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Systematic Review

Effectiveness of Exercise-Based Rehabilitation in Chronic Fatigue Syndrome: A Systematic Review and Meta-analysis

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Abstract

International Journal of Exercise Science 18(5): 495-530, 2025. https://doi.org/10.70252/DAYA4589 Chronic Fatigue Syndrome is a complex and debilitating disorder characterized by persistent fatigue, musculoskeletal pain, sleep disturbances, and cognitive impairments. The global prevalence is estimated between 0.2% and 0.4%, affecting over 17 million individuals worldwide, with an estimated burden exceeding 40,000 cases in Spain. Despite the exploration of exercise-based rehabilitation as a therapeutic strategy, its clinical efficacy remains a subject of ongoing debate. This study aims to evaluate the effectiveness of exercise-based rehabilitation relative to conventional treatments in improving functional capacity and alleviating fatigue among adults with CFS A systematic review and meta-analysis were conducted following PRISMA guidelines and registered in the PROSPERO database (CRD42024573955). Searches were systematically performed across MEDLINE, PEDro, CINAHL, Google Scholar, Scopus, and SportDiscus, covering studies published between January 2010 and January 2024. Methodological quality and risk of bias, assessed using the validated PEDro Scale and Cochrane tool, ranged from moderate to good, with bias levels varying from low to high. Inclusion criteria targeted studies investigating structured therapeutic exercise interventions, including aerobic training, resistance exercises, and mind-body therapies. A total of 11 studies were included in the qualitative review, and with 7 randomized controlled trials (n = 2,276 participants) were finally incorporated in the meta-analysis. Exercise-based interventions, including aerobic training, resistance exercises, graded exercise therapy (GET), mind-body therapies and multimodal programs, showed significantly significant reductions in fatigue in both the short term (n = 720) SMD = −0.50; 95% CI: [−0.75, -0.24]; Z = 3.81; p < 0.001) and medium term (n = 501; SMD = −0.53; 95% CI: [−0.95, -0.12]; Z = 2.52; p = 0.01). Medium-term improvements in functionality were also significant (n = 685; SMD = 0.31; 95% CI: [0.11, 0.52]; Z = 2.96; p = 0.003), whereas short-term functionality outcomes were lesser compared to controls (n = 366; SMD = 0.10; 95% CI: [−0.05, 0.25]; Z = 1.29; p = 0.20). Notably, the meta-analytic findings indicated that medium-term functional outcomes slightly favored control groups over exercise interventions, and no significant long-term benefits were observed in either fatigue reduction or functional capacity enhancement. These findings underscore the selective efficacy of exercise-based rehabilitation for CFS, particularly in mitigating fatigue over the short to medium term. However, the transient nature of functional improvements highlights the need for further research to optimize exercise protocols, determine the most effective modalities, and

develop strategies to sustain long-term therapeutic outcomes. While the results support exercise as a potential adjunctive therapy for CFS, they also emphasize the necessity of rigorous, longitudinal investigations to establish its clinical applicability and long-term efficacy.

Keywords: Fatigue syndrome, chronic, exercise therapy, physical endurance

Introduction

Chronic Fatigue Syndrome (CFS), also termed Myalgic Encephalomyelitis (ME), is a debilitating multisystem disorder characterized by profound fatigue, musculoskeletal pain, unrefreshing sleep, and cognitive dysfunction.[1,2] Its pathophysiology remains incompletely understood, though viral infections have been implicated as potential etiological factors.[3,4] Despite its substantial burden on global health, the absence of definitive biomarkers and standardized diagnostic criteria continues to impede precise clinical identification and epidemiological characterization.[5,6] CFS exhibits significant clinical overlap with fibromyalgia, with a global prevalence estimate ranging from 0.5% to 2%, affecting over 17 million individuals worldwide.[7,8] In Spain, the epidemiological landscape remains poorly delineated, though estimates suggest that more than 40,000 individuals may be afflicted.[9,10] Notably, the post-COVID-19 era has introduced additional complexities, as emerging evidence suggests shifts in symptomatology and diagnostic patterns, potentially influencing the reported prevalence and clinical presentation of CFS.[11]

A cardinal clinical feature of CFS is post-exertional malaise, a phenomenon characterized by an exacerbation of symptoms following minimal physical or cognitive exertion.[12,13] This core symptom, often accompanied by fatigue, cognitive impairment, orthostatic intolerance, and widespread pain, significantly disrupts daily functioning and deteriorates quality of life.[14,15] Consequently, there is an urgent imperative to develop and implement efficacious therapeutic interventions. Emerging non-pharmacological modalities, including mindfulness-based practices and yoga, have demonstrated promising outcomes and cost-effectiveness when juxtaposed with conventional pharmacological approaches.[16] Among these interventions, exercise-based interventions has garnered increasing attention as a potential cornerstone in the management of chronic fatigue and pain syndromes[17], offering benefits that extend beyond symptom amelioration to encompass overall functional restoration and quality-of-life enhancement.[18,19,20]

The mechanistic underpinnings of exercise therapy in CFS are hypothesized to involve multiple physiological pathways. Exercise has been postulated to enhance mitochondrial bioenergetics, augmenting cellular ATP production and mitigating bioenergetic deficits commonly observed in CFS.[20-23] Additionally, it has been shown to attenuate systemic inflammation, thereby modulating chronic immune activation—a proposed contributor to disease pathogenesis.[24,25] Furthermore, exercise exerts a regulatory influence on autonomic nervous system function, optimizing stress resilience and cardiovascular homeostasis.[26-28] From a neurophysiological standpoint, exercise has been demonstrated to suppress hyperactive nociceptive signaling via the endogenous analgesic system, facilitated by the release of β-endorphins and enkephalins, which inhibit nociceptive transmission at both spinal and supraspinal levels.[29] Additionally,

neuroplastic modifications within the descending pain modulatory network—particularly within the periaqueductal gray and rostroventral medulla—have been implicated in the enhancement of endogenous pain inhibition, thereby mitigating maladaptive nociceptive processing in CFS.[30,31] These physiological adaptations collectively contribute to reductions in fatigue, improvements in functional capacity, and attenuation of hyperalgesia, thereby underscoring the therapeutic potential of exercise-based interventions.

Despite these mechanistic insights, the clinical application of exercise-based rehabilitation in CFS has been met with considerable debate and caution.[18,32] Concerns regarding impaired physical activity tolerance and the risk of symptom exacerbation have engendered inconsistent implementation and patient adherence.[33,34] Furthermore, existing evidence regarding the efficacy of exercise in ameliorating fatigue and functional impairments remains inconclusive, with methodological heterogeneity across studies contributing to conflicting findings.[35] These uncertainties necessitate a comprehensive synthesis of the available literature to elucidate the therapeutic efficacy, safety, and clinical applicability of exercise-based rehabilitation in the management of CFS.

This study aims to critically evaluate the effectiveness of exercise-based rehabilitation relative to conventional treatments in improving functional capacity and alleviating fatigue among adults with CFS. Specifically, it seeks to determine whether structured exercise interventions confer significant therapeutic benefits across distinct temporal phases—short-term (0–3 months), medium-term (3–6 months), and long-term (≥ 6 months). Given the current limitations in sustained management strategies for CFS, this investigation addresses a critical gap in the literature by systematically appraising the durability and clinical viability of exercise-based interventions. By integrating and synthesizing the existing evidence base, this study aspires to delineate a more precise framework for the clinical adoption of exercise-based rehabilitation and to inform future research endeavors aimed at optimizing treatment paradigms for this complex condition.

Research Question (PICO-T Framework)

This research studies the following research question: In adults with CFS, is exercise-based rehabilitation more effective than conventional treatment in improving fatigue and functional capacity over the short-term (0–3 months), medium-term (3–6 months), and long-term (≥ 6 months)?

Methods

Data Sources and Search Strategy

A systematic literature review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The protocol for this review was previously registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD42024573955. This

study was carried out in full compliance with the ethical standards of the *International Journal of Exercise Science* (IJES).[36]

A systematic literature search was conducted from August 2 to September 2, 2024, to identify studies on the effectiveness of exercise-based rehabilitation for pain, fatigue, function, quality of life, cognitive disturbances, sleep, and memory in adults with CFS. The databases searched included MEDLINE (PubMed), PEDro Database, CINAHL Complete, SportDiscus, Scopus, and Google Scholar. The MEDLINE search strategy used the following terms: "Chronic fatigue syndrome" [MeSH] OR "Myalgic encephalomyelitis" [MeSH] OR "Exercise Therapy" [MeSH] OR "Sleep quality" [MeSH] OR "Exercise" [MeSH] OR "Fatigue" [MeSH] OR "Pain" [MeSH] OR "Memory" [MeSH] OR "Quality of life" [MeSH] OR "graded" [tw] OR "Training" [tw] OR "Cognitive Function" [tw] OR "Physiotherapy" [tw] OR "Functionality" [tw] OR "Exercis*" [tw] OR "Therap*" [tw]. Additionally, a manual search was conducted to ensure comprehensive inclusion of relevant studies. Similar search strategies were applied across other databases.

Table 1. Search Strategy. A detailed overview of the systematic search strategy conducted in this PRISMA-based review.

Search Date	Databases	Search Terms	Search Equations
2/08/24	MEDLINE (PubMed)	Chronic fatigue syndrome [MeSH]; Myalgic encephalomyelitis [MeSH]; Exercise Therapy [MeSH]	(((Chronic Fatigue Syndrome) OR (Myalgic Encephalomyelitis)) AND (Exercise Therapy))
03/08/24	MEDLINE (PubMed)	Chronic fatigue syndrome [MeSH]; Myalgic encephalomyelitis [MeSH]; Exercise Therapy [MeSH]; graded [tw]	(((Chronic Fatigue Syndrome) OR (Myalgic Encephalomyelitis)) AND (Exercise Therapy) AND (Graded))
16/08/24	MEDLINE (PubMed)	Chronic fatigue syndrome [MeSH]; Myalgic encephalomyelitis [MeSH]; Exercise Therapy [MeSH]; Sleep quality [MeSH]	(((Chronic fatigue syndrome) OR (Myalgic encephalomyelitis)) AND (Exercise Therapy)) AND (Sleep quality)
19/08/24	MEDLINE (PubMed)	Myalgic encephalomyelitis [MeSH]; Exercise [MeSH]; Fatigue [MeSH]; Pain [MeSH]	(myalgic encephalomyelitis) AND (exercise) AND (fatigue) AND (pain)
19/08/24	MEDLINE (PubMed)	Chronic fatigue syndrome [MeSH]; Myalgic encephalomyelitis [MeSH]; Exercise Therapy [MeSH]; Training [tw]	(((Chronic fatigue syndrome) OR (Myalgic encephalomyelitis)) AND (Exercise Therapy)) AND (Training)
20/08/24	MEDLINE (PubMed)	Chronic fatigue syndrome [MeSH]; Myalgic encephalomyelitis [MeSH];	(((Chronic fatigue syndrome) OR (Myalgic encephalomyelitis)) AND

		Cognitive Function [tw]; Physiotherapy [tw]	(Cognitive Function)) AND (Physiotherapy)
20/08/24	MEDLINE (PubMed)	Chronic fatigue syndrome [MeSH]; Myalgic encephalomyelitis [MeSH]; Exercise Therapy [MeSH]; Functionality [tw]; Pain [MeSH]	((((Chronic fatigue syndrome) OR (Myalgic encephalomyelitis)) AND (Exercise Therapy)) AND (Functionality)) AND (Pain)
22/08/24	PEDro Database	Chronic fatigue syndrome [MeSH]; Exercis* [tw]	Abstract and Title: chronic fatigue syndrome, AND exercis*, Methods: clinical trial, Since: 2010
23/08/24	PEDro Database	Chronic fatigue syndrome [MeSH]; Myalgic encephalomyelitis [MeSH]; Exercis* [tw]; Therapy* [tw];	Abstract and Title: chronic fatigue syndrome, AND exercis* AND therapy*, Methods: clinical trial, Published Since: 2010
25/08/24	CINAHL Complete	Chronic fatigue syndrome [CINAHL Headings]; Myalgic Encephalomyelitis [CINAHL Headings]; Exercise [CINAHL Headings]	("Chronic Fatigue Syndrome" [CINAHL Headings]) AND ("Myalgic Encephalomyelitis" [CINAHL Headings]) AND ("Exercise Therapy" [CINAHL Headings])
26/08/24	CINAHL Complete	Chronic fatigue syndrome [CINAHL Headings]; Myalgic encephalomyelitis [CINAHL Headings]; Memory [CINAHL Headings]; Exercis* [tw]	("Chronic Fatigue Syndrome" [CINAHL Headings]) OR ("Myalgic Encephalomyelitis" [CINAHL Headings]) AND ("Memory" [CINAHL Headings]) AND ("Exercise" [CINAHL Headings] OR exercis* [tw])
26/08/24	CINAHL Complete	Chronic fatigue syndrome [CINAHL Headings]; Myalgic encephalomyelitis [CINAHL Headings]; Quality of life [CINAHL Headings]; Exercise [CINAHL Headings]; Exercis* [tw]	("Chronic Fatigue Syndrome" [CINAHL Headings]) OR ("Myalgic Encephalomyelitis" [CINAHL Headings]) AND ("Quality of Life" [CINAHL Headings]) AND ("Exercise" [CINAHL Headings] OR exercis* [tw])
01/09/24	SPORTDiscus	Chronic fatigue syndrome [MeSH]; Exercise Therapy [MeSH]	(chronic fatigue syndrome) AND (exercise therapy)
01/09/24	Scopus	Chronic fatigue syndrome [MeSH]; Exercise Therapy [MeSH]	"chronic fatigue syndrome" AND "exercise therapy"
02/09/24	Google Scholar	Chronic fatigue syndrome [MeSH]; Exercise Therapy [MeSH]	(chronic fatigue syndrome) AND (exercise therapy)

02/04/25	MEDLINE (PubMed)	Chronic fatigue syndrome [MeSH]; Myalgic encephalomyelitis [tw]; Systemic Exertion Intolerance Disease [tw]; Exercise [MeSH]	("Chronic Fatigue Syndrome"[MeSH] OR "Myalgic Encephalomyelitis"[MeSH] OR "Systemic Exertion Intolerance Disease"[MeSH]) AND ("Exercise"[MeSH] OR "Exercise"[tw])
05/04/25	PEDro Database	Chronic fatigue syndrome [MeSH]; Myalgic encephalomyelitis [tw]; Systemic Exertion Intolerance Disease [tw]; Exercise [MeSH]	Abstract and Title: chronic fatigue syndrome, OR myalgic encephalomyelitis, OR systemic exertion intolerance disease AND exercis* Methods: clinical trial, Published Since: 2010
06/04/25	CINAHL Complete	Chronic fatigue syndrome [CINAHL Headings]; Myalgic encephalomyelitis [CINAHL Headings]; Systemic Exertion Intolerance Disease [CINAHL Headings]; Exercise [CINAHL Headings]	("Chronic Fatigue Syndrome" [CINAHL Headings]) OR ("Myalgic Encephalomyelitis" [CINAHL Headings]) OR ("Systemic Exertion Intolerance Disease" [CINAHL Headings]) AND ("Exercise" [CINAHL Headings])
07/04/25	SPORTDiscus	Chronic fatigue syndrome [MeSH]; Myalgic encephalomyelitis [tw]; Systemic Exertion Intolerance Disease [tw]; Exercise [MeSH]	(chronic fatigue syndrome) OR (myalgic Encephalomyelitis) OR (systemic exertion intolerance disease) AND (exercise)
09/04/25	Scopus	Chronic fatigue syndrome [MeSH]; Myalgic encephalomyelitis [tw]; Systemic Exertion Intolerance Disease [tw]; Exercise [MeSH]	"chronic Fatigue Syndrome" OR "myalgic encephalomyelitis" OR "systemic exertion intolerance disease"AND "exercise"
09/04/25	Google Scholar	Chronic fatigue syndrome [MeSH]; Myalgic encephalomyelitis [tw]; Systemic Exertion Intolerance Disease [tw]; Exercise [MeSH]	(chronic fatigue syndrome) OR (myalgic Encephalomyelitis) OR (systemic exertion intolerance disease) AND (exercise)

Eligibility criteria

The inclusion criteria for this study were defined as follows: (1) clinical trials employing randomized or non-randomized designs; (2) studies published between 2010 and January 2024; (3) articles available in English or Spanish; (4) full-text accessibility; (5) studies involving adult participants (≥18 years) of both sexes diagnosed with chronic fatigue syndrome or myalgic encephalomyelitis, with explicit reporting of age distribution when available; (6) inclusion of at least one intervention group engaged in a structured therapeutic exercise program; (7)

assessment of primary outcomes related to fatigue, functional capacity, and quality of life; (8) follow-up evaluations conducted at short-term (≤3 months), medium-term (3–6 months), and/or long-term (≥ 6 months) intervals; and (9) explicit documentation of participants' age, disease duration, and severity classification (e.g., mild, moderate, severe) when reported. In order to ensure the methodological rigor and reproducibility, included studies were required to specify the diagnostic criteria applied for CFS or ME, as well as provide a detailed description of the therapeutic exercise intervention, including type, frequency, intensity, and duration.

Study selection

To ensure a rigorous and transparent study selection process, we adopted a dual-reviewer approach at every stage, adhering to best practices for systematic reviews.[37,38] In this regard, two independent researchers (AVM and ADS) conducted the initial literature search and screened all retrieved articles based on their titles and abstracts. With the aim of minimizing bias and reduce the risk of excluding relevant studies, a third researcher (SMP) independently reviewed the screening results, adding an extra layer of verification. Subsequently, for the full-text assessment, AVM and SMP independently evaluated each publication's eligibility, engaging in discussions to resolve any discrepancies. In cases where consensus could not be reached, a fourth author (IMP) served as a referee, thereby ensuring fairness and methodological consistency.

Data extraction

Data extraction was conducted independently by two authors (AVM and ADS). In cases of discrepancies, both authors discussed the differences in order to reach a consensus. If disagreements persisted, a third author (SMP) also mediated the resolution process. For systematic data collection, a standardized template, structured according to the PICO (Population, Intervention, Comparison and Outcomes) framework was employed. Specifically, the extracted information included authorship, year and country of publication, study design, research objectives, key findings, participant characteristics (age, CFS duration, and severity levels), intervention and control details, measured outcomes, and study conclusions. This process adhered to the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0).[39] To further enhance data reliability, the extraction table was pre-tested on a representative subset of the included studies before its full implementation.

Methodological Quality Assessment (PEDro Scale)

The PEDro scale was employed to evaluate the methodological quality of the clinical trials included in this review.[40] This scale comprises 11 items, each scored with one point, designed to assess whether a randomized clinical trial possesses adequate internal validity (criteria 2 to 9) and sufficient statistical information to render its results interpretable (criteria 10 to 11). Trials scoring 9 to 10 on the PEDro scale were considered to have excellent methodological quality, those scoring between 6 and 8 were deemed to have good methodological quality, and studies scoring below 4 were categorized as having poor methodological quality.

Risk of bias Assessment (RoB 2.0)

The risk of bias in randomized clinical trials was assessed using the Cochrane Risk of Bias for Randomized Clinical Trials (RoB 2.0) tool.[41] This tool evaluates the methodological approaches employed by researchers and rates the presence of biases in five specific domains: (1) the randomization process, (2) deviations from intended interventions, (3) missing outcome data, (4) measurement of outcomes, and (5) selection of the reported outcome. The interpretation of these assessments considers a low risk of bias as indicative that any bias present is unlikely to meaningfully alter the study results, while a high risk of bias reflects reduced confidence in the findings. Any disagreements among the authors were resolved through discussion, and in cases of contradictory assessments, the decision of a third review author (SMP) was final.

Grade of Recommendation (GRADE)

The certainty of the evidence was determined using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework, which evaluates evidence across five domains: study design, imprecision, indirectness, inconsistency, and publication bias[42]. Evidence was categorized into four levels: high quality (all domains satisfied), moderate quality (one domain not satisfied), low quality (two domains not satisfied), and very low quality (three or more domains not satisfied).

Data Synthesis

Meta-analyses were conducted using Review Manager (RevMan v.5.3; Cochrane Collaboration, Oxford, UK)[43] when more than two studies reported the same outcome. For pooled analyses, outcome data were categorized by duration into short-term (≤ 3 months), medium-term (3-6 months), and long-term (≥ 6 months), based on previous research frameworks. When conversion of units was not feasible, standardized mean differences (SMDs) were employed. Results are presented as SMDs with 95% confidence intervals (CIs).

The I^2 statistic was used to quantify statistical heterogeneity: 0-40% as probably not important; 30-60% as moderate heterogeneity; 50-90% as substantial heterogeneity; and 75-100% as considerable heterogeneity. A fixed-effect model was initially used for analysis; however, if substantial heterogeneity ($I^2 > 40\%$) was detected, a random-effects model was applied.

Results

Study selection

The study selection process, as shown in the diagram, begins with the identification of studies through various databases and registers. A total of 372 records were identified from MEDLINE (PubMed) (n = 197), CINAHL Complete (n = 64), PEDro (n = 54), Google Scholar (n = 25), SportDiscus (n = 21), and Scopus (n = 11). Of these, 203 duplicate records were removed before the initial screening.

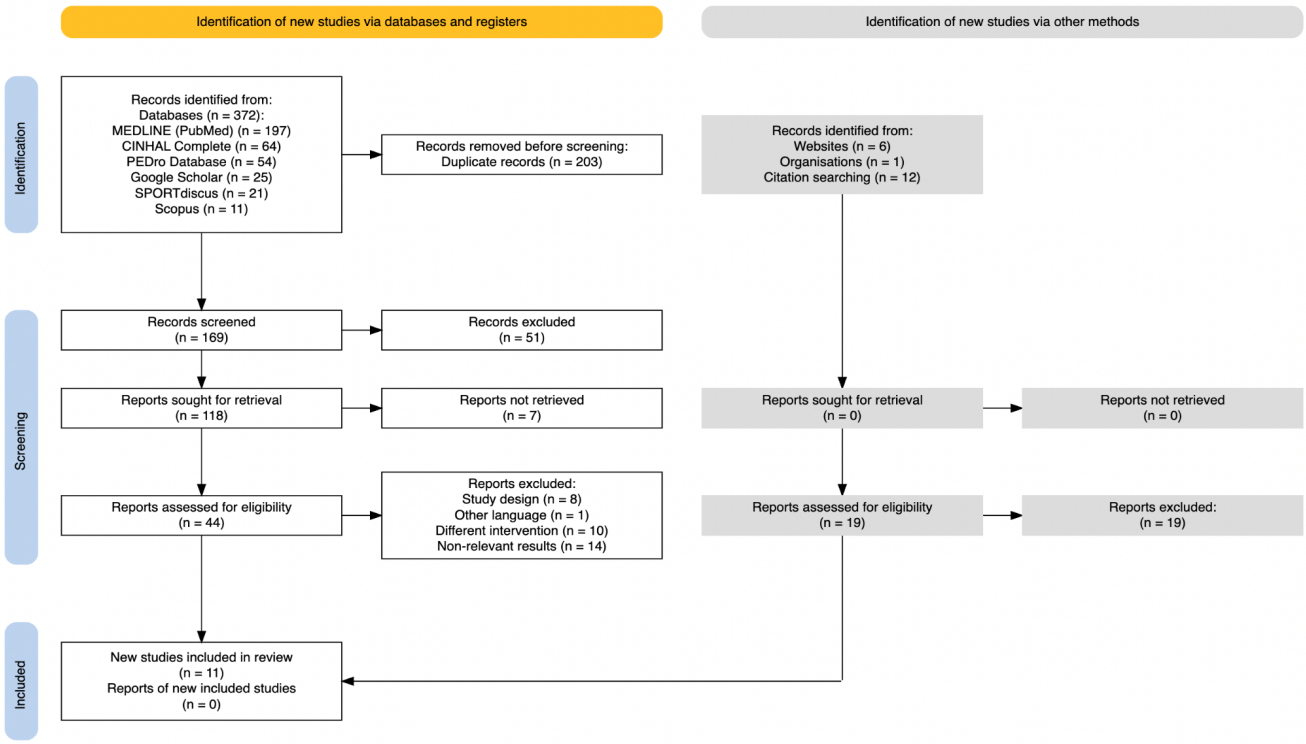


Figure 1. Study Selection Diagram (PRISMA, 2020). Adapted from: Haddaway NR, Page MJ, Pritchard CC, McGuinness LA. PRISMA2020: An R package and Shiny app for producing PRISMA 2020-compliant flow diagrams, with interactivity for optimized digital transparency and Open Synthesis. *Campbell Syst Rev.* 2022;18:e1230. doi: 10.1002/cl2.1230.

In the screening phase, 169 records were reviewed after the removal of duplicates. From these, 118 full-text reports were requested for retrieval. Fifty-one records were excluded in this initial phase, and 7 reports could not be retrieved. Subsequently, 44 full-text articles were assessed for eligibility. After this evaluation, 33 articles were excluded for not meeting the established inclusion criteria: 8 for inappropriate study design, 1 for being in a non-included language, 10 for focusing on different interventions, and 14 for providing non-relevant results to the research question.

In the inclusion phase, 11 studies were selected for qualitative review and 7 were included in the meta-analysis,[44,47,48,51-54] with 4 articles[45,46,49,50] excluded due to low methodological quality or a high risk of critical bias. Further details are provided in Figure 1. Study Selection Diagram (PRISMA, 2020).

Study characteristics

The 11 studies included in this review encompassed a range of clinical trial designs, including 5 randomized controlled trials,[46,47,48,50,52] 2 prospective randomized controlled trials,[45,53] 2 parallel four-arm multicenter controlled trials,[49,54] 1 randomized crossover design study,[45] and 1 open-label pragmatic randomized controlled trial.[44] These studies focused on populations diagnosed

with CFS undergoing treatments incorporating physical exercise, with a total sample size of 2,443 patients (437 men and 2,006 women, mean age 39.84 years).

Most studies implemented exercise interventions, primarily supervised multimodal programs, with walking being the most commonly utilized activity (n = 4).[44,50,53,54] Other exercise modalities included flexibility and relaxation exercises (n = 1),[53] continuous and interval cycle ergometer exercise (n = 1),[45] Qigong exercise (n = 3),[46,47,52] graded exercise therapy (GET) (n = 4),[44,49,53,54] and isometric yoga (n = 1).[48] Follow-up periods varied from 25 minutes[45] to 12 months.[49,53,54]

These studies were conducted across several countries, including the United Kingdom (n = 4),[44,49,53,54] China (n = 4),[46,47,50,52] Japan (n = 1),[48] Spain (n = 1),[53] and Australia (n = 1).[45] See Table 2 for the detailed characteristics of the included studies.

Methodological Quality Assessment (PEDro Scale)

The methodological quality of the studies included in our review was generally considered good, with a mean PEDro score of 6.72 out of 10 (SD = 1.13). In assessing methodological quality, 6 studies were identified as moderate methodological quality,[44, 48,51,52,53,54] 3 had acceptable methodological quality,[45,47,49] and 2 studies were rated as having low methodological quality.[46,50] Most studies demonstrated systematic deficiencies in blinding, as none blinded either patients or therapists. Outcome assessors were blinded in only 2 of the studies.[44,53] Further details are available in Table 3.

Risk of Bias Assessment (RoB 2.0)

The risk of bias in the included randomized clinical trials, as assessed using the ROB 2.0 tool, ranged from low to moderate. Analysis of specific biases revealed a high risk associated with deviations from intended interventions in most of the studies, primarily due to the lack of blinding of participants and staff (n = 8)[44-50,52]. Additionally, there was a high risk of bias concerning the blinding of outcome assessors (n = 8)[44-50,52]. Regarding the randomization

Table 2. Characteristics of the included studies.

Author, Year	Study Design	Participants	Intervention	Comparison	Outcomes	Conclusion
Clark et al (2017)[44] United Kingdom	Pragmatic randomized controlled trial. Participants and therapists were not blinded.	N=211 (M=44; F=167) **Inclusion**: Adults diagnosed with CFS based on UK NICE criteria (≥4 months of clinically evaluated fatigue with activity reduction and associated symptoms). **Exclusion:** Under 18, psychiatric conditions, contraindicated exercise, prior GET	**IG (N=107):** *Graded Exercise Therapy (GET)* Self-help graded exercise program with standard medical care **Protocol duration:** 12 weeks, daily sessions via phone/Skype with a physiotherapist	**CG (N=104):** *Standard medical care* **Protocol duration:** 12 weeks	**- Fatigue (Chalder Fatigue Questionnaire):** • IG pre: 26.3 (4.8), post: 19.1 (7.6) • CG pre: 26.0 (4.6), post: 22.9 (6.9). • Difference: p<0.0001, ES=0.5 **- Physical Function (SF-36 PF):** • IG pre: 47.3 (22.2), post: 55.7 (23.3) • CG pre: 50.1 (22.6), post: 50.8 (25.3). • Difference: p=0.006, ES=0.2	GET is a safe intervention that may reduce fatigue and, to a lesser extent, physical disability in CFS patients. Findings require confirmation and extension to other healthcare settings.
Sandler et al (2016)[45] Australia	Randomized crossover trial	N=14 (M=5; F=9) **Inclusion**: Meets international CFS criteria, stable symptom pattern, regular walking without symptom exacerbation	**IG1 (N=14)**: *Continuous Exercise (CONT)* 1 session on ergometer at a constant intensity of 70% expected max HR during 15-25 minutes.	**IG2**: *High-Intensity Interval Training (HIIT)* (N=15) 1 session of high-intensity interval exercise on ergometer; 100s at 75-80% expected max	**- Fatigue (Fatigue and Energy Scale-FES):** • HIIT: Pre 4.5 (1.8), Post 5.5 (2.1) • CONT: Pre 4.1 (1.7), Post 5.6 (1.9) Difference: p = 0.20	HIIT did not exacerbate fatigue more than continuous exercise at a comparable workload. This supports the inclusion of HIIT

		Exclusion: Drugs affecting heart rate, conditions preventing exercise	**Protocol duration:** 2 weeks	HR followed by 175 second active rest during 15-25 minutes. **Protocol duration:** 2 weeks **CG**: Crossover design, participants served as their own controls.	**Sleep Quality (modified PSQI):** • IG1: pre: 2.7 (1.4), post: 2.9 (2.1), p=0.36 • IG2 pre: 3.6 (2.4), post: 2.5 (1.4) Difference: p = 0.07	in graded exercise therapy for CFS patients.
Li et al (2015)[46] Hong Kong, China	Prospective randomized controlled trial	N=46 (M=6; F=40) **Inclusion**: Persistent, unexplained CFS not alleviated by rest, accompanied by more than 4 symptoms. **Exclusion**: Over 60 years, any medical condition.	**IG:** *Qigong exercises* (N=22). **Frequency**: Group training twice a week for 2 hours during the first 4 weeks; home exercises 3 times per week for 15-30 minutes over 12 weeks. **Protocol duration:** 3 months	**CG:** *Normal activity* (N=24). Waitlist, maintaining usual lifestyle. **Protocol duration:** 3 months	**- Fatigue (Chalder Fatigue Questionnaire):** • IG pre: 41.5 (28-53), post: 21 (8-34) • CG pre: 40 (31-53), post: 37 (11-50) Difference: p=0.003. **- Mental Health (12-Item Short-Form Health Survey):** • IG pre: 31.49 (12.20-49.65), post: 45.54 (28.88-57.16) • CG pre: 35.63 (11.09-49.14), post: 36.59 (16.43-54.25) Difference: p=0.002.	Qigong improved fatigue, psychological quality of life, and spiritual well-being in bereaved individuals with CFS-like illness.

					-Spiritual Well-being: • IG: Pre 63, Post 72 • CG Pre 78.5, Post 68 Difference: p = 0.013.	
Chan et al (2014)[47] Hong Kong, China	Randomized, waitlist-controlled trial. Participants were not blinded.	N=150 (M=42; F=108) **Inclusion:** Fatigue >6 months with >4 symptoms, no medical history **Exclusion:** Recent Qigong practice, over 50 years	**IG (N=75)**: *Qigong exercise* **Protocol duration:** 3 months **Frequency:** 16 group sessions of 90 minutes, daily home exercises for 30 minutes	**CG (N=75)**: *Normal activity* Waitlist, maintaining ther lifestyle. **Protocol duration:** 3 months	**-Fatigue (Chalder Fatigue Questionnaire):** • IG Pre 37.4 (6.2), Post 25.6 (12.6) • IG 3 months: 25.2 (12.7) • CG Pre 36.4 (8.3), Post 32.3 (9.7) • CG 3 months: 31.1 (10.9) Difference: p<0.001 **- Sleep Quality (PSQI):** • IG pre: 10.0 (3.7), post: 8.2 (3.4) • CG pre: 10.2 (3.8), post: 9.5 (3.7). Difference: p=0.002 **-Anxiety (HADS)**: • IG: Pre 10.9 (3.7), Post 8.5 (4.0) • IG 3 months: 8.8 (4.4) • CG: Pre 11.2 (3.6), Post 10.4 (4.0) • CG 3 months: 10.2 (4.0)	Qigong was an effective and acceptable treatment for sleep disorders.

					Difference: p = 0.016. **- Depression (HADS):** • IG Pre 9.4 (3.5), Post 6.6 (3.7), • IG 3 months: 7.2 (4.1) • CG: Pre 9.5 (3.4), Post 8.8 (3.9) • CG 3 months: 8.5 (4.0) Difference: p < 0.001.	
Oka et al (2014)[48] Japan	Randomized controlled trial	N=30 (M=6; F=24). Inclusion: 20-70 years old, fatigue causing absence from work, ability to sit for over 30 minutes, able to visit hospital weekly. Exclusion: Previous yoga practice, any medical condition.	**IG (N=15):** Isometric Yoga + Conventional Pharmacotherapy Frequency: Bi-weekly 20-minute sessions with a tutor and daily home sessions. **Protocol duration:** 2 months.	**CG (N=15):** Conventional Pharmacotherapy **Protocol duration:** 2 months.	**-Fatigue (Chalder Fatigue Scale, FS)** • **IG pre:** 25.9 (6.1), **post:** 19.2 (7.5) • **CG pre:** 26.1 (6.2), **post:** 25.8 (5.9) **Difference:** *p = 0.002* (significant improvement in yoga group) **-Fatigue (Profile of Mood States, POMS Fatigue Score)** • **IG pre:** 21.9 (7.7), **post:** 13.8 (6.7) **Difference:** *p* < 0.001	Isometric yoga as a complementary therapy is feasible and effective in relieving fatigue and pain.

					-Pain (SF-8 Bodily Pain Subscale) • **IG pre:** 41.3 (6.7), **post:** 48.1 (7.9) **Difference:** p = 0.0001 **-Health-related Quality of Life (SF-8 General Health & Physical Component Summary)** • **General Health (GH) pre:** 39.3 (5.3), **post:** 43.6 (6.0) (p = 0.002) • **Physical Component Summary (PCS) pre:** 35.8 (7.2), **post:** 40.6 (4.7) **Difference:** p = 0.024	
White et al (2013)[49] United Kingdom	Randomized, multicenter,	N=640 (M=147; F=493). Inclusion: Fatigue for over 6 months with more than 4	**IG1 CBT (N=161):** *Cognitive Behavioral Therapy* **IG2**: GET (N=160) -	**CG (N=160):** *Specialist Medical Care (SMC)* Explanation of CFS, self-help advice, and	**-Fatigue (Chalder Fatigue Questionnaire**): • CBT vs APT: 3.36 (1.64–6.88), p=0.001 • CBT vs SMC: 3.69 (1.77–7.69), p<0.001 • GET vs APT: 3.38 (1.65–6.93), p=0.001	The study confirms that recovery from CFS is possible, with CBT and GET

	parallel-group trial	symptoms, no medical history.	Graded Exercise Therapy **IG3**: APT (N=159) - Adaptive Pacing Therapy. **Protocol duration:** 52 weeks.	pharmacotherapy. **Protocol duration:** 52 weeks.	• GET vs SMC: 3.71 (1.78–7.74), p<0.001 • APT vs SMC: 1.10 (0.47–2.58), p=0.83.	being the therapies most likely to lead to recovery.
Chan et al (2013)[50] Hong Kong, China	Randomized, waitlist-controlled trial. Participants were not blinded.	N=137 (M=32; F=105) **Inclusion:** CFS-like illness based on CDC criteria (self reported symptoms for ≥6 months	**IG (N=72):** *Qigong Exercise.* Daily home training for 30 minutes over 12 weeks. Frequency: 10 group sessions of 2 hours over 5 weeks. **Protocol duration:** 4 months	**CG (N=65):** *Normal activity.* Participants were asked not to attend any Qigong exercise classes during the protocol duration. **Protocol duration:** 4 months	**-Fatigue (Chalder Fatigue Questionnaire):** • GI: Pre 39.7 (6.6), Post 26.6 (13.6) • GC: Pre 39.8 (6.3), Post 33.2 (9.6) Difference: p<0.001 **-Depression (HADS):** • GI: Pre 9.1 (2.0), Post 7.7 (3.2) • GC: Pre 9.4 (2.2), Post 9.8 (4.1) Difference: p <0.001 **-Anxiety (HADS)**: No significant differences (p = 0.584)	Qigong can be used as an alternative therapy or rehabilitation as it may effectively reduce fatigue and depression.

Ridsdale et al (2012)[51] United Kingdom	Randomized controlled trial	N=222 (M=48; F=174). **Inclusion:** Age 16-75, fatigue for more than 3 months as the main symptom, completion of relevant tests. **Exclusion:** Score <4 on fatigue scale, conditions that could cause fatigue, psychiatric illness and/or treatment, inability to travel to hospital.	**IG1 (N=71):** *Graded Exercise Therapy*. **Frequency**: 8 sessions at 2-week intervals. **IG2**: COUNS (N=76) - 50-minute counseling sessions. **Frequency**: 8 sessions at 2-week intervals. **Protocol duration:** 12 months.	**CG (N=75):** *Usual care* (BUC) Usual medical care plus a self-help CBT booklet. **Protocol duration:** 12 months.	**- Fatigue (Chalder fatigue score):** • GET: pre 24.8 (4.9), post (6 months) 14.6 (8.5), post (12 months) 14.5 (7.7) • COUNS: pre 24.8 (4.7), post (6 months) 16.2 (8.2), post (12 months) 15.2 (8.4) • BUC: pre 23.4 (4.5), post (6 months) 15.3 (8.0), post (12 months) 13.8 (7.7). Differences: GET vs BUC: p=0.94; COUNS vs BUC: p=0.24.	Compared to BUC, patients treated with graded exercise therapy or counseling did not significantly improve in terms of fatigue, although they were less dissatisfied after 1 year. This evidence is generalizable both nationally and internationally.
Ho et al (2012)[52] Hong Kong, China	Randomized controlled trial	N=64 (Male: 13; Female: 51) Inclusion Criteria: Adults aged 18-55 who met CDC criteria for Chronic Fatigue Syndrome (CFS). Availability to participate in the study.	**IG:** N=33 - Group Qigong training sessions (2 hours) and a home-based Qigong exercise program (30 minutes). Frequency: Group training twice a week;	**CG**: N=31 - Engaged in regular daily activities. Participants were asked not to attend any Qigong exercise classes during the study duration.	**- Fatigue (Chalder Fatigue Scale):** • IG: Pre 39.9 (6.3), Post (5 weeks) 26.3 (10.9), Post (4 months) 21.6 (10.4) • CG: Pre 39.7 (6.1), Post (5 weeks) 34.8 (8.0), Post (4 months) 32.1 (8.8) • Difference: $p < 0.001$	Qigong exercise can be used as an alternative and complementary therapy or rehabilitation program for chronic fatigue and CFS.

		Exclusion Criteria: Presence of chronic limiting pathology or any condition that could explain fatigue. Participation in Qigong exercises within the last 6 months.	daily home exercises **Protocol Duration:** 4 months (5 weeks of group training, followed by 12 weeks of home exercises).	**Protocol Duration:** 4 months.	**- Functionality (Medical Outcomes Study 12-Item Short-Form Health Survey):** ● Physical: ○ IG: Pre 36.9 (7.2), Post (5 weeks) 38.4 (6.1), Post (4 months) 42.7 (7.2) ○ CG: Pre 35.7 (7.1), Post (5 weeks) 37.5 (8.1), Post (4 months) 35.7 (9.5) ○ Difference: p = 0.48 ● Mental: ○ IG: Pre 32.5 (10.7), Post (5 weeks) 43.8 (6.9), Post (4 months) 0.102 (0.051) ○ CG: Pre 33.5 (9.6), Post (5 weeks) 34.6 (9.6), Post (4 months) 37.8 (5.6) ○ Difference: p = 0.001	

Núñez et al (2011)[53] Spain	Prospective randomized controlled trial with a 12-week follow-up	N = 113 (M = 12; F = 101)	**IG** (N = 58): Multidisciplinary treatment including group CBT, GET, and conventional symptomatic pharmacological treatment. Frequency: GET 3 times a week (1-hour sessions) **Protocol Duration:** 3 months	**CG** (N = 57): Standard treatment for CFS; exercise counseling and conventional symptomatic pharmacological treatment. **Protocol Duration:** 3 months	**-Health-Related Quality of Life (HRQL) (SF-36):** *Pain:* • IG: Pre 27.09 (24.22), Post 21.81 (21.43), Difference: p = 0.838 • CG: Pre 27.41 (19.04), Post 29.34 (21.58), Difference: p = 0.051 **Difference:** p = 0.04 *Physical Functionality:* • IG: Pre 39.69 (22.8), Post 32.63 (22.52), Difference: p = 0.004. • CG: Pre 40.04 (22.09), Post 38.28 (22.73), Difference: p = 0.975 **Difference:** p = 0.147 *Fatigue (FIS):* • IG: Pre 137.3 (9.6), Post 139.2 (8.3) CG: Pre 135.7 (10.5), Post 137.4 (10.1)	The multidisciplinary treatment was not superior to the standard treatment after 12 months in terms of HRQL. The potential benefits of GET as part of the multidisciplinary treatment for CFS should be evaluated individually for each patient.
White et al (2011)[54] United Kingdom	Randomized, multicenter, parallel,	N = 641 (M = 145; F = 496)	**IG1 APT (N=159):** Adaptive Pacing Therapy based on "envelope	**CG SMC (N=160)**: Standard medical care, including an	**-Fatigue (Chalder Fatigue Questionnaire):** • APT: Pre 28.5 (4), Post (12 weeks) 24.2 (6.4), Post (24 weeks)	

	four-group trial		theory" provided by an occupational therapist. **IG2:** CBT (N=161): Cognitive Behavioral Therapy provided by a clinical psychologist or nurse. **IG3:** GET (N=160): Graded Exercise Therapy primarily conducted by physiotherapists. Frequency: 14 sessions over the first 23 weeks; the first 4 sessions were once a week and then once every 2 weeks. A booster session was	explanation of CFS, generic and specific self-help advice, and symptomatic pharmacotherapy. **Protocol duration**: 12 weeks	23.7 (6.9), Post (52 weeks) 23.1 (7.3) • CBT: Pre 27.7 (3.7), Post (12 weeks) 23.6 (6.5), Post (24 weeks) 21.5 (7.8), Post (52 weeks) 20.3 (8.0) • GET: Pre 28.2 (3.8), Post (12 weeks) 22.8 (7.5), Post (24 weeks) 21.7 (7.1), Post (52 weeks) 20.6 (7.5) • SMC: Pre 28.3 (3.6), Post (12 weeks) 24.3 (6.5), Post (24 weeks) 24 (6.9), Post (52 weeks) 23.8 (6.6) **- Fatigue (Chalder Fatigue Questionnaire):** Difference (52 weeks): • APT vs. SMC: p=0.38 • CBT vs. SMC: p=0.0001 • GET vs. SMC: p=0.0003 • GET vs. APT: p=0.0059 **-Physical Functionality (Short Form-36 Physical Function Subscale)**: • APT: Pre 37.2 (16.9), Post (12 weeks) 41.7	CBT and GET can be safely added to standard medical treatment to moderately improve outcomes in Chronic Fatigue Syndrome, while APT is not an effective addition.

			offered at 36 weeks. **Protocol duration:** 12 weeks		(19.9), Post (24 weeks) 43.2 (21.4), Post (52 weeks) 45.9 (24.9) • CBT: Pre 39 (15.3), Post (12 weeks) 51 (20.7), Post (24 weeks) 54.2 (21.6), Post (52 weeks) 58.2 (24.1) • GET: Pre 36.7 (15.4), Post (12 weeks) 48.1 (21.6), Post (24 weeks) 55.4 (23.3), Post (52 weeks) 57.7 (26.5) • SMC: Pre 39.2 (15.5), Post (12 weeks) 46.6 (20.4), Post (24 weeks) 48.4 (23.1), Post (52 weeks) 50.8 (24.7) **-Physical Functionality (Short Form-36 Physical Function Subscale)** Difference (52 weeks): • APT vs. SMC: p=0.18 • CBT vs. SMC: p=0.0068 • GET vs. SMC: p=0.0005 • GET vs. APT: p<0.0001	

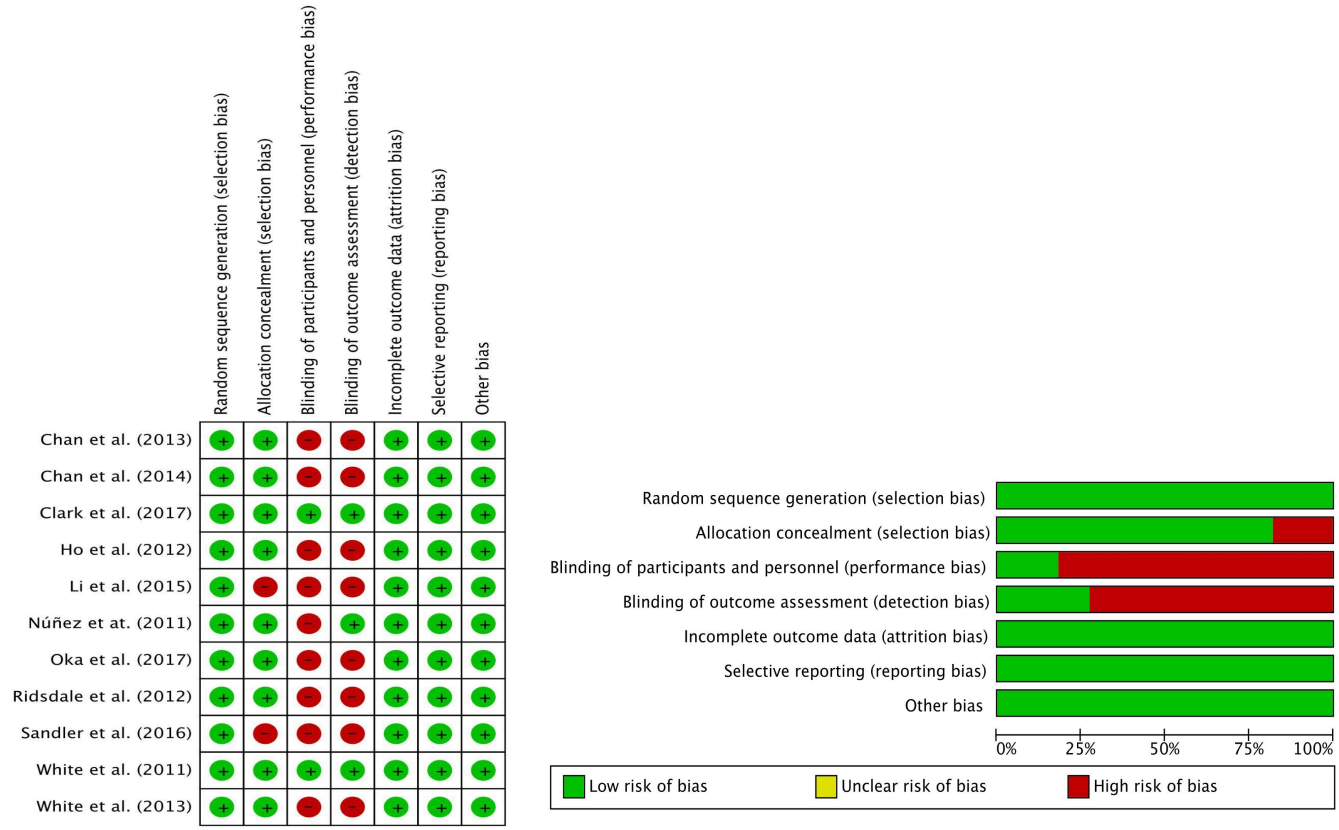
Abbreviation. APT: Adaptive Pacing Therapy; BUC: Usual Care; CBT: Cognitive Behavioral Therapy; CDC: Centers for Disease Control and Prevention; CFS: Chronic Fatigue Syndrome; CG: Control Group; Chalder Fatigue Questionnaire: A tool for measuring the severity of fatigue; COUNS: Counseling; ES: Effect Size; F: Female; FIS: Fatigue Impact Scale; GET: Graded Exercise Therapy; GI: Group Intervention; HADS: Hospital Anxiety Depression Scale; HRQL: Health-Related Quality of Life; IG: Intervention Group; M: Male; N: Number of Participants; PSQI: Pittsburgh Sleep Quality Index; Qigong: A form of exercise involving coordinated movements, breathing, and meditation; RCT: Randomized Controlled Trial; SF-36: Medical Outcomes Study Short-Form; SF-36 PF: Short Form-36 Physical Function Subscale; SMC: Specialist Medical Care.

process, a high risk of bias was noted in some studies due to inadequate concealment in the randomization sequence (n = 2)[46,50]. Further details can be found in Table 4.

Table 3. Methodological Quality Analysis (PEDro Scale). This table presents the assessment of the methodological quality of the studies included in the review. Each criterion is scored as "Y" (Yes) if the study meets the criterion and "N" (No) if it does not.

Author, Year	Score	Quality	1	2	3	4	5	6	7	8	9	10	11
Clark et al (2017)[44]	8	Moderate	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y
Sandler et al (2016)[45]	6	Good	Y	Y	N	Y	N	N	N	Y	Y	Y	Y
Li et al (2015)[46]	5	Low	Y	Y	N	Y	N	N	N	Y	N	Y	Y
Chan et al (2014)[47]	6	Good	Y	Y	Y	Y	N	N	N	N	Y	Y	Y
Oka et al (2014)[48]	7	Moderate	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y
White et al (2013)[49]	6	Good	Y	Y	Y	Y	N	N	N	Y	Y	Y	N
Chan et al (2013)[50]	5	Low	Y	Y	N	Y	N	N	N	Y	Y	Y	Y
Ridsdale et al (2012)[51]	8	Moderate	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y
Ho et al (2012)[52]	7	Moderate	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y
Núñez et al (2011)[53]	8	Moderate	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y
White et al (2011)[54]	8	Moderate	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y

Table 4. Risk of Bias Analysis (ROB 2.0). This table presents the risk of bias evaluation for each included study, conducted using the Cochrane Risk of Bias 2.0 (ROB 2.0) tool.



Grade of Recommendation (GRADE)

The GRADE evaluation of exercise-based rehabilitation studies in CFS patients indicates low to moderate quality of evidence for both physical functionality and fatigue reduction. For physical functionality, 5 studies involving 552 subjects were analyzed,[44,49,50,53,54] while for fatigue, 8 studies with 1,746 subjects were assessed.[44-49,52,54] Both categories exhibited serious risk of bias and notable inconsistency, primarily due to methodological limitations such as lack of blinding of participants, therapists, and outcome assessors.

However, the studies did not present serious concerns regarding indirectness, imprecision, or publication bias. Consequently, the recommendation for exercise-based interventions remains weak but favorable, supporting exercise as a viable approach for improving physical function and fatigue in CFS patients. Further details are available in **Table 5** GRADE of Recommendation**.**

Table 5. Grade of recommendation (*GRADE*). This represents a summary of evidence quality and strength of recommendations using the *GRADE* system. Notes: *Risk of Bias: Some studies showed limitations in the design and implementation of interventions, which may introduce bias. ‡Inconsistency: Significant variations were observed in the study results, which may be due to differences in population, intervention, and measurement methods. The results presented are based on individual studies and should be interpreted with caution. The quality assessment and recommendation were conducted following the *GRADE* criteria (Grading of Recommendations Assessment, Development, and Evaluation).

Outcomes	**Number of Studies (subjects)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**	**Quality**	**Grade of Recommendation**
Physical Functionality	4 (n=344)	Serious *	Serious‡	Not serious	Not serious	Not serious	Low	Weak in favor
Fatigue	7 (n=1157)	Low	Not serious	Not serious	Not serious	Not serious	Moderate quality	Weak in favor

Data synthesis

Effect size of exercise-based rehabilitation for Chronic Fatigue Syndrome in the short-term (< 3 months).

Our meta-analysis indicates that exercise-based programs (aerobic training, resistance exercises, GET, Qigong, and multimodal interventions) lead to a modest but significant reduction in fatigue in CFS patients. Aerobic training (20–40 min, 3–5 times/week)[44,54] and resistance exercises (*low-to-moderate* load) were progressively intensified[52]. GET followed a structured, gradual increase in activity,[54] while Qigong incorporated breathing and relaxation techniques.[47,52] The studies included in this analysis were of moderate to high methodological quality, with a low to moderate risk of bias.[44, 47, 52, 54] Despite substantial heterogeneity across studies ($Tau^2 = 0.04$; $I^2 = 62\%$), the overall effect size remained small yet significant (n = 720, SMD = −0.49; 95% CI: [−0.75, -0.24]; Z = 3.81; p = 0.0001), as detailed in Figure 2.

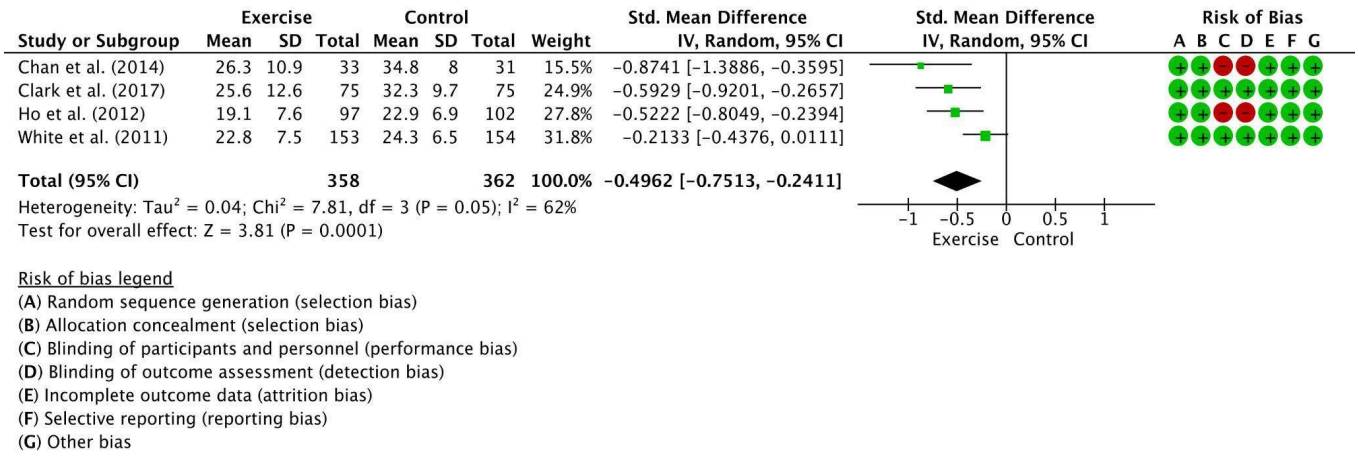


Figure 2. Forest plot of the effectiveness of exercise-based rehabilitation vs control on Short-term fatigue in CFS.

Regarding functionality, exercise-based programs showed a small, non-significant improvement in CFS patients. Aerobic and resistance training were performed 3–5 times per week, with gradual intensity progression, while GET followed a structured increase in activity[44,52,53,54].Qigong incorporated breathing and relaxation techniques[54], and multimodal approaches combined various methods [44,53,54]. The analyzed studies were of moderate to high quality, with a low to moderate risk of bias [44,52,53,54] and no significant heterogeneity (Tau^2 = 0.000; I^2 = 0%). However, the effect size was small and slightly favored the control group, though the difference did not reach statistical significance(n = 685, SMD = 0.09; 95% CI: [−0.05, 0.249]; Z = 1.29; p = 0.20). See details in Figure 3.

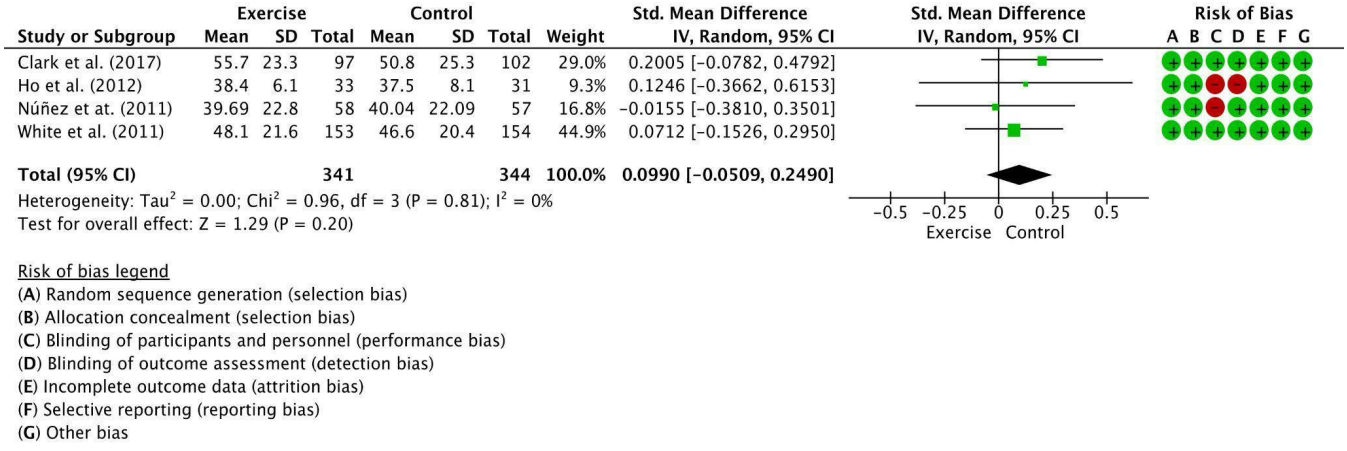


Figure 3. Forest plot of the effectiveness of exercise-based rehabilitation vs control on Short-term physical functionality in CFS.

Effect size of exercise-based rehabilitation for Chronic Fatigue Syndrome in the Medium-term (3 to 6 months).

In the medium term, exercise-based programs produced a small but significant reduction in fatigue among CFS patients. Aerobic training (3–5 times/week, 20–40 min/session) included moderate-intensity walking or cycling with progressive overload.[52,54] Resistance training (2–3

times/week) targeted major muscle groups at low-to-moderate intensity[52] while GET followed a structured, gradual increase in activity, adjusting intensity was needed to avoid post-exertional malaise.[51,54] Qigong (2–4 times/week, 30–60 min/session) integrated slow movements, breathing control, and meditation to enhance relaxation.[42,52] The studies included in this analysis were of moderate to high methodological quality and presented a low to moderate risk of bias,[48,51,52,54] although significant heterogeneity was observed (Tau² = 0.12; I² = 73%). The effect size was small (n = 501, SMD = −0.53; 95% CI: [−0.947, -0.119]; Z = 2.52; p = 0.01) is in detailed in Figure 4.

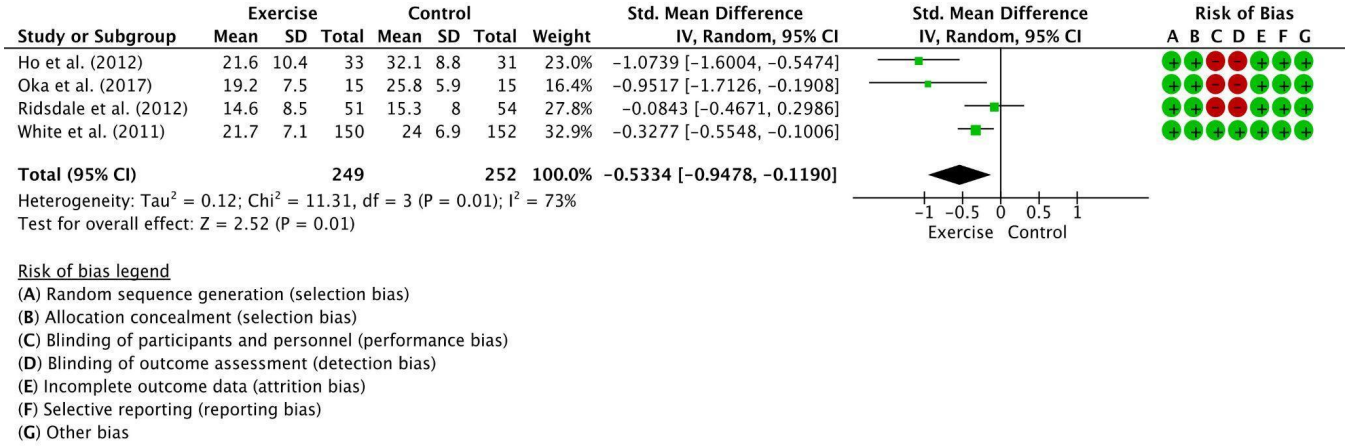


Figure 4. Forest plot of the effectiveness of exercise-based rehabilitation vs control on Medium-term fatigue in CFS.

However, exercise therapy did not show improvement in functionality compared to conventional treatments in the medium term. The interventions included aerobic training (3–5 times/week, 20–40 min/session), resistance exercises and graded exercise therapy to enhance tolerance.[52,54] The studies analyzed were of moderate to high quality with a low to moderate risk of bias[52,54] and no significant heterogeneity was detected (Tau² = 0.00; I² = 0%). The effect size for functionality was small (n = 366, SMD = 0.31; 95% CI: [0.105, 0.517]; Z = 2.96; p = 0.003). More details in Figure 5.

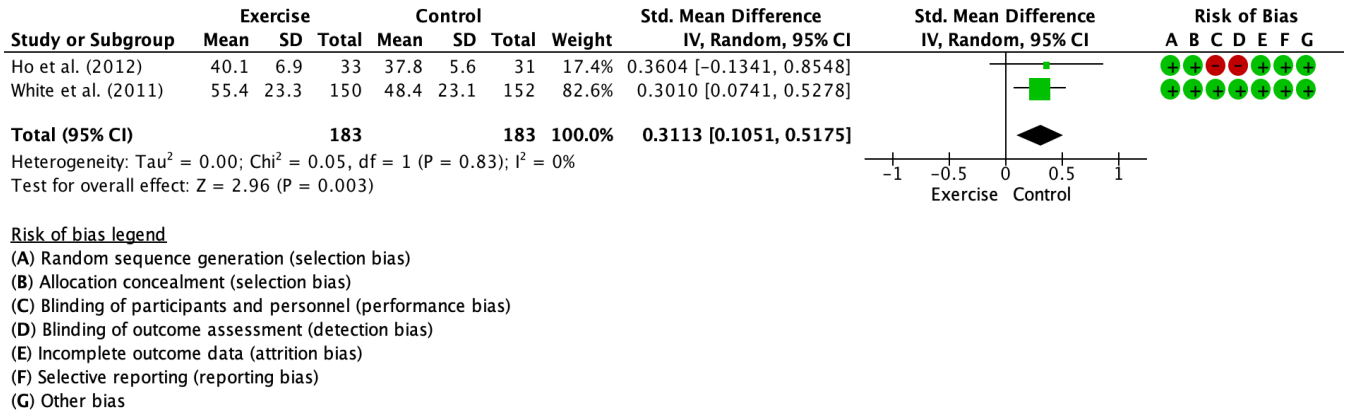


Figure 5. Forest plot of the effectiveness of exercise-based rehabilitation vs control on Medium-term physical functionality in CFS.

Effect size of exercise-based rehabilitation for Chronic Fatigue Syndrome in the Long-Term (≥ 6 months).

For long-term outcomes, exercise programs did not show a significant effect on reducing fatigue in patients with CFS compared to control treatments. Interventions included aerobic training (3–5 times/week, 20–40 min/session, moderate intensity),[53,54] resistance exercises (low-to-moderate intensity, 2–3 times/week),[53] and GET with a structured, gradual increase in activity to improve tolerance.[51,54] Multimodal programs combined different approaches for comprehensive rehabilitation.[51,53] The studies analyzed were of moderate to high methodological quality, with a low to moderate risk of bias, and exhibited substantial heterogeneity (Tau^2 = 0.12; I^2 = 83%)[51,53,54] The effect size was small and not statistically significant (n = 531, SMD = −0.07; 95% CI: [−0.517, 0.365]; Z = 0.34; p = 0.74), as detailed in Figure 6.

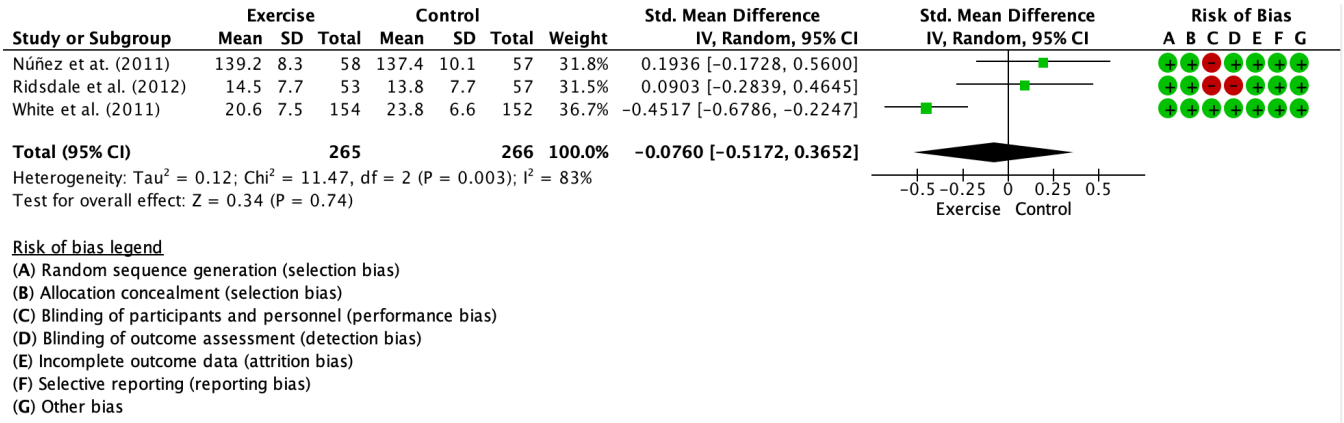


Figure 6. Forest plot of the effectiveness of exercise-based rehabilitation vs control on Long-term fatigue in CFS.

Similarly, no significant improvements in functionality were observed with exercise programs in the long term compared to conventional treatments. For long-term outcomes, exercise programs did not show a significant effect on reducing fatigue in CFS patients compared to control treatments. Aerobic training was prescribed at moderate intensity (50–70% VO_2 max), 3–5 times per week, with sessions lasting 20–40 minutes, progressively increasing based on patient tolerance.[53,54] Resistance exercises targeted major muscle groups using low-to-moderate loads (30–50% 1RM), performed 2–3 times per week, with 2–3 sets of 8–12 repetitions per exercise.[53] The studies reviewed were of moderate to high quality, with a low to moderate risk of bias, and significant heterogeneity (Tau^2 = 0.11; I^2 = 82%).[53,54] The effect size for functionality was also small and did not reach statistical significance (n = 421, SMD = 0.03; 95% CI: [−0.473, 0.536]; Z = 0.12; p = 0.90), as depicted in Figure 7.

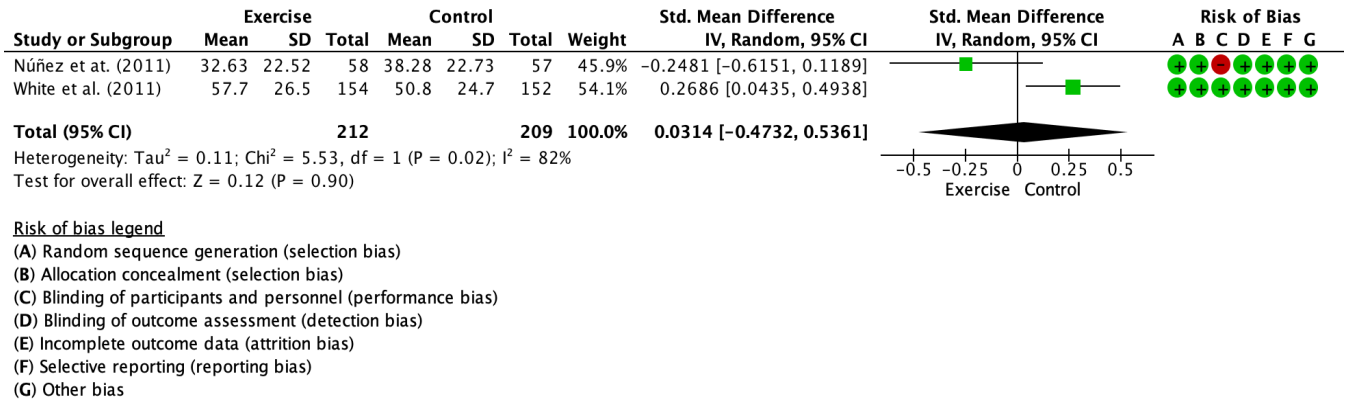


Figure 7. Forest plot of the effectiveness of exercise-based rehabilitation vs control on Long-term physical functionality in CFS.

Discussion

The findings of this meta-analysis highlight the potential of exercise-based rehabilitation to alleviate fatigue in CFS, particularly in the short and medium terms. However, the limited impact on functionality and the progressive decline in benefits over time underscore the need for a more comprehensive and sustained approach to rehabilitation in this population. While structured exercise interventions can provide initial symptomatic relief, their long-term effectiveness remains uncertain, raising questions about the sustainability of these benefits and the need for adjunctive strategies.

The early-phase improvements in fatigue observed align with existing evidence suggesting that graded exercise can enhance mitochondrial function, improve lactate metabolism, and optimize neuromuscular efficiency, all of which are impaired in CFS.[55-57] Furthermore, the potential role of psychological mechanisms cannot be overlooked, as gradual exposure to physical activity has been associated with improved autonomic regulation[58,59] and reduced stress-related symptom exacerbation.[60]

However, these physiological and psychological adaptations do not appear to translate into significant functional gains, suggesting that fatigue reduction alone may not be sufficient to restore overall physical performance in CFS patients. This discrepancy highlights the complex and multifactorial nature of the syndrome, in which persistent neuroinflammation,[61,62] metabolic dysfunction,[63] and autonomic dysregulation[64] contribute to activity limitations beyond the effects of fatigue itself.

Despite the continued benefits of exercise on fatigue reduction in the medium term, the heterogeneity of responses suggests that factors such as adherence, symptom variability, and differences in exercise protocols influence outcomes among patients with chronic musculoskeletal diseases.[65,66] Moreover, the lack of significant functional improvements raises concerns about whether physical training alone an adequate intervention for this population is.

Interestingly, the findings of our meta-analysis suggest that functionality outcomes may even favor the control group in the medium term, a result that could be attributed to the inclusion of

alternative strategies such as symptom management education,[67] pacing techniques,[68] and cognitive-behavioral approaches within the control interventions.[69] Given the central role of post-exertional malaise in CFS, these findings further emphasize the need for rehabilitation programs that carefully balance physical activity with appropriate recovery periods to prevent symptom exacerbation.[70,71]

The decline in the effectiveness of exercise interventions in the long term raises important considerations regarding the sustainability of rehabilitation strategies for CFS. The progressive reduction in the benefits of exercise is consistent with findings in other chronic conditions, where initial gains are often lost over time unless reinforced through periodic engagement.[72,73] This can be explained by the lack of adherence to exercise programs,[74,75] particularly in populations with fluctuating symptom severity and a high risk of lasting fatigue. Furthermore, the underlying pathophysiology of CFS—including chronic neuroimmune activation[77] and metabolic disturbances[78]—suggests that a single intervention approach may be insufficient to provide lasting improvements. These findings support the growing consensus that multimodal interventions, rather than exercise alone, are needed to achieve meaningful and sustained benefits in CFS management.[79]

In this sense, the implementation of individualized and graded *booster sessions*—periodic follow-ups allow enhancing adherence and prevents symptom relapse.[80] It is supported by evidence from chronic pain and fatigue-related conditions,[81] where long-term rehabilitation success has been linked to continued patient engagement and structured reinforcement of behavioral strategies.[82] Furthermore, given that CFS shares pathophysiological mechanisms with chronic pain syndromes, such as altered central sensitization[83] and dysfunctional energy metabolism,[84] it is reasonable to hypothesize that a similar approach could enhance the long-term efficacy of exercise rehabilitation in this population.

Moreover, the implementation of *booster sessions* could serve multiple functions beyond maintaining adherence. Periodic supervision would allow for ongoing adjustments to exercise prescriptions based on individual symptom trajectories, thereby minimizing the risk of persistent fatigue while optimizing functional adaptations.[44,68,84] Additionally, they can provide an opportunity to integrate complementary interventions, such as pacing education, cognitive restructuring techniques, and self-management strategies, which have been shown to improve long-term outcomes in CFS and related conditions.[85,86]

Limitations

This meta-analysis has several limitations. A high degree of heterogeneity was observed across studies, particularly in short- and medium-term fatigue outcomes, likely due to differences in exercise type, duration, and adherence. Methodological concerns, including lack of blinding and deviations from planned interventions, increased the risk of bias. Follow-up durations were limited, with long-term effects showing no significant benefits, suggesting that adherence and reinforcement sessions may be crucial.

The generalizability of the findings is further restricted by the low number of studies included, alongside variability in participant characteristics and study locations. Additionally, inconsistent reporting of adverse events limits the ability to assess safety accurately. The GRADE evaluation rated the quality of evidence as low to moderate, leading to a weak recommendation for exercise in the management of CFS. Future research should focus on improving study design, assessing long-term adherence, and standardizing adverse event reporting.

Implications for clinical practice

The findings of this meta-analysis suggest that exercise-based rehabilitation provides a modest but significant reduction in fatigue among patients with CFS, particularly in the short and medium terms. While functionality improvements remain limited, structured exercise programs seem to be an essential component of symptom management. In clinical practice, implementing individualized, gradually progressive exercise interventions can enhance patient outcomes.

However, given the diminishing long-term effects, integrating multimodal strategies such as cognitive-behavioral therapy, relaxation techniques, and lifestyle modifications is crucial. Clinicians should emphasize patient education, pacing strategies, and sustained engagement in tailored rehabilitation programs to optimize long-term benefits while minimizing post-exertional malaise. A multidisciplinary approach remains key in addressing the complex and multifaceted nature of CFS.

This meta-analysis suggests that exercise-based rehabilitation moderately reduces fatigue in CFS patients in the short and medium term but has minimal impact on functionality and no sustained long-term benefits. High heterogeneity and methodological limitations weaken the strength of the evidence, leading to a weak recommendation for exercise as a standalone treatment. Future research should refine intervention strategies and ensure rigorous methodological standards to improve long-term effectiveness and safety.

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