented as standardized mean difference (SMD) and 95% confidence intervals (95%CI), as the included studies reported BDNF concentrations using different analytical methods and units of measurement (e.g., pg/mL, ng/L). The effect estimation was computed using the inverse variance random effects method. Heterogeneity was assessed using the I^2 statistic. The following thresholds were applied as general guidance for interpretation: 0–40% might not be important; 30–60% may represent moderate heterogeneity; 50–90% may represent substantial heterogeneity; and 75–100% may indicate considerable heterogeneity. In addition, between-study variance was evaluated using the τ^2 statistic, with values $\tau^2 > 1$ interpreted as indicating substantial heterogeneity[37]. The statistical significance threshold was set at a $p < 0.05$. Additionally, effect size threshold values were defined as 0.2 for a small effect, 0.5 for a moderate effect, and 0.8 for a large effect[38]. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used to assess the certainty of the evidence[39].

Effects of covariates: meta-regression and sub-group analysis

Sub-group analysis utilized the Review Manager software (RevMan 5.2) to investigate the impact of categorical variables. Thus, studies were categorized to assess the influence of various parameters in physical exercise sessions, including intensity (classified as low [< 40% VO_2max], moderate [40-80% VO_2max][40], and high [> 80%

VO_2max]), session duration (categorized as short duration [≤30 min] or long duration [>30 min]), interval or continuous training, and cycling or walking modality. For studies missing intensity reporting via VO_2max values, established equivalence tables from prior publications were employed[41]. Subsequently, the SMD and 95% CI were calculated before and after the session in each study. The effect estimate was derived utilizing the inverse variance random effects method. Group differences were assessed using the chi-square test. Additionally, a random-effects restricted maximum-likelihood estimator was used to analyze the effects of continuous covariates: age (yr.), EDSS, duration of disease (yr.), and session duration (min). These analyses were conducted using the JASP software, version 0.14. Significance was set at $p < 0.05$.

Results

Search results and characteristics of included studies

The initial search identified 8778 studies. When the duplicates were removed, 4882 studies were screened, and 82 full-text articles were consulted. After applying the inclusion and exclusion criteria, eight articles were included in the quantitative analysis[27–29,42–46], and nine in the qualitative analysis[27–29,42–47] (Fig. 1).

General characteristics of studies

The participant's characteristics are presented in (Table 1). There were 259 participants with MS. The mean age of the participants was 46.6 years (range: 54.1–39.2), the mean height was 169.0 cm (range: 162.0–172.7), the mean EDSS score was 4.0 (range: 2.3–6.7), and the mean time from diagnosis was 14.2 years (10.5–17.6). Among the nine included studies, two did not specify the phenotype of MS in the sample[42,46], two studies consist of patients with RRMS[28,47], three studies encompass individuals with PPMS and SPMS[27,43,44], one study involved participants with both RRMS and SPMS[29], and, finally, another study included samples with PPMS, SPMS, and

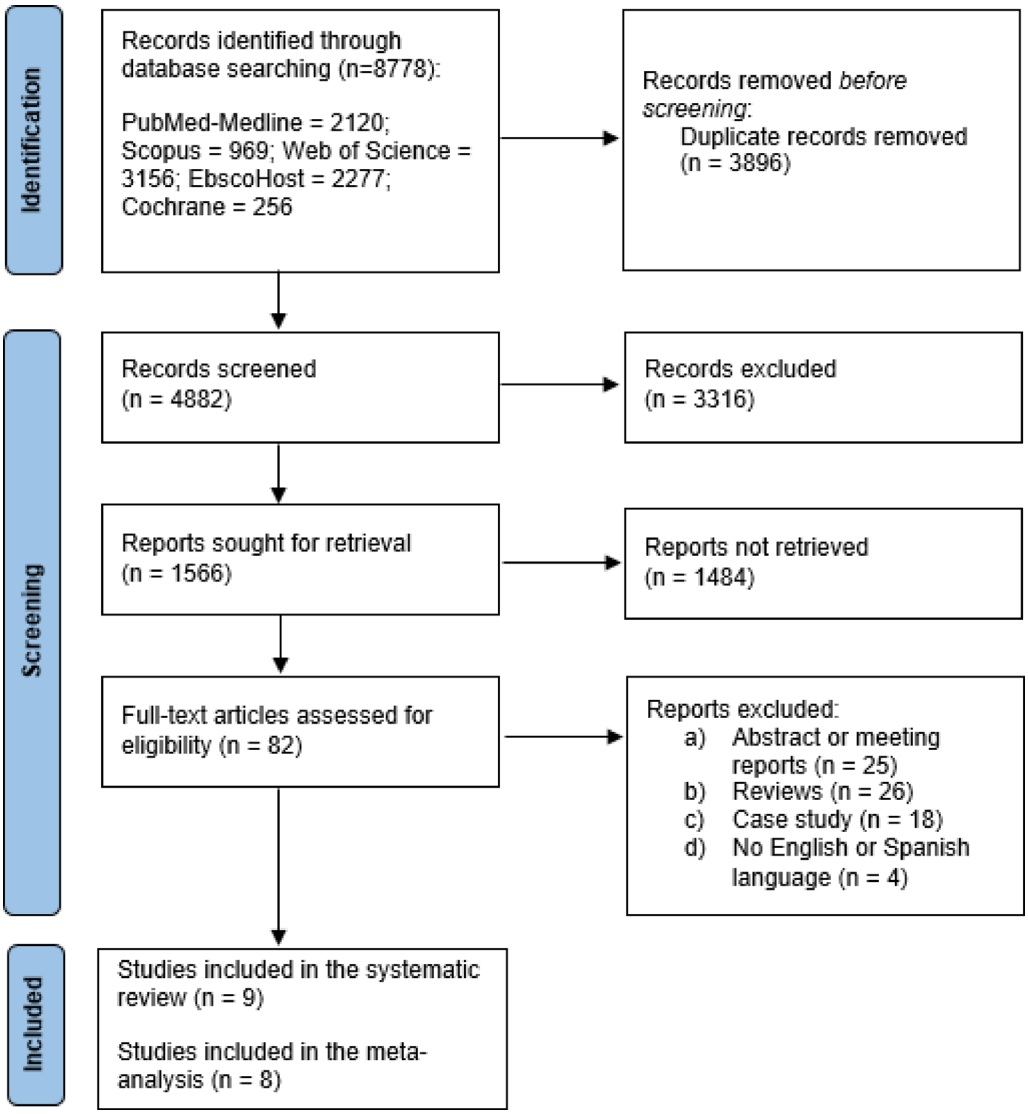

Fig. 1. PRISMA flow diagram of study selection.

Authors	Year of publication	Country	Design	Group	*n*	Sex	Age (yr.)	Weight (kg)	Height (cm)	EDSS	MS phenotype	Duration of disease (yr.)
Bansi et al.[42]	2013	Switzerland	RCT	Exp 1	28	Both	52.0	69.0	162.0	4.7	Not specific	–
				Exp 2	24	Both	50.0	69.0	170.0	4.6	Not specific	–
Briken et al.[27]	2016	Germany	RCT	Exp	32	Both	48.9 ± 7.6	–	–	4.9 ± 0.9	PPMS, SPMS	15.5 ± 7.6
Castellano & White[28]	2008	USA	RCT	Exp 1	11	Both	40.0 ± 10.0	72.0 ± 14.0	168.0 ± 10.0	0–5.5	RRMS	–
Devasahayam et al.[43]	2020	Canada	Non-RCT	Exp	10	Both	53.2 ± 15.6	–	–	6.7 ± 0.5	PPMS, SPMS	17.6 ± 10.2
Devasahayam et al.[44]	2021	Canada	RCT	Exp1	14	Both	54.1 ± 8.5	–	–	6.0 ± 0.5	PPMS, SPMS	16.6 ± 9.7
Gold et al.[45]	2003	Germany	RCT	Exp 1	25	Both	39.2 ± 1.8	69.5 ± 2.3	172.7 ± 1.6	2.3 ± 0.2	PPMS, SPMS, RRMS	10.5 ± 1.5
Jørgensen et al.[47]	2019	Denmark	RCT	Exp 1	16	Both	44.0	72.6	171.0	3.0	RRMS	–
				Control	14	Both	45.0	80.6	170.0	3.0	RRMS	–
Schulz et al.[46]	2004	Germany	RCT	Exp 1	15	Both	39.0 ± 9.0	–	–	2.0 ± 1.4	Not specific	–
				Exp 2	13	Both	40.0 ± 11.0	–	–	2.5 ± 0.8	Not specific	–
Zimmer et al.[29]	2018	Switzerland	RCT	Exp 1	27	Both	51.0 ± 9.9	–	–	4.4 ± 1.4	RRMS, SPMS	12.0 ± 11.3
				Exp 2	30	Both	48.0 ± 12.1	–	–	4.4 ± 1.0	RRMS, SPMS	13.3 ± 9.3

Table 1. Characteristics of the participants. Data are presented as mean ± SD. *EDSS* expanded disability status scale, *Exp* experimental, *MS* multiple sclerosis, *N/A* not available, *RCT* randomized controlled trial, *RRMS* relapsing remitting multiple sclerosis, *PPMS* primary progressive multiple sclerosis, *SPMS* secondary progressive multiple sclerosis.

RRMS[45]. All studies were published between 2003 and 2021. The GRADE summary of findings is reported in Supplementary Table 2.

Table 2 shows the characteristics of the interventions of the nine studies included. Eight carried out interventions based on aerobic exercise (quantitative analysis), and one study implemented resistance training (qualitative analysis).

Risk of bias assessment

According to RoB 2.0. Cochrane tool,[34] one study was considered to have a "low risk of bias"[47], five studies were rated as having "some concerns"[27,29,42,45,46], and two studies were rated as having "high risk"[28,44]. The risk of bias is presented in Supplementary Fig. 1 and Supplementary Table 3. Based on the ROBINS-I tool, the study[43] was rated as having a "moderate risk of bias" (Supplementary Table 4).

Funnel plot

Visual inspection of the funnel plot reveals an asymmetric distribution of points around the effect line, suggesting the potential influence of confounding factors or biases in the results (Fig. 2). Funnel plotting was also performed as a function of blood extraction time points for BDNF analysis (i.e., post-exercise, 30 min), and heterogeneity persisted in the funnel plot. However, it is interesting to note that Egger's test for publication bias was not significant (Z = -1.191; $p = 0.264$).

Authors	Group	Type of exercise	Characteristics of the training intervention	Duration (weeks)	Sessions	Session duration (min)	Intensity
Bansi et al.[42]	Exp 1	Cycling on an ergometer	Heart rate-controlled cycling at 50–60 rpm at the lactate threshold. The first and the last 2 min of session was the warm-up and cool-down phases.	3	15	30	70% HR_{peak}
	Exp 2	Cycling on an aquatic bike		3	15	30	70% HR_{peak}
	Exp 1	Cycling on an ergometer	Progressive cardiopulmonary exercise test on a cycle ergometer. The exercise protocol consisted of a first 3-min of unloaded pedaling as a warm up and a phase until the participant reached a symptom limited maximum. Workload was continuously ramp type increased by 5–10 W every minute to ensure 8–12 min of test. A final phase (3-min) was performed to cool down.	0	1	–	Until exhaustion
	Exp 2	Cycling on an ergometer		0	1	–	Until exhaustion
Briken et al.[27]	Exp	Cycle ergometer performance test	Participants started cycling at 25 W and resistance was steadily increased with an incline of 12.5 W/min. Depending on their physical condition, for some patients an easier protocol was applied starting at 8 W with an incremental increase of 8 W/min.	0	1	–	Until exhaustion
Castellano & White[28]	Exp 1	Cycle ergometer performance test	Subjects cycled at 60% of their individual derived $VO_{2\ peak}$ for 30-min.	0	1	30	60% $VO_{2\ peak}$
	Exp 2 (no MS)	Cycle ergometer performance test		0	1	30	60% $VO_{2\ peak}$
Devasahayam et al.[43]	Exp	Graded exercise test on treadmill	Graded exercise test until exhaustion. The workload was increased in 20 W every 2-min, starting from 21 W.	0	1	–	Until exhaustion
Devasahayam et al.[44]	Exp 1	Graded exercise test on recumbent stepper	Graded exercise test until exhaustion on seated recumbent stepper. The workload was increased in 20 W every 2-min, starting from 21 W.	0	1	–	Until exhaustion
	Exp 2 (no MS)	Graded exercise test on recumbent stepper		0	1	–	Until exhaustion
Gold et al.[45]	Exp 1	Cycle ergometer performance test	Endurance test on cycle ergometer. 30-min at 60% of $VO_{2\ max}$.	0	1	30	60% $VO_{2\ max}$
	Exp 2 (no MS)	Cycle ergometer performance test		0	1	30	60% $VO_{2\ max}$
Jørgensen et al.[47]	Exp 1	Resistance training session	Four lower body exercises (leg press, hip flexion, leg extension, hamstring curl). Intensity: 10 reps at 10 RM. Sets: 4. Rest between set: 2–3 min.	0	1	–	10 reps at 10 RM
	Control	No training	–	–	–	–	–
Schulz et al.[46]	Exp 1	Incremental cycle ergometer test	Subjects cycled for 30-min at 60% of $VO_{2\ max}$.	0	1	30	60% $VO_{2\ max}$
	Exp 2	Incremental cycle ergometer test		0	1	30	60% $VO_{2\ max}$
Zimmer et al.[29]	Exp 1	HIIT	Five 3-min high-intensity intervals of cycling at 80–100 r/min (85–90% HR max) or 80% of VO_{2peak}. During intervals, the cadence was reduced to 50–60 r/min for 1.5 min to reduce HR of HR_{max}.	3	9	20	85–90% HR_{max} or 80% $VO_{2\ peak}$
	Exp 2	Continuous endurance sessions	Defined HR controlled cycling at 60 r/min at the lactate threshold (70% of HR_{max} or 65% of VO_{2peak}).	3	15	20	70% HR_{max} or 65% $VO_{2\ peak}$

Table 2. Characteristics of the training programs. *Exp* experimental, *HIIT* high-intensity interval training, HR_{max} maximum heart rate, HR_{peak} peak heart rate, *MS* multiple sclerosis, *RM* repetition maximum, *rpm* revolutions per minute, VO_2 max maximum oxygen uptake, VO_{2peak} peak oxygen uptake, *W* watts.

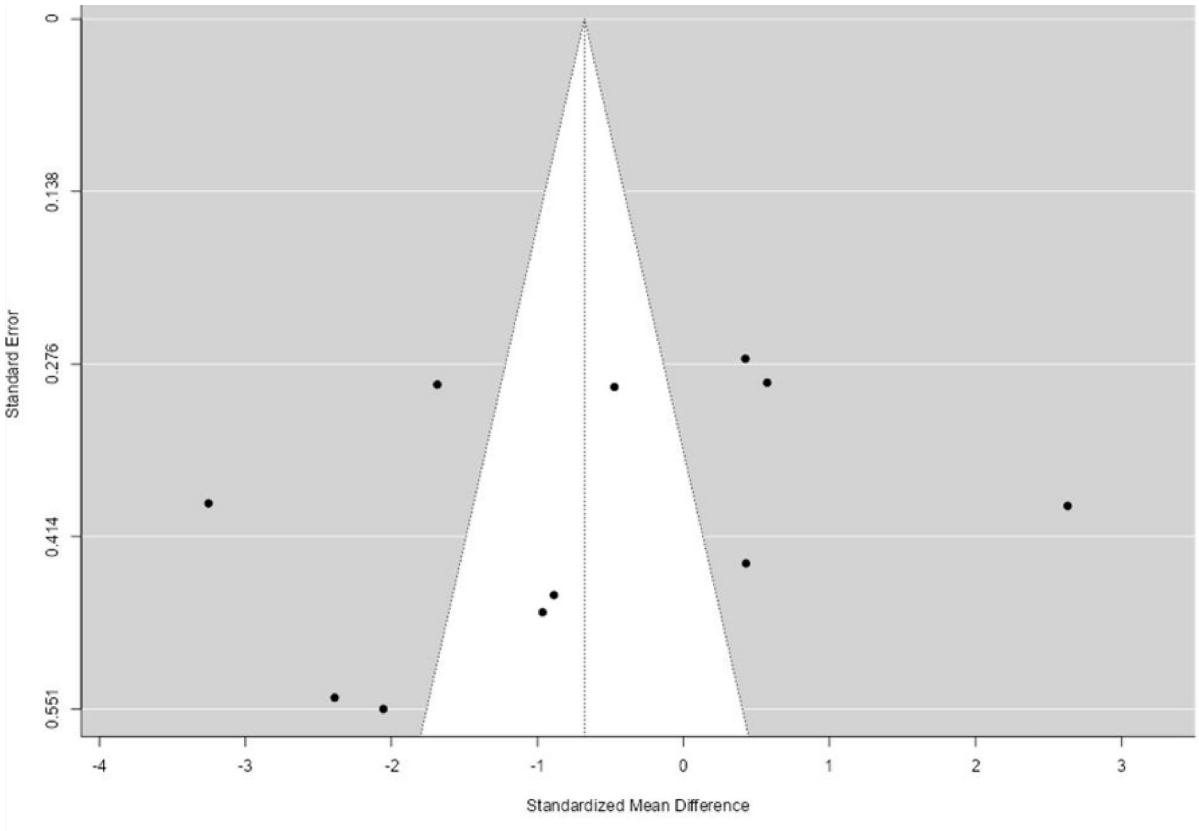

Fig. 2. Funnel plot of the study.

Meta-analysis

Immediately after a training session, a significant increase in BDNF markers was observed, although with high heterogeneity between the effect sizes of different groups (3 studies, 5 groups, 112 participants, SMD = 1.52 [large]; $p = 0.01$; $I^2 = 95\%$). However, 30 min after the session, no significant effect was observed (SMD = 0.45; 95%CI=-2.17, 3.07; $p = 0.74$). In this regard, only one study analyzed the effect immediately after exercise and after 30 min[27], observing a significant decrease in BDNF values (Fig. 3). High values of heterogeneity were observed that could be explained by multiple sources. In the case of the immediate post-exercise analysis, considerable heterogeneity was observed (I^2 = 95%), probably attributable to differences in exercise duration and intensity (e.g., 10–12 min to 30 min; from progressive load to 60% VO_2max), clinical characteristics of the participants (age, EDSS, MS phenotype), and the exact time of sample extraction after exercise. This methodological and clinical variability is also reflected in the analysis at 30 min post-exercise, where heterogeneity was even greater (I^2 = 97%).

Only two studies showed marker kinetics at different time points[28,45] after a 30-min session at 60% of VO_2max (Fig. 4). Despite the small number of studies ($n = 2$) and similar training characteristics, substantial heterogeneity was observed at the 30-minute post-exercise time point (I^2 = 93%), which could be explained by differences in individual participant characteristics (e.g., MS phenotype, EDSS score, or disease duration) or unreported methodological details (e.g., fasting status, time of day, serum versus plasma BDNF measurements).

Finally, two studies[29,42] analyzed the effect of 3 weeks of training on the BDNF marker (Fig. 5) and observed a small and significant overall effect (2 studies, 4 groups, 109 participants, SMD = 0.27 [small]; $p = 0.05$; $\tau^2 = 0.00$; $Chi^2 = 2.94$, d.f. = 3; $p = 0.40$; $I^2 = 0\%$).

Subgroup analysis and meta-regression

Although subgroup analysis and meta-regression were planned a priori, they could not be conducted as more articles were needed to perform this analysis.

Discussion

The results of this systematic review with meta-analysis suggest that peripheral BDNF concentration increases significantly immediately after a physical training session in patients with MS. However, no increases are found when peripheral BDNF measurement is performed 30 min after the end of the session. Regarding the short-term effects following 3 weeks of physical exercise, our preliminary results indicate a small but significant increase in BDNF.

Out of the nine studies included in this systematic review with meta-analysis, eight reported aerobic training sessions, and only one study reported strength training sessions. Therefore, in the quantitative analysis, only

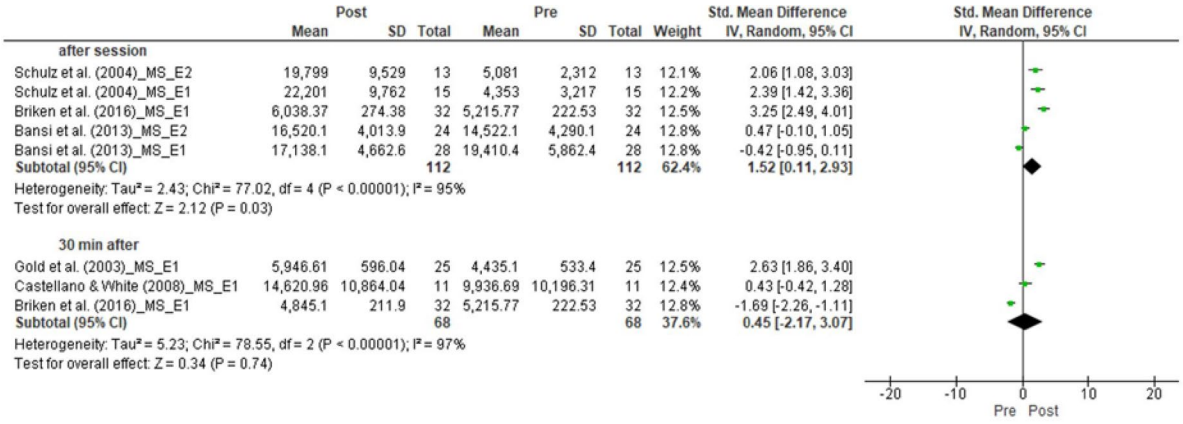

Fig. 3. Forest plot depicting the results of a random-effect meta-analysis for the acute effect (immediately post and at 30-min) of a physical exercise session compared with baseline values (pre-exercise), shown as mean difference with 95% CI on brain-derived neurotrophic concentration (BDNF) in people with MS. For each study, green squares represent the standardized mean difference in physical exercise session effect with the lower and upper 95% CI limits. The size of the square is proportional to the relative weight of each study in relation to the overall effect. Black diamonds represent the overall effect of physical exercise session in people with MS. Immediate after session, Total: 1.52% (95% CI 0.11, 2.93, p = < 0.01); 30 min after session, Total: 0.45% (95% CI −2.17, 3.07, p = < 0.01). *MS* multiple sclerosis, *E1* experimental group 1, *E2* experimental group 2, *SD* standard deviations, *CI* confidence interval.

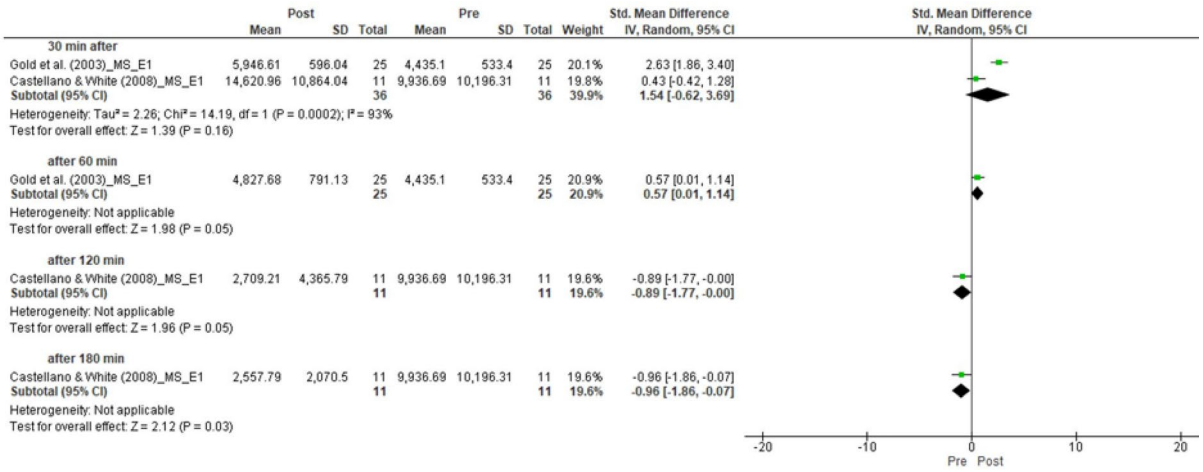

Fig. 4. Forest plot depicting the results of a random-effect meta-analysis for the acute effect (from 30-min to 180-min) of a physical exercise session compared with baseline values (pre-exercise), shown as mean difference with 95% CI on brain-derived neurotrophic concentration (BDNF) in people with MS. For each study, green squares represent the standardized mean difference in physical exercise session effect with the lower and upper 95% CI limits. The size of the square is proportional to the relative weight of each study in relation to the overall effect. Black diamonds represent the overall effect of physical exercise session in people with MS. 30 min after, Total: 1.54% (95% CI −0.62, 3.69, p = < 0.16); 60 min after session, Total: 0.57% (95% CI 0.01, 1.14, p = < 0.05); 120 min after, Total: −0.89% (95% CI −1.77, −0.00, p = < 0.05); 180 min after session, Total: −0.96% (95% CI −1.86, −0.07, p = < 0.03).
MS multiple sclerosis, *E1* experimental group 1, *E2* experimental group 2, *SD* standard deviations, *CI* confidence interval.

the studies ($n = 8$) that carried out aerobic training were included. Regarding the immediate effects of aerobic physical exercise on BDNF, our results show a large effect size and a significant increase in the release of this neurotrophin. Three studies[27,42,46] were included in this analysis. Although the overall analysis reflects a significant increase, the study by Briken et al.[27] found the highest increase immediately after, followed by Schulz et al.[46] Finally, the study by Bansi et al.[42] found small changes after training. All three studies included men and women, with a similar time since diagnosis and a sample of different disease phenotypes. However, it is necessary to highlight that the patients included in the study by Schulz et al.[46] present significantly lower EDSS

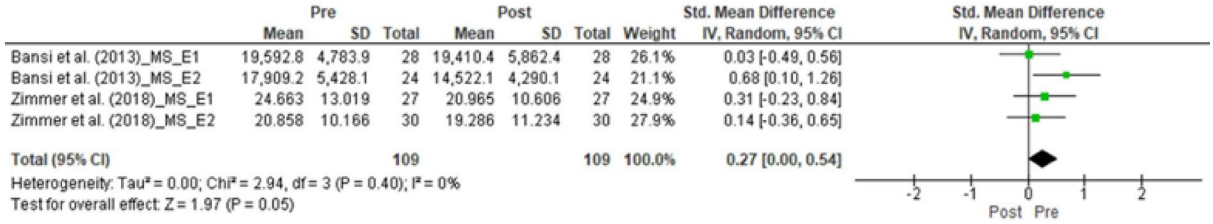

Fig. 5. Forest plot depicting the results of a random-effect meta-analysis for the short-term effect (3 weeks of physical exercise) compared with baseline values (pre-exercise), shown as mean difference with 95% CI on brain-derived neurotrophic concentration (BDNF) in people with MS. For each study, green squares represent the standardized mean difference in physical exercise session effect with the lower and upper 95% CI limits. The size of the square is proportional to the relative weight of each study in relation to the overall effect. Black diamonds represent the overall effect of physical exercise session in people with MS. 3-weeks of physical exercise, Total: 0.27% (95% CI 0.00, 0.54, p = < 0.40). *MS* multiple sclerosis, *E1* experimental group 1, *E2* experimental group 2, *SD* standard deviations, *CI* confidence interval.

scores (mean 2.0 and 2.5 vs. 4.9, 4.7, and 4.6). This lower EDSS score in the Schulz et al.[46] sample may be one of the reasons why BDNF increased more compared to, for example, those found in Bansi et al.[42]. Regarding the training sessions, there are some similarities and differences between studies. These three studies were conducted on a cycle ergometer; however, the session duration is only specified in the study by Schulz et al.[46] (30-min) and in that of Bansi et al.[42] (10–12 min). The short duration of the aerobic exercise session in the study by Bansi et al.[42] may explain the lack of significant BDNF release found immediately after exercise. Previous studies show that longer exercise sessions result in greater releases of BDNF and other neurotrophic and inflammatory factors compared to shorter durations[48]. A recent study shows that short exercise duration increases BDNF immediately after exercise in young, healthy men[49]; however, it is necessary to prescribe a very high exercise intensity (i.e., above the anaerobic ventilatory threshold)[49]. The study by Bansi et al.[42], prevented patients from accumulating time at high intensity using a progressive test to exhaustion on a cycle ergometer.

Only two studies examined the effect before and 30-min following aerobic exercise, without finding a significant effect. Both studies[28,45] used the cycle ergometer and included samples with similar characteristics. The session's characteristics were similar (30-min at 60% of VO_2max). It is important to note that both studies found mean increases in BDNF measured at 30-min post-exercise, in line with previous studies in healthy individuals[50]. However, the high standard deviation in the measurements prevented significant post-pre differences from being reflected.

Finally, our study also analyzed changes after 3 weeks of training in BDNF. Preliminary results indicate a small but significant improvement after the training period, as only two studies[29,42] and four experimental groups were included. All included groups consisted of men and women with similar disease-associated characteristics. Although all groups showed baseline increases in BDNF release, the best results were found by one experimental group in the study by Bansi et al.[42] These results were found with a very high training frequency (5 sessions/week) and moderate intensities (at lactate threshold). To our knowledge, no studies have analyzed the influence of training frequency on BDNF release. However, it can be assumed that, in such short training programs (3 weeks of training), higher frequencies will lead to higher training stimuli and thus to better results in the release of neurotrophins such as BDNF[29]. In the study by Zimmer et al.[29] high-intensity interval training (HIIT) was used in the experimental group, which also found significant and large increases in release. Extensive research shows that high intensity is an effective tool for neurotrophic stimulation in healthy populations[29]. The results of Zimmer et al.[29] indicate that the use of high intensity could also be feasible in patients with MS.

Although not included in the quantitative analysis, the study by Jørgensen et al.[47] which analyzed the effect of an acute strength exercise session on BDNF, found decreases immediately following the session and after 45- and 75-min. These decreases may be due to the high intensity and volume performed during the study (four lower body exercises, Intensity: 10 reps at 10 RM; Sets: 4). This exercise session in a population with MS with a mean EDSS of 3 may have been too high a stimulus centrally, preventing an increase in peripheral BDNF release. However, similar studies with older people and similar training sessions (6 exercises with 10 repetitions at 65–70% of one repetition maximum) found increased BDNF after the session[51]. A recent systematic review with meta-analysis by Babiarz et al.[52], which included studies examining the chronic effect of strength training in young individuals without pathologies, concludes that there is no evidence that strength training increases BDNF values. In this context, further studies are needed to analyze the effect of this exercise modality on the release of this neurotrophin.

Our systematic review with meta-analysis has some limitations that we would like to acknowledge. The first and most important limitation lies in the limited number of studies included in the meta-analysis, which prevents us from increasing the statistical power of the results. A wide variety of handling variables is also included in the studies. This variability among studies could stem from differences in research designs, studied populations, exercise interventions, and the measures and methods of assessing BDNF levels. Additionally, the risk of bias was high in two studies, medium in six, and low in only one. The two studies showing a high risk of bias were those by Devasahayam et al.[44] and Castellano and White[28], mainly due to the non-randomization of participants and low specificity in intervention characteristics. Furthermore, BDNF measurements in each

study were performed at different post-exercise intervals, preventing a homogeneous analysis of acute effects. Finally, subgroup analyses were not performed due to the small number of participants; thus, our results might also be influenced by sex (male, female), disease phenotype (RRMS, PPMS, SPMS), and time since diagnosis. In addition, training variables, mainly the duration and intensity of aerobic training, may impact BDNF release and thus decrease the significance of the results.

From a neurobiological and neurophysiological point of view, BDNF plays a critical role in modulating neuronal survival, synaptic transmission, and neurogenesis, primarily through its interaction with the TrkB receptor[3]. The transient rise in peripheral BDNF following exercise may reflect an upregulation of central BDNF expression, particularly in the hippocampus and motor cortex, regions heavily involved in cognitive and motor functions commonly impaired in MS. Exercise-induced activation of molecular pathways such as PGC-1α, FNDC5/irisin, and CREB signaling has been shown to mediate BDNF expression both centrally and peripherally, enhancing synaptic strength and neuroplastic potential[53]. Additionally, exercise reduces neuroinflammation—a hallmark of MS—by modulating microglial activation and cytokine profiles, indirectly promoting a neuroprotective environment conducive to BDNF function[54]. These mechanisms suggest that targeted exercise interventions may act as a disease-modifying strategy, especially in early stages of MS, by enhancing resilience against demyelination and supporting remyelination processes. Understanding the clinical implications of the association between exercise and BDNF, the collective evidence suggests the potential of exercise interventions to modulate BDNF levels and consequently influence neuroplasticity and cognitive function.

Conclusions

Our findings suggest that physical exercise may serve as a stimulus for increasing BDNF release in individuals with MS. Although the observed acute elevations in this neurotrophin are promising, they should be interpreted cautiously given the limited number of studies and their methodological variability. These transient increases in BDNF could contribute to the neuroprotective effects associated with exercise in neurodegenerative populations, although this remains to be confirmed. Further RCTs are needed to better understand the acute impact of exercise on BDNF in people with MS and to identify the most effective exercise modalities and doses for promoting BDNF release.

Data availability

The data supporting the findings of this study are available within the article. Additional data may be available from the corresponding author upon reasonable request.

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Author contributions

LAC contributed to the research design, implementation of research, methodology, analysis of the result, and writing the manuscript. JÁRA contributed to the research design, implementation of research, methodology, analysis of the result, and editing of the manuscript. DJRC contributed to the implementation of research, methodology, analysis of the result, and editing of the manuscript. JMJ contributed to the editing of the manuscript. OAA contributed to the editing of the manuscript.

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Declarations

Competing interests
The authors declare no competing interests.

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