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REVIEW

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Effects of exercise interventions to reduce chemotherapy-induced peripheral neuropathy severity: A meta-analysis

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Objectives: The two aims of this systematic review and meta-analysis were to (1) analyze the effect of exercise on chemotherapy-induced peripheral neuropathy (CIPN) severity and (2) determine the best type of exercise for the management of CIPN.

Methods: We systematically searched the MEDLINE, WOS, Sportdiscus, Scopus, and Cochrane databases from inception to December 2020 for experimental studies addressing the effect of exercise on CIPN severity, as measured by symptom severity (SSS) and peripheral deep sensitivity (PDS). The DerSimonian and Laird method was used to compute pooled estimates of the standardized mean differences (SMDs) and its respective 95% confidence intervals (CIs). Subgroup analyses were performed based on the types of exercise and the frequency and length of the interventions.

Results: Thirteen studies were included in this meta-analysis. In the analyses comparing exercise interventions versus controls, there was an improvement in the SSS (SMD = −0.21; 95% CI: −0.40 to −0.01; %change: −20.34%) and the PDS (SMD = 0.49; 95% CI: 0.06 to 0.91; %change: 31.64%) in favor of the intervention group. In the pre–post analyses, there was an improvement in the SSS (SMD = −0.72; 95% CI: −1.10 to −0.34; %change: −15.65%) and the PDS (SMD = 0.47; 95% CI: 0.15 to 0.79; %change:18.98%).

Conclusions: This meta-analysis provides an overview of the evidence supporting exercise as a suitable intervention to reduce the severity of CIPN by reducing the severity of the symptoms and the peripheral deep sensitivity among patients with cancer or cancer survivors. Furthermore, sensoriomotor training and mind–body exercises appear to be more effective in reducing symptom severity, and active nerve-specific exercises and mind–body exercises seem to be more effective in improving peripheral deep sensitivity.

KEYWORDS
cancer, chemotherapy-induced peripheral neuropathy, exercise, meta-analysis

1 | INTRODUCTION

Cancer is one of the leading causes of death worldwide and is the leading cause of premature death in 134 out of 183 countries.[1] Cancer mortality rates are declining in most countries because of advances in cancer diagnosis and treatment, and there has been a threefold increase in the number of cancer survivors over the last 4 decades.[1] Among the treatments for cancer, chemotherapy has been postulated in recent years to be one of the most effective for some types of cancer.[2] However, chemotherapy is associated with some complications (digestive, dermatologic or neurologic disorders) that can reduce the quality of life of cancer patients.[3,4] Among the possible neurological disorders, chemotherapy-induced peripheral neuropathy (CIPN) is the most frequent.[5]

CIPN is characterized by damage to the peripheral nerves as a consequence of treatment with chemotherapeutic drugs such as platinum compounds, taxanes, vinca alkaloids, bortezomib, and thalidomide.[6] CIPN can cause permanent symptoms and disability in 30–60% of cancer survivors, affecting both the young and the elderly.[7] CIPN produces sensory symptoms (such as paresthesias, dysesthesias, pain, sensory loss and numbness, burning, or tingling in the hands and feet) and motor symptoms (such as reduced deep tendon reflexes, ataxia, muscle weakness, and reduced balance control),[6,7] which can become crucial limiting factors for therapy, leading to treatment delays, dose reductions, or even the discontinuation of therapy, potentially compromising survival rates.[8] Furthermore, the symptoms may continue to worsen even after stopping treatment in a large number of cases, thus deteriorating the patient's functional ability and quality of life.[6]

Exercise improves CIPN symptom management and, as a consequence, improves the health-related quality of life (HRQoL) of cancer survivors.[9] Most previous studies aimed at assessing the effectiveness of strategies for the management of CIPN symptoms and HRQoL life in cancer survivors have been primarily focused on pharmacologic treatments, neglecting nonpharmacological alternatives, although previous systematic reviews[7,10–13] and a meta-analysis[14] have suggested that exercise interventions based on aerobic exercise, balance training, strength training, and sensorimotor training have a positive effect on the control of symptoms in patients with CIPN. However, these studies have not separately shown the effect on specific outcomes of CIPN such as symptoms severity scores (SSS) or the peripheral deep sensitivity (PDS), nor the effect of the different types of exercise in insolation in the management of CIPN. Additionally, some novel randomized controlled trials on the effectiveness of exercise in treating CIPN have been published. Thus, the two aims of this systematic review and meta-analysis were (1) to analyze the effect of exercise interventions on SSS and PDS in patients with CIPN and (2) to determine the best type of exercise in the management of CIPN.

2 | MATERIALS AND METHODS

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[15] guidelines and the recommendations of the Cochrane Collaboration Handbook.[16] The protocol for this systematic review and meta-analysis was previously registered on PROSPERO (registration number: CRD42021225622).

2.1 | Data sources and searches

Systematic searches of MEDLINE (via PubMed), Web of Science, Sportdiscus and Scopus databases and the Cochrane Database of Systematic Reviews were conducted from inception to December 1, 2020. The search strategy included the following terms: (CIPN OR "chemotherapy-induced peripheral neuropathy" OR "Cancer-related neuropathic pain") AND (exercise OR "physical activity" OR "physical therapy" OR physiotherapy). In addition, the references of the articles considered suitable for the systematic review were reviewed.

2.2 | Study selection

The eligible articles were experimental studies (RCTs or non-RCTs and single-arm pre–post studies) aiming to measure the efficacy of exercise interventions in reducing the severity of CIPN in patients with cancer or cancer survivors. Studies not written in English or Spanish and noneligible types of publications, such as review articles, editorials, comments, guidelines, and case reports, were excluded.

2.3 | Categorization of interventions and outcome

After selection of the included studies, the types of exercise were categorized as endurance, resistance, combined (endurance with resistance), sensoriomotor, mind–body and nerve-specific active exercises.

Endurance training included interventions aimed at increasing energy expenditure and heart rate, such as treadmill, cycling or walking, and resistance training aimed to increase muscular strength and power.

Nerve-specific active exercises are active movements of the joints with the aim of elongating the nerve, restoring mobility, and decreasing neural edema by promoting axoplasmic flow.[17] Sensoriomotor training included exercises aimed at improving the neuromuscular system through coordination and balance, and resistance or endurance training could be added. Mind–body exercises include those based on balance and resistance, focusing on breathing and postural control, such as Pilates or yoga.

The severity of CIPN was measured by scoring the symptom severity (SSS) through clinical rating scales or patient-reported questionnaires and by measuring the peripheral deep sensitivity (PDS) through the vibration perception threshold. When the CIPN severity was measured using the SSS, most scales indicate that higher scores indicate greater symptom severity. However, when a study was scaled reversely, the mean of each group was multiplied by −1. Finally, when the studies reported the same outcome measures with more than one scale, we calculated a combined estimate.

The literature search was conducted independently by two reviewers (SN-A and AT-C), and disagreements were resolved by consensus or by discussion with a third researcher (IC-R).

2.4 | Data extraction

The following data were extracted from the original reports: (i) author information and year of publication; (ii) study population characteristics (country, sample size, age distribution, type of cancer, and type of chemotherapy); (iii) intervention characteristics (intervention and control regimen, frequency and length); (iv) outcomes assessed, including the SSS and the PDS; and (v) adherence rate. When necessary, the authors were contacted at least three times to retrieve any missing information.

2.5 | Quality assessment

The methodological quality of the RCTs was assessed using the Cochrane Collaboration's tool for assessing the risk of bias (RoB2).[18] This tool assesses the risk of bias according to five domains: randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Overall, a study was considered to have a "low risk of bias" if all domains were considered to have a "low risk," to have "some concerns" if there was at least one domain rated as having "some concerns," and to have a "high risk of bias" if there was at least one domain rated as having a "high risk" or several domains rated as having "some concerns" that could affect the validity of the results.

The methodological quality of the nonrandomized studies was assessed using the Risk of Bias in Nonrandomized Studies of Intervention (ROBINS-I).[19] This tool assesses the risk of bias according to six domains: bias due to confounding, bias in the selection of participants, bias in the classification of interventions, bias due to deviations from the intended interventions, bias due to missing data, and bias in the selection of the reported results. Each domain could be considered low, moderate, serious, a critical risk of bias or no information. Overall bias will be considered a "low risk of bias" if all domains have been classified as a low risk of bias; "moderate risk of bias" if all domains have been classified as a low or moderate risk of bias; "serious risk of bias" if there is at least one domain rated as serious risk; "critical risk of bias" if there is at least one domain rated as critical risk; and "no information" if there is no clear indication that the study is at a serious or critical risk of bias and there is a lack of information about one or more key domains of bias.

The risk of bias assessment was conducted independently by two reviewers (SN-A and SR-G), and inconsistencies were resolved by consensus or discussion with a third researcher (IC-R). The agreement rate between reviewers was calculated using the kappa statistic.

2.6 | Statistical analysis

The restricted maximum likelihood (REML) method was used to estimate the pooled standardized mean difference (SMD) and its respective 95% confidence interval (95% CI). When studies were RCTs, a SMD score was calculated for SSS and PDS using Cohen's d index,[20] in which negative SMD values indicate a decrease in the SSS, and positive SMD values indicate improvements in the PDS in favor of the exercise interventions versus the control group. In addition, Cohen's d index was used to estimate pre–post exercise intervention changes in the SSS and the PDS. When the studies included two intervention groups, their data were analyzed as independent samples. Cohen's d values of 0.2, 0.5, 0.8 and >1.0 were considered weak, moderate, strong, and very strong effects. Moreover, we estimated the pooled percentage of change in SSS and PDS for the analysis of exercise intervention versus control, pre–post and subgroup analyses.

The level of heterogeneity of the results among the studies was assessed using the I^2 statistic. The level of heterogeneity was categorized as follows: might not be important (0–30%), may represent moderate heterogeneity (30–50%), indicates substantial heterogeneity (50–75%),

or indicates considerable heterogeneity (75–100%). The corresponding p values were also considered.[15]

A sensitivity analysis was conducted by removing studies one by one to assess the robustness of the summary estimates. Furthermore, assuming that the quality of the RCTs is usually higher than that of pre–post studies, we decided to perform a sensitivity analysis within the pre–post analyses to assess whether there were differences in pooled SMD estimates between studies with a pre–post design by removing the pre–post SMD estimates of the intervention groups from the RCTs.

Subgroup analyses were performed according to the type of exercise intervention (endurance training, resistance training, combined exercise, nerve-specific active exercises, sensorimotor training, and mind–body exercise). Univariate random-effects meta-regressions were used to assess whether the results differed according to the mean age of the participants, the number of sessions per week, or the length of the intervention.

Publication bias was assessed by Egger's regression asymmetry test,[21] and p values <0.10 were considered statistically significant. Statistical analyses were performed using R software V4.2.1 and Stata/SE software V.16.

3 | RESULTS

3.1 | Systematic review

Thirteen studies were identified (seven RCTs[22–28] and six pre–post studies[29–34]) (Figure 1), including 746 participants (the excluded studies with reasons are available in Table S1). The studies were conducted on four continents: seven in North America, four in Europe, one in Asia, and one in Oceania. The included participants ranged in age from 47 to 70 years, and the sample size ranged from three to 355 subjects (Table 1).

Regarding the characteristics of the populations evaluated in the studies, many types of cancer were described, including endometrial, breast, uterine, ovarian, colorectal, gynecological, gastrointestinal, lung, pancreatic, bladder, colon and urothelial cancers, myeloma, Hodgkin's lymphoma, adeno-cancer, appendix, and plasmocytoma. Furthermore, the types of chemotherapy used were carboplatin, docetaxel, paclitaxel, cyclophosphamide, 5-fluorouracil, epirubicin, vinca alkaloids, bortezomib, FOXFIRE, FOLFIX, capecitabine, cisplatin, vincristine, and combinations of these drugs.

The interventions included several types of exercises: Endurance training was performed in one study (such as walking, stationary bicycle, cross-trainer, and treadmill), resistance training in two studies (such as theraband, kinematic change exercises, bench press, pulldowns, leg press, seated row, abdominal exercises, and posture training), combined exercises were performed in four studies, nerve-specific active exercises in one study, sensoriomotor training in four studies, and mind–body exercises (yoga exercises) in three studies. The length of the interventions ranged from three to 25 weeks, with a frequency between one to seven sessions per week.

Concerning adherence to the exercise intervention, most of the included studies showed an adherence rate between 72% and 100%, except the study of Wonders,[34] which had an adherence rate of 42.85%. In addition, some studies described adverse events associated with the cancer stage or chemotherapy treatment, such as lymphopenia, neutropenia, multiorgan failure, dyspnea, nausea, death, infection, surgery, diarrhea, and thrombosis. However, only one study[22] described adverse events associated with the exercise intervention regimen as myalgias and cramps.

3.2 | Study quality

The overall risk of bias for RCTs, as assessed by the RoB2 tool, showed some concerns for all included studies (mainly related to the selection of the reported results, randomization process, and the measurement of the outcome domains) (Figure S1). The overall risk of bias for the non-RCTs, as assessed by the ROBINS-I tool, showed a moderate risk of bias in 16.7% of the included studies, a serious risk of bias in 66.6% of the included studies and a critical risk of bias in 16.7% of the included studies (mainly due to a critical risk of bias due to the method used to measure the outcomes) (Figure S2).

3.3 | Meta-analysis

For the analysis of exercise intervention versus control, a decrease in the SSS (SMD = −0.27; 95% CI: −0.53 to −0.01; change: −20.34%) and an increase in the PDS (SMD = 0.49; 95% CI: 0.06 to 0.91; change: 31.64%) in favor of the intervention group were observed, both with no important heterogeneity ($I^2 = 9.0\%$; $p = 0.356$ and $I^2 = 0.0\%$; $p = 0.69$, respectively) (Figures 2 and 3). Additionally, when the SMD was estimated considering only the effect on the intervention groups, there was a decrease in the SSS (SMD = −0.87; 95% CI: −1.60 to −0.14; change: −15.65%) and an increase in the PDS (SMD = 0.47; 95% CI: 0.15 to 0.79; % change: 18.98%) with considerable heterogeneity ($I^2 = 89\%$; $p < 0.001$) and substantial heterogeneity ($I^2 = 67\%$; $p = 0.006$), respectively (Figures 2 and 3).

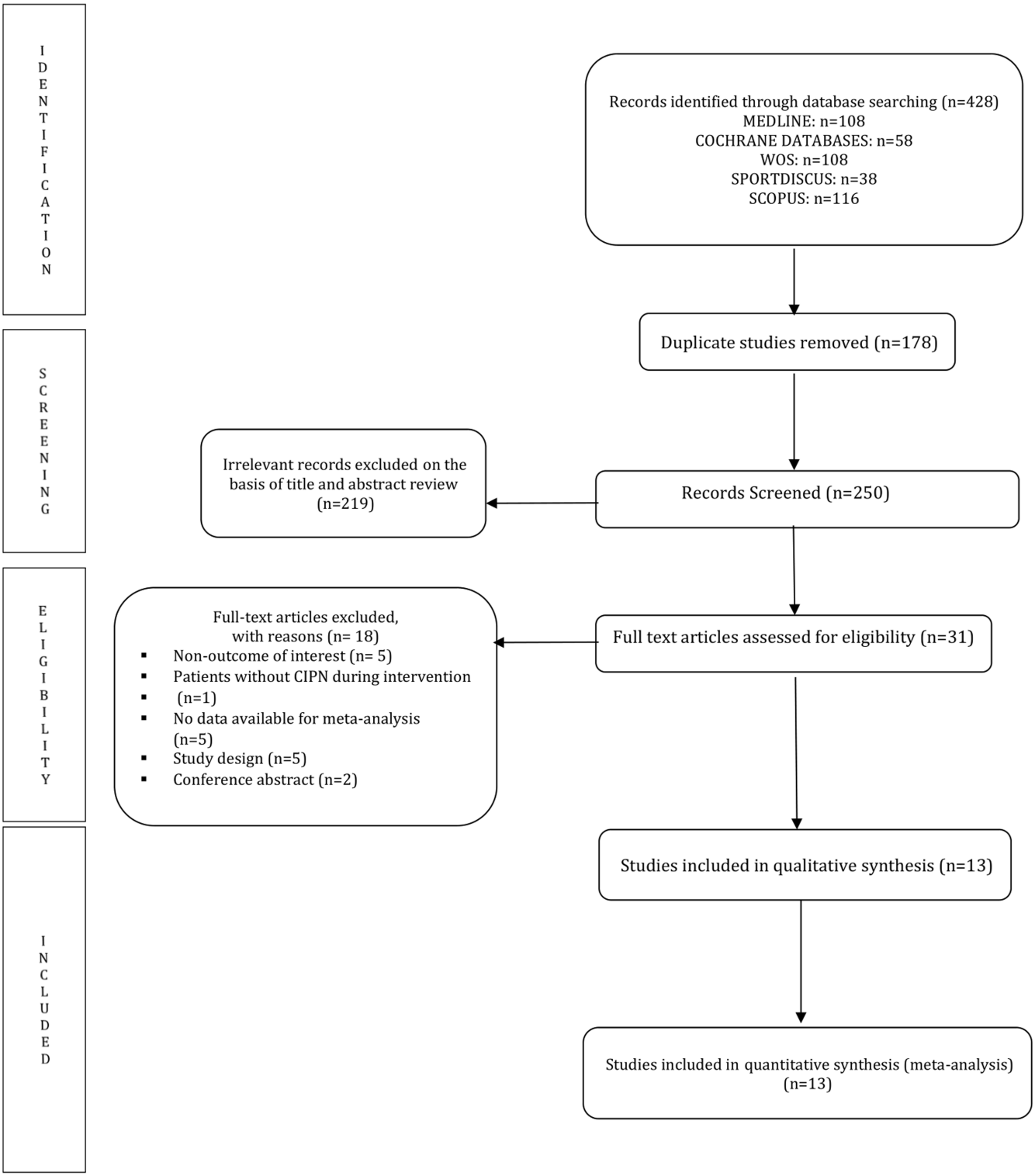

FIGURE 1 Flow chart.

3.4 | Sensitivity analysis

When the impact of the individual studies was examined by removing studies from the analysis one at a time, the pooled SMD estimates for exercise interventions on the SSS and the PDS did not significantly change. Furthermore, when sensitivity analysis was performed in the pre–post analysis by removing the intervention groups of the RCTs, the pooled SMD changed slightly for the SSS (SMD = −1.28; 95% CI: −2.50 to −0.06; % change: −22.92%) and the PDS (SMD = 0.47; 95% CI: 0.14 to 0.79; % change: 10.29%).

3.5 | Subgroup analyses and meta-regression

According to the different types of exercise, sensoriomotor training (SMD = −0.65; 95% CI: −0.86 to −0.44; % change: −19.95%) and mind–body exercises (SMD = −0.49; 95% CI: −0.88 to −0.09; % change: −13.96%) showed an effect on the SSS (Figure S3). Furthermore, nerve-specific active exercises (SMD = 1.24; 95% CI: 0.78 to 1.69; % change: 42%) and mind–body exercises (SMD = 0.43; 95% CI: 0.10 to 0.76; % change: 14.98%) showed an effect on the PDS (Figure S4).

The random-effects meta-regression model showed that the age of the participants was positively related to the ES estimates across the studies for the SSS ($p = 0.032$) and the number of sessions/week for the PDS ($p = 0.018$) (Figure S5).

3.6 | Publication bias

The funnel plot asymmetry and Egger's test suggested there was publication bias for the exercise intervention versus control analysis ($p = 0.056$) and the pre–post intervention analysis ($p = 0.003$) in the SSS.

4 | DISCUSSION

Increasing evidence supports the implementation of exercise promotion in cancer care. This systematic review and meta-analysis provides an overview of the evidence supporting the hypothesis that exercise is a suitable intervention in patients with CIPN for improving symptom severity (SSS by −20.34% and PDS by 31.64%). Furthermore, sensoriomotor training and mind–body exercises seem to be more effective for SSS and nerve-specific active and mind–body exercises for improving PDS.

Previous systematic reviews[7,10–13] and a meta-analysis[14] suggested that patients receiving chemotherapy should be referred to rehabilitation services when they develop symptoms of CIPN, supporting exercise as an effective intervention. However, these studies combined different outcomes such as balance, symptoms severity scores, and functional status in the same analysis, making it difficult to provide recommendations for specific outcomes. Furthermore, these reviews highlighted that the type of exercise could play a key role in reducing the different CIPN symptoms. Our findings reinforce that exercise is an effective intervention to improve core outcomes such as SSS and PDS in patients with CIPN and provides additional evidence regarding the effect of different exercise interventions considering some confounding factors, such as the age of the participants and the frequency and length of the intervention.

Exercise has anti-inflammatory effects on the nervous system by decreasing proinflammatory cytokines and normalizing brain-derived neurotrophic factor and glial cell activation, which could attenuate the symptoms of neuropathic pain.[35] Differences in the efficacy of the different types of exercise can be attributed to the improvement achieved in the neuromuscular system with sensorimotor exercises, which can increase the blood supply to the peripheral nerves, reduce the primary myelin sheath degeneration and peripheral nerve hyperexcitability, restore the axonal voltage-gated sodium ion channel, and improve the acute neurotoxicity. Mind–body exercises can modulate autonomic function and beneficially alter markers of sympathetic and parasympathetic activity, reducing the effects of stress and leading to positive impacts on neuroendocrine, metabolic, and inflammatory responses that can reduce neurotoxicity.[36,37] Finally, nerve-specific active exercise reduces intraneural edema and enhances the immune response to nerve injury.[38]

Currently, there is no standardized approach to the assessment of CIPN, and the consensus is that the assessment should include objective evidence of the neurological deficits and an assessment of symptoms from the patient's point of view.[6] Quantitative sensory testing, such as the vibration perception threshold, is a sensitive method for the assessment of CIPN. Furthermore, there is evidence to support clinical rating scales (such as the modified Total Neuropathy Score) and patient-reported outcomes (such as the FACT-GOG-Ntx or CIPN20) as sensitive assessments of the CIPN symptom severity.[6] Although the studies included in this meta-analysis used different scales for the assessment of the SSS, the SMDs are similar in all included studies. However, Fernandes et al.[29] showed the greatest improvement in the SSS. This could be because the sample in Fernandes´ study is the youngest among the included studies and that the frequency of sessions per week was higher than that of the other interventions. When the analyses were performed for SSS removing this study, the overall effect size decreased (SMD = −0.43; 95% CI: −0.64 to −0.22) although it remained statistically significant in favor of the physical exercise group and subgroups analysis did not change substantially for resistance training (SMD = −0.50; 95% CI: −1.40 to 0.39).

Traditionally, physicians have recommended that patients rest during cancer treatment. However, the evidence suggests that exercise is safe and feasible during cancer treatment,[39] and recent guidelines support the hypothesis that encouraging people to be physically active at all stages of cancer can improve clinical and quality-of-life outcomes.[40] The most important factors associated with

TABLE 1 Characteristics of the studies included in the meta-analysis.

Randomized controlled trials					
Study characteristics		**Population characteristics**			
First author, year of publication	**Country**	**Sample size (%female)**	**Age (years)**	**Type of Cancer**	**Type of chemotherapy**
Bao et el, 2020	USA	IG: $n=21$ (NR) CG: $n=20$ (NR)	IG: 60.0 (35.5–77.9)[a] CG: 62.3 (42.4–79.0)[a]	Breast cancer Uterine cancer Ovarian cancer	Carboplatin, Docetaxel, docetaxel + carboplatin, paclitaxel, paclitaxel + carboplatin
Hammond et al, 2020	Canada	IG: $n=22$ (NR) CG: $n=26$ (NR)	IG: 56.3 ± 9.9 CG:53.0 ± 10.3	Breast cancer	Taxane chemotherapy (docetaxel, cyclophosphamide, 5-fluorouracil, epirubicin).
Kleckner et al, 2018	USA	IG: $n=170$ CG: $n=185$	IG: 55.6 ± 11.8 CG: 55.9 ± 9.7	All types other than leukemia	Taxanes, platinums and vinca alkaloids.
Kneis et al, 2019	Germany	IG1: $n=18$ (78) IG2: $n=12$ (63)	IG1:70 (44–82)[a] IG2: 60 IG2: 60(46–75)[a] Ig	Breast cancer Colorectal cancer Gynecological cancer Gastrointestinal cancer Lung cancer Non-Hodgkin's lymphoma Multiple myeloma	NR
Schönsteiner et al, 2017	Germany	IG1: $n=66$ (56) IG2: $n=65$ (48)	IG1:59 (28–70)[a] IG2:62 (24–71)[a]	All types of cancer	Taxanes, platinums, bortezomib and vinca alkaloids.
Streckmann et al, 2019	Germany	IG1: $n=10$(60) IG2: $n=10$(80) IG3: $n=10$(70)	IG1:56 (47–74)[b] IG2:59 (51–69)[b] IG3:59 (49–70)[b]	Breast cancer Ovarial cancer Adeno-cancer Colorectal cancer Pancreatic cancer Hodgkin lymphoma Plasmocytoma Multiple myeloma Lung cancer	Taxane, platinums and vinca alkaloids.

Intervention characteristics					
Intervention	**Frequency**	**Length (weeks)**	**Outcomes (scale/tool)**	**Change (%)**	**Adherence rate (%)**
IG: Yoga. CG: wait list.	Daily	8	SSS (FACT-GOG Ntx)	Vs Control: SSS: −12.26% Pre–post: SSS: −12.60%	IG: 76.0%
IG: Stretch and nerve-specific active exercises (3 times daily, 5–10 min, throughout and after chemotherapy until the symptoms of neuropathy subsided) and education program. CG: No exercises.	3 times/daily	25	SSS (S-LANSS) PDS (Vibration Sensory Analyzer)	Vs Control: SSS: −36.87% PDS: 19.35% Pre–post: SSS: −28.57% PDS: 42%	IG: 78.6%
IG: Daily aerobic exercise (walking prescription) + daily resistance exercise (therapeutic band prescription). CG: No intervention.	Daily	6	SSS (NRS)	Vs Control: SSS: −18.73% Pre–post: SSS:51.38%	IG: 73.6%
IG1: 30 min of endurance training of moderate intensity +30 min balance exercises (3 rep/30 s). IG2: 30 min of endurance training of moderate intensity.	2 times/week	12	SSS (CIPN20 score, FACT-GOG Ntx) PDS (Rydel-Seiffer tuning fork)	Pre–post IG1: SSS: −15.24% PDS: 6.71% Pre–post IG2: SSS: −7.47% PDS: 8.63%	IG1: 72.0% IG2: 76.0%
IG1: WBV (18 min) in different positions and frequencies + resistance exercises. IG2: Resistance and balance exercise focus on training posture and transport movements.	2 times/week	8	SSS (Symptoms score)	Pre–post IG1: SSS: −22.31% Pre–post IG2: SSS: −20.25%	IG1: 81.8% IG2: 89.2%
IG1: Sensorimotor training. Four exercises progressively more difficult balance exercises on progressively unstable surfaces. (3 rep/20 s). IG2: Vibration training. Four progressing sets (30-s to 1-min exercise) with a frequency from 18–35 Hz and amplitude of 2–4 mm. IG3: No intervention.	2 times/week	6	SSS (FACT-GOG Ntx) PDS (Rydel-Seiffer tuning fork)	Vs Control IG1: SSS: −18.26% PDS:61.25% Vs Control IG2: SSS: −17.85% PDS:32.99% Pre–post IG1: SSS: −24.33% PDS: 42.10% Pre–post IG2: SSS: −23.92% PDS: 13.84%	IG1: NR IG2: NR

TABLE 1 (Continued)

Randomized controlled trials					
Study characteristics		**Population characteristics**			
First author, year of publication	**Country**	**Sample size (%female)**	**Age (years)**	**Type of Cancer**	**Type of chemotherapy**
Zimmer et al, 2017	Germany	IG: $n = 17$ (29.4) CG: $n = 13$ (30.8)	IG: 68.53 (50–81)[b] CG: 70.00 (50–81)[b]	Colorectal cancer	FOLFIRI, FOLFOX, 5-fluorouracil, capetitabine

Pre–post studies					
Study characteristics		**Population characteristics**			
First author, year of publication	**Country**	**Sample size (%female)**	**Age (years)**	**Type of Cancer**	**Type of chemotherapy**
Fernandes et al, 2016	India	IG: $n = 25$ (52)	47 ± 12	N. R	N. R
Galantino et al, 2019	USA	IG: $n = 10$ (90)	64.4 (47–81)[b]	Ovarian cancer Colon cancer Uterine cancer Bladder cancer	N. R
Galantino et al, 2020	USA	IG: $n = 8$ (87.5)	65 (49–73)[b]	Colorectal cancer Breast cancer Ovarian cancer Pancreatic cancer	Taxanes, platinum and vinca alkaloids.
McCrary et al, 2019	Australia	IG: $n = 29$ (72.4)	61.6 (32–79)[b]	Colorectal cancer Breast cancer Ovarian cancer Endometrial cancer Appendix cancer Myeloma Urothelial	Paclitaxel, Oxaliplatin, Paclitaxel + carboplatin, Bortezomib, Cisplatin, Vincristine.
Tofthagen et al, 2014	USA	IG: $n = 3$ (66.6)	69.0	Colorectal cancer	N. R
Wonders et al, 2013	USA	IG: $n = 6$ (100)	51.6 ± 2.6	Breast cancer	N. R

Note: Values are presented as mean ± SD unless otherwise indicated.

Abbreviations: CG, Control group; CIPN20 score, CIPN20 module of the EORTC-QLQ (European Organization for Research and Treatment of Cancer Quality o Neurotoxicity questionnaire; IG, Intervention group; mTNS, modified total neuropathy score; N.R, Not reported; NRS, Numeric rating scale; PDS, Peripheral de

[a]Median (interquartile range).

[b]Mean (range).

Intervention characteristics					
Intervention	**Frequency**	**Length (weeks)**	**Outcomes (scale/tool)**	**Change (%)**	**Adherence rate (%)**
IG: Balance training (10 min), coordination practices (5 min), endurance training (10 min), resistance training (20 min) and stretching, breathing and mobilization exercises (10–15 min). CG: Waitlist.	2 times/week	8	SSS (FACT-GOG Ntx)	Vs Control: SSS: −21.36% Pre–post: SSS: −6.39%	IG: 80%

Intervention characteristics					
Intervention	**Frequency**	**Length (weeks)**	**Outcomes**	**%Change**	**Adherence rate (%)**
IG: 7 lower limb closed kinematic chain exercises.	Daily	3	SSS (mTNS)	Pre–post: SSS: −53.84%	IG: 100%
IG: Yoga (90 min) based on combines postures, breath work and meditation.	2 times/week	8	SSS (FACT- GOG NTx, PNQ) PDS (bioesthesiometer)	Pre–post: SSS: −15.46% PDS: 15.92%	IG: 80%
IG: Yoga (90 min) based on combines postures, breath work and meditation.	1 time/week	8	SSS (FACT- GOG NTx, PNQ) PDS (bioesthesiometer)	Pre–post: SSS: −13.63% PDS: 13.80%	IG: 100%
IG: One hour of resistance training (20 min), balance training (20 min) and cardiovascular exercises (20 min).	3 times/week	8	SSS (mTNS, CIPN20 score)	Pre–post: SSS: −30.17%	IG: 83.1%
IG: strength training (20 min), balance training (20 min), stretching (10 min) and functional balance training (10 min).	2 times/week	12	SSS (TNS, CIPNAT symptom experience)	Pre–post: SSS: −23.25%	NR
IG: resistance exercise with thereaband at moderate intensity and aerobic exercise.	3 times/week	10	SSS (S-LANSS)	Pre–post: SSS: −52.94%	IG: 42.85%

.T, Chemotherapy-Induced Peripheral Neuropathy Assessment Tool; FACT-GOG Ntx, the Functional Assessment of Cancer/Gynecologic Oncology Group-Neuropathy Questionnaire; S-LANSS, Self-report version of Leeds Assessment for Neuropathic Symptoms and Signs; SSS, Symptoms severity score; vs, versus.

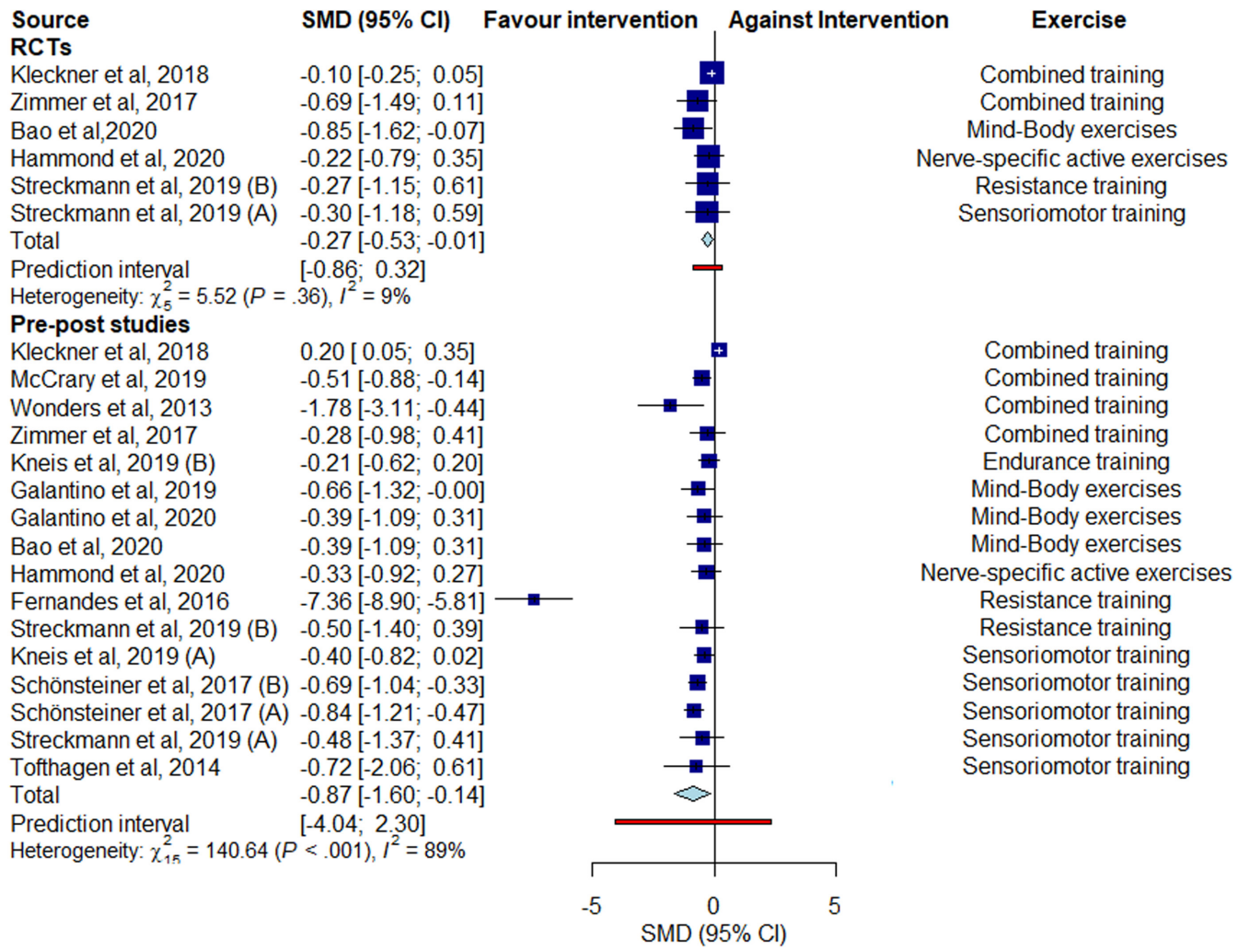

FIGURE 2 Forest plot showing the SMD for the symptom severity score. RCTs: Randomized controlled trials.

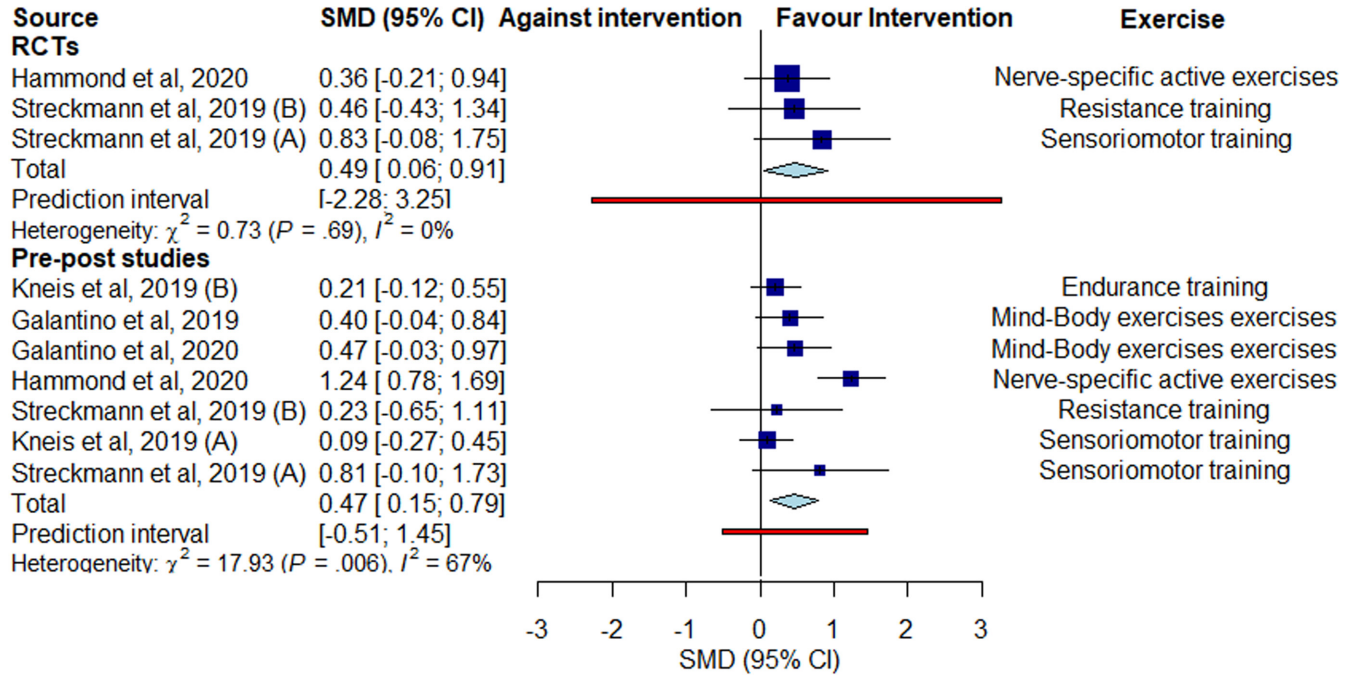

FIGURE 3 Forest plot showing the SMD for the Peripheral Deep Sensitivity outcome. RCTs: Randomized controlled trials.

increased adherence to exercise of patients with cancer are individual drivers (related to the person's emotional state), social networks (related to support from the family and friends), physical symptoms (cancer-specific), and the physical environment (having access to adequate facilities).[41] Therefore, exercise interventions to reduce CIPN severity in patients with cancer should be organized from a multidisciplinary approach.

Our findings showed that a combined intervention of sensoriomotor training, nerve-specific active exercises, and mind–body exercises could be recommended for the management of CIPN in patients with cancer or among cancer survivors. Additionally, the influence of the number of sessions per week on the PDS should be considered, since exercise interventions with more sessions per week showed a greater effect.

Some limitations of this review should be acknowledged. First, the studies included in this systematic review and meta-analysis reported on many types of cancer, which could compromise our results because adherence to an exercise intervention depends on the physical symptoms of each type of cancer.[41] Second, although the type of chemotherapy could influence the effect of physical exercise in improving CIPN symptoms, a subgroup analysis by type of chemotherapy could not be performed because the studies included patients with different types of cancer and different chemotherapy treatments, without reporting the isolated effect of exercise by each chemotherapy group separately. Third, the analyses of the pre–post studies included the intervention groups of the RCTs and may differ in their design characteristics; however, we conducted a sensitivity analysis removing the RCTs, and the effect was only slightly modified. Fourth, the scarcity of studies and the small sample size in most of them may decrease the reliability of our findings.

5 | CONCLUSIONS

Our meta-analysis enables us to conclude that exercise interventions effectively reduce the severity of CIPN, improving the SSS and the PDS among patients with cancer or cancer survivors. Furthermore, sensoriomotor training and mind–body exercises seem to be more effective on SSS, and nerve-specific active exercises and mind–body exercises seem to be more effective in improving PDS. Our results have clinical implications since they suggest that exercise is an effective intervention for the management of CIPN. However, further research is needed to compare the effects of the different exercise interventions, as our results may be affected by the lack of adequate comparable RCTs.

6 | PERSPECTIVES

Cancer mortality rates are declining because of advances in cancer diagnosis and treatment, and there has been a threefold increase in the number of cancer survivors over the last 4 decades. CIPN can cause permanent symptoms and disability in 30% to 60% in patient with cancer, producing sensory and motor symptoms which can become crucial limiting factors for therapy, leading to treatment delays, dose reductions, or even the discontinuation of therapy, potentially compromising survival rates. Exercise should be considered as a suitable intervention to reduce the severity of CIPN by improving the severity of the symptoms and the peripheral deep sensitivity among patients with cancer or cancer survivors.

AUTHOR CONTRIBUTIONS

SN-A and VM-V conceived the study and participated in its design and coordination. SN-A, IC-R, and SR-G carried out the literature search, data extraction, and quality assessment. AT-C, PL-G, and SR-G were involved in the data analysis and the interpretation of the data. SN-A and IC-R were involved in the writing of the manuscript. All authors approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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