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Title: Effects of physical exercise in people with epilepsy: A systematic review and meta-analysis

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1. Introduction

Epilepsy is a disease characterized by the existence of two or more unprovoked or reflex seizures greater than 24 hours apart, or by a single unprovoked or reflex seizure in a person who has a 60% risk of having another seizure over the next 10 years [1]. Epilepsy negatively affects physical and mental health [2] so that it has been ranked as the second most burdensome neurologic disorder worldwide in terms of disability-adjusted life years [3].

Antiseizure medications are the mainstay of epilepsy treatment, but their efficacy is limited [4]. In addition, psychiatric, behavioural and physical side effects have been associated with their use [5,6]. Surgery has been proposed as an alternative option, especially for those suffering from drug-resistant epilepsy, but not all patients are considered candidates for brain surgery. Besides, neurologist, patients and families are usually reluctant to advice or to undergo this procedure due to misconceptions and perceived risks [7].

In this context, nonpharmacologic approaches aimed at controlling seizures should be considered for people with epilepsy [8]. In this regard, physical exercise stands out as an interesting option, since findings from some studies suggest that its practice is linked to a better control and reduction in the number of seizures, and to improvements in the psychosocial dimension, associated comorbidities as well as to a higher quality of life (QoL) [9,10]. However, before providing counselling on physical exercise to people with epilepsy, neurologists and fitness professionals should be provided with the most accurate evidence-based guidelines currently available for its prescription and its potential benefits within this population. This goal can be achieved through conducting systematic reviews that summarize and critically analyse the existing scientific evidence on this topic. To the very best of the

authors' knowledge, no systematic review specifically focused on the effects of physical exercise training programmes on people with epilepsy has been published so far. The current scientific evidence on this topic comes either from literature reviews [11], or from comprehensive reviews on physical activity levels and sport, in which very few high-quality investigations on the impact of exercise training programmes are usually found [9,12]. In addition, in both reviews the authors could not offer concise information on the effects of exercise on seizure frequency, due to studies' heterogeneity. This fact also prevented the performance of a meta-analysis on this important hallmark of the disease. Similarly, few studies were found on the impact of exercise on the patients' quality of life, indicating the need for further investigations in order to obtain more solid conclusions.

In the light of all this, the purpose of this study is to conduct a systematic review in order to identify and critically analyse the best available evidence concerning the effects of physical exercise training programmes on people with epilepsy. A further aim is to offer information on the impact of exercise training programmes on seizure frequency and QoL through the performance of a metanalysis.

2. Methods

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13].

2.1. Search strategy

Four electronic databases (MEDLINE/PubMed, PEDro, SPORTDiscuss and Scopus) were searched systematically from their inception until April 2022. The following search terms, Boolean operators, and combinations were used: "Epilepsy" OR "Exercise" AND "Physical Activity".

2.2. Eligibility criteria

Intervention studies that provided information regarding the effects of physical exercise training programmes on people with epilepsy were considered eligible. Investigations were excluded if: a) exercise training was performed in combination with other therapies; b) the study included people with several neurological pathologies, unless separate data were available for the epilepsy subgroup; c) the intervention was based on the performance of a single exercise training session; d) the full text of the study was not available; and e) the research was not written in English, Portuguese or Spanish language.

2.3. Study selection

Two authors screened the titles and abstracts of the identified studies for eligibility. After independently reviewing the selected studies for inclusion, these were compared by both authors to reach an agreement. Once the agreement had been reached, a full-text copy of every potentially relevant study was obtained. If it was unclear whether the study met the selection criteria, advice was sought from a third author and a consensus of opinion was reached. The reference lists of the articles selected, as well as studies that quoted them, were checked for potential new articles eligible for this review.

2.4. Data extraction

Information on participants' characteristics, exercise training programme, variables assessed, main outcomes, adverse events and drop-outs were extracted from the original reports by one researcher and checked by a second investigator. Missing data were obtained from the study authors, whenever possible.

2.5. Quality appraisal

The methodological quality of each randomized controlled trial (RCT) was retrieved from the Physiotherapy Evidence Database (PEDro). If a trial was not included in PEDro, two authors appraised its quality and disagreements were solved by consensus. The suggested cut-off points to categorize studies by quality were excellent (9–10), good (6–8), fair (4–5), and

poor (<3) [14]. The Methodological Index for Non-Randomized Studies (MINORS) [15] was used to determine the methodological quality of comparative studies. The MINORS instrument includes 12 items corresponding to an equal number of quality criteria for comparative studies. The items are scored 0 (not reported), 1 (reported but inadequate), and 2 (reported and adequate). The global ideal score is 24 points for comparative studies. The methodological quality of comparative studies was assessed by one author and then checked by a second author. In case of disagreement, advice from a third author was sought. High quality was considered if the total MINORS score was 17 or more, whereas a total score less than 17 was deemed as low quality [16].

The methodological quality of the non-controlled studies was performed by two authors independently, using the Quality Assessment Tool for Before–After Studies with No Control Group [17]. This tool includes 12 questions, and it is indicated that general rules or scores are not useful, as each study has specific nuances. Authors must define each study's quality ("poor", "fair" or "good") according to how much risk of bias they consider to exist. In case of disagreement, advice was sought from a third author. Methodological quality was classified as follows: "poor": < 4 points; "fair": ≥ 4–8 points; "good": > 8 points [18]. In case of disagreement, advice was sought from a third author.

2.6. Statistical analysis

Data extracted from the articles was processed in an Excel spreadsheet and the statistical analysis was performed using the RevMan v5.4.1 software. Inverse variance or generic inverse variance was used to report mean difference or standardized mean difference for continuous data and their 95% confidence intervals (CIs). Heterogeneity was assessed with the chi-squared test and I^2 test.

3. Results

3.1. Design and samples

Out of the 4020 references initially obtained, 82 were retrieved for reading their full text and 14 investigations were finally selected (Figure 1): eight RCTs [19–26], one comparative study [27], four quasi-experimental studies [28–31] and one pilot study [32]. Three pairs of articles shared the same sample and methodological design [21–23,25,28,29]. Table 1 shows a summary of the characteristics of the 14 reviewed studies.

The total sample size from all studies was 331 participants, with the smallest and the largest study sample including 9 [32] and 90 [26] participants, respectively. Two studies provided a priori sample size calculation [21,22]. All studies identified the sex of participants, with a predominance of women (62.31%). The characteristics of the participants differed between the samples, exhibiting a wide range of ages (mean ± SD: 29.35 ± 10.61 years, range: 8–65 years). Participants were diagnosed with either general or focal [33] epilepsy [19,20,24,25,27–29]. Three studies did not report information in this regard [21–23]. In six studies participants had drug-resistant epilepsy [19,20,24,27,30,31], whilst epilepsy was controlled in five studies [23,25,26,28,29]. In three studies the participants had either drug resistant or controlled epilepsy [21–32]. Antiepileptic drug (AED) administration was reported in all but five studies [23,27,29,30,32].

The mean age of epilepsy onset was 12.19 ± 3.34 years, according to the six studies that included information about it [20,26–29,32]. Five studies reported illness duration [20,26,27,30,31], which was set at 15.75 ± 6.63 years.

Across the selected investigations, one study did not mention inclusion criteria [25], one did not mention exclusion criteria [30] and three did not mention any selection criteria [28,29,32]. Overall, the most repeated inclusion criteria were confirmed epilepsy diagnosis

[19,10,21–24,26,30], age range [19–23,26,27,30] and different seizure frequency in the past month [19], or three months [20,24] or a year [30] before the study.

As for the exclusion criteria, the most repeated was not being pregnant [19–21,23,26,27]. In addition to pregnancy, one study did not accept participants in the puerperium [19] and in other study breastfeeding participants were also excluded [27]. Besides, other recurrent exclusion criteria included having any physical impairment that did not allow physical exercise practice [19,21,22,25,26]. In addition, having psychological [19], behavioural [26] or cognitive problems [20–22,25,26] or other impairments like cardiorespiratory [23,25–27], endocrinal [23,25,26] or neurological diseases [25,27], having an ongoing progressive illness [24–27] or any condition which may interfere with the evaluation procedures or the objectives of the study [19] were some other recurrent exclusion criteria. In two studies alcohol or substance abuse were also mentioned as exclusion criteria [19,27].

3.2. Quality appraisal

One RCT study exhibited "poor" methodological quality [26], five scored "fair" methodological quality [19,20,22,23,25] and two obtained "good" methodological quality [21,24] (Table 2).

The non-randomized comparative study scored "high quality" [27] (Table 3) and as for the four quasi-experimental studies (Table 4), all of them obtained "fair" quality [28–31], except for Conant et al. [32], which had a poor quality.

3.3. Intervention characteristics

The selected studies carried out different exercise interventions, based on the performance of aerobic exercise [19] or a combination of multiple forms of exercise (aerobic

and strength [20,26] or aerobic and flexibility [26] or aerobic, strength and stretching [21–23,25]. Other studies proposed interventions based on yoga [24,27], Kempo karate [32], supervised therapeutic exercises (basketball, soccer, tennis, badminton or jump rope and line dancing) [28,29], or other activities such as swimming, jogging, hiking, volleyball, horseback riding, table tennis, bicycling and rowing [31]. One study included a specific exercise programme (the Norwegian Aerobic Fitness Model) [30]. Mostly, the exercise intervention was conducted by a professional [20–25,27–32]. However, in two studies the exercise intervention was home-based [19,26].

Three studies had an active control group where participants took part in yoga sessions [24], muscular relaxation sessions [19] or performed simple physical exercise [27]. Meanwhile, one study mentioned that participants of the control group received advice about healthy weight and the importance of physical activity [26] and another study lacked specific information on the activities performed by the control group [20]. In the remainng studies the control group participants were asked to maintain their level of activity and to carry on with their usual daily activities [21–23,25,26].

Of the 14 articles reviewed, the most common intervention duration was 12 weeks [21–23,25,26], with the longest intervention duration being 35 weeks [29] and the shortest 4 weeks [19,31]. Some of the studies performed a follow-up period [19,23–25,30], exhibiting a wide range of follow-up times between studies: from 4 weeks [23,25] to 12 months [24].

The average of exercise sessions per week was 2.6 ± 0.7. Two studies lacked specific information on the frequency of sessions but one reported that participants performed a total of 12 hours of therapy [24] and the other indicated that participants exercised 60 minutes a day for 10 weeks [27]. The most frequent session duration was 60 minutes [20–23,25,27,30,32] and the shortest and the longest duration 30 [19] and 180 minutes [28,29], respectively.

3.4. Main outcomes

Significant changes between pre- and post-intervention results in the exercise intervention groups were observed for different outcomes in all the studies. Moreover, four out of the fourteen studies obtained significant changes between pre- and follow-up period results [23,25,30]. In addition, an intergroup time by group interaction was observed in seven studies when analysing exercise impact [19–22,24,26,27]. However, in four studies significant improvements between pre- and post-results were observed in the control groups in seizures and symptoms [24], neurocognitive [20] and psycho-affective outcomes [22] and QoL [25].

3.4.1. Seizures/symptoms

Ten studies analysed the impact of exercise on seizure frequency [19,22,24,25,27–32]. Significant improvements were reported in four of them. In three of these investigations participants had drug-resistant epilepsy [21,22,32], while in Häfele et al. [22] participants had either drug-resistant or controlled epilepsy.

Five studies in adults were pooled in the meta-analysis for determining pre-and post-exercise intervention changes on seizure frequency in people with non-controlled epilepsy [19,22,24,25,30]. The obtained findings indicated that moderate exercise led to a non-significant decrease ($p=0.08$, chi-squared test) in this hallmark of the disease (SMD 0.33 95% CI 0.04; 0.70) (Figure 2A). This effect was not superior to that of other therapies, according to the results observed after pooling data from four studies in which inter-group comparisons were carried out ($p=0.28$, chi-squared test) (Figure 2B) [19,22,24,25]. In none of the analysed studies was there a trend by which the number of seizures was increased after exercising.

3.4.2. Quality of life

Nine studies measured QoL [19,20,22,24–28,32] and significant positive effects of exercise were observed on six of them [22,24,25,27,28,32].

Pooled data from five studies in adults [19,20,22,24,25] comparing pre–post results, confirmed the significant effect of exercise on QoL (Figure 3A), with a mean improvement of 4.72 percentage points (95% CI 0.58; 8.86, p=0.03). Participants in the exercise group also obtained significant improvements on their QoL in comparison with those who followed other therapies or kept their usual activities, with a difference of 4.34 points (95% CI 0.15; 8.53, p=0.04) (Figure 3B).

3.4.3. Psycho-affective outcomes

Eight studies measured psycho-affective outcomes [19,20,22,25,27,28,30,32]. Significant improvements were observed in six of them on mood state [20,25], stress [22], physical self-concept, children's behaviouoral problems [28,29] and subjective somatic and psychological problems [30].

3.4.4. Physical fitness outcomes

3.4.4.1. Cardiorespiratory efficiency

Within the six studies that reported cardiorespiratory efficiency [19,22,23,26,28,31], improvements were observed in three of them [23,26,31].

3.4.4.2. Muscular strength

Muscular strength was measured in five studies [20–23,28], of which muscular strength gains were reported in four of them [20,22,23,28].

3.4.4.3. Anthropometry

Anthropometry was also measured in five studies [21–23,26,31] and positive effects of exercise were observed in weight [26,31] and body fat [23].

3.4.5. Neurocognitive outcomes

Four studies measured neurocognitive outcomes [20,21,28,29]. Overall, significant improvements were obtained in all tests except in the Digit Span Test (DST) [21].

3.4.6. Physiological outcomes

Other variables measured within physiological outcomes, but which did not obtain any significant changes, were maximal and rest heart rate [20,22,30], ECG [28,29,31], blood pressure and vital capacity [30,31], lactate and Borg scale [30]. As different, Sathyaprabha et al. [27] measured sympathetic and parasympathetic dysfunction but a significant positive effect was only observed on the latter. Also, a positive effect of exercise was shown in the lipid profile [23,30].

3.4.7. Physical activity

Three studies assessed the impact of the exercise programme on the prevalence of physical activity [19,20,23], with two of them reporting significant increments [19,23].

3.5. Recruitment, adherence and adverse events

Six studies stated the recruitment rate (range between 9.14% and 60%) [19,20,26,30–32]. While two studies failed to report attrition rates [24,32], four studies pointed out that all participants completed the intervention [20–29,31], but two of them had small sample sizes (n = 10) [28,29]. In the remaining studies, the completion rate ranged between 80% and 90.90% [19,20,21,22,23,25,26,27,30]. Compliance rates in the control group ranged between 76.36% and 100%. Adherence was only reported in three studies [20,28,30] with ratios between 75% and 100%.

Two studies informed about adverse events directly associated with the exercise intervention. In one study one participant stopped exercising due to an increase in seizure frequency [19] and in other study a participant had “exercise-induced” seizures [31]. On the

other hand, four studies reported no adverse events related with the intervention [20,21,26,30]. The remaining studies did not report adverse events related to exercise.

4. Discussion

In this research, the scientific evidence regarding the effectiveness of physical exercise as a coadjutant therapy for people with epilepsy was examined and critically reviewed. To achieve this objective with the maximum accuracy, the search was not limited to RCTs, which seems a useful strategy when reviewing the feasibility, characteristics and effects of novel therapies [34]. Thus, the spectrum of the results was broader, so, in this sense, the data and conclusions drawn from this review can provide a greater clearness related to the state of the issue. Indeed, we found five more exercise-based training intervention studies than those referred to in the works by van den Bogard et al. [12], and by Johnson et al. [9], who also searched for investigations regardless of their methodological design.

The studies analysed in the present review showed an acceptable methodological quality and most of them included a comparison group. Judging from their findings, several aspects are worthy of being discussed and can help clinicians to encourage the practice of physical exercise among people with epilepsy.

In the first place, exercise appeared to be feasible and safe, although exercise-induced seizures were noted in two participants. Interestingly, this adverse effect was found only among patients with drug-refractory epilepsy. Overall, the scientific literature indicates that cases of exercise-induced seizures are rare, while studies tend to report that physical activity can decrease seizure frequency [35]. In an attempt to shed light on this matter, we performed a meta-analysis. Our results indicate that exercise seemed to reduce the frequency of seizures, but the observed changes were not significant. Moreover, the impact of exercise in this hallmark of the disease was not superior to that of other therapies. All together, these findings

imply that while exercise has no negative effect on seizure frequency, it cannot be considered as an effective therapy for controlling seizures in people with drug-resistant epilepsy.

Another finding worth mentioning is related to the fact that epilepsy is also associated with comorbidities such as cognitive and psychological problems, as well as social difficulties [33]. In the present review, exercise showed to be effective when improving psycho-affective outcomes, and also neurocognitive function. However, it should be noted that in some investigations, exercise effects were not superior to those obtained by the administration of other therapies. On a more positive note, the meta-analysis performed confirmed that exercise led to significant improvements in QoL. Severity and frequency of seizures have been mentioned as major factors that determine patients' QoL [36]. However, not all the studies that resulted in significant changes in QoL also led to improvements on seizures. Thus, other factors related to exercise practice that have also been shown to negatively affect QoL among epilepsy patients, such as stigma, self-esteem or social integration, might be responsible for the observed changes.

Another significant and common problem usually observed among people with epilepsy is physical inactivity. Low levels of physical activity (PA) can lead to reduced fitness levels, which in turn negatively affects both the physical and mental health of this population (Johnson, 2020). According to our findings, clinicians should encourage patients to exercise, given that increases in strong and independent markers of health such as muscular and cardiorespiratory fitness [37], are achievable. Moreover, exercise also seemed to have a positive effect on different anthropometric factors. This is another important reason for promoting exercise, since obesity and overweight have been well established as comorbidities of epilepsy in adults [38]. In relation to this, it should be noted that not all the studies that assessed PA levels observed an increase in PA prevalence once the exercise training programme was over. Among the barriers that prevent people with epilepsy from exercising,

are safety concerns raised by family and friends, as well as medical professionals requesting termination of some physical activities, which are frequently acknowledged [39]. The results of this review can help to overcome such barriers, since it provides information on the safety of exercise and also on its several benefits.

On a final note, it should be mentioned that exercise showed positive effects in children with epilepsy, a population that have long been subjected to excessive restrictions on physical activities due to concerns over risk of injury [40]. Although these results are promising and help to provide confidence and positive encouragement to exercise, it should be noted that only three investigations on the topic were found. Thus, further research in this line of investigation is strongly needed.

In closing, our results seem to indicate that exercise can lead to improvements in QoL, neurocognitive and psycho-affective outcomes, as well as in fitness in people with epilepsy. The findings shown here indicated that the effects of exercise on seizures were not statistically significant. However, we must acknowledge that the heterogeneity of the studies analysed and the low number of patients included prevent us from extracting solid conclusions on a number of important details. First, we could not determine whether the impact of exercise differed taking into account whether the patients had general/focal epilepsy, nor could we identify whether having controlled or drug-resistant epilepsy was a detrimental factor in this regard. Second, due to the huge diversity of exercise training programmes proposed, it was not possible to extract and offer concrete practical exercise guidelines (i.e. exercise modality, duration, intensity, frequency) for people with epilepsy. This heterogeneity also prevented us from performing a meta-analysis on several outcomes of interest. In this regard, it is worth mentioning that we pooled a reduced number of studies with generally small samples in the performed meta-analysis conducted. Thus, the conclusions regarding the impact of exercise on seizures and QoL should be considered as

preliminary evidence. Finally, the existence of certain methodological limitations inherent to the review design (e.g. language restrictions, not having reviewed grey literature or publication bias) should be considered as well, as they may have conditioned the present results.

5. Conclusion

People with epilepsy can benefit from exercising. Improvements in their QoL, fitness level, psycho-affective and neurocognitive outcomes can be achieved through its practice. Patients with drug-resistant epilepsy should be aware that exercise does not seem to have a significant impact on seizure frequency. Further controlled studies with larger samples are needed to confirm these findings.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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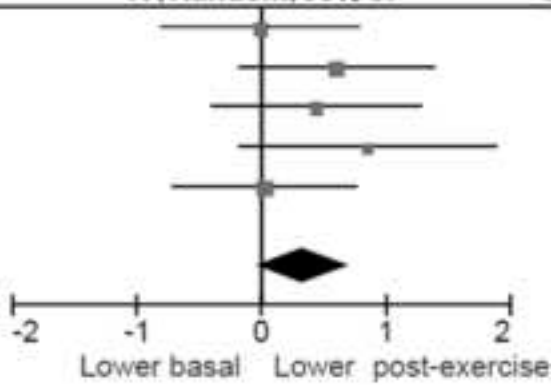
2A

	Basal			Post-exercise				Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
AKERLUND 2021	136.5	382.5	12	138.3	382.2	12	21.4%	-0.00 [-0.80, 0.80]	
ERIKSEN1994	36	20.93	13	24.36	15.96	13	22.0%	0.61 [-0.18, 1.39]	
HAFELE 2021	2	2.68	11	0.8	2.53	11	19.0%	0.44 [-0.41, 1.29]	
LUNDGREN 2008	4.13	6.1	8	0.23	0.28	8	12.7%	0.85 [-0.18, 1.89]	
McAULEY 2001	10.07	24.22	14	9.29	24.16	14	24.9%	0.03 [-0.71, 0.77]	
Total (95% CI)			58			58	100.0%	**0.33 [-0.04, 0.70]**	

Heterogeneity: Tau² = 0.00; Chi² = 2.81, df = 4 (P = 0.59); I² = 0%

Test for overall effect: Z = 1.76 (P = 0.08)

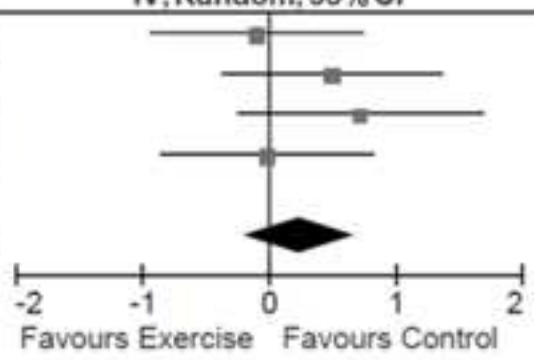


2B

	Exercise			Control				Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
AKERLUND 2021	1.8	264.9	12	22.2	51.6	10	27.1%	-0.10 [-0.94, 0.74]	
HAFELE 2021	-1.2	1.81	11	-2.5	3.12	10	25.1%	0.50 [-0.38, 1.37]	
LUNDGREN 2008	-3.9	5.89	8	-34.61	54.12	10	20.5%	0.72 [-0.25, 1.68]	
McAULEY 2001	-0.78	16.76	14	-0.55	2	9	27.3%	-0.02 [-0.85, 0.82]	
Total (95% CI)			45			39	100.0%	**0.24 [-0.20, 0.68]**	

Heterogeneity: Tau² = 0.00; Chi² = 2.25, df = 3 (P = 0.52); I² = 0%

Test for overall effect: Z = 1.08 (P = 0.28)

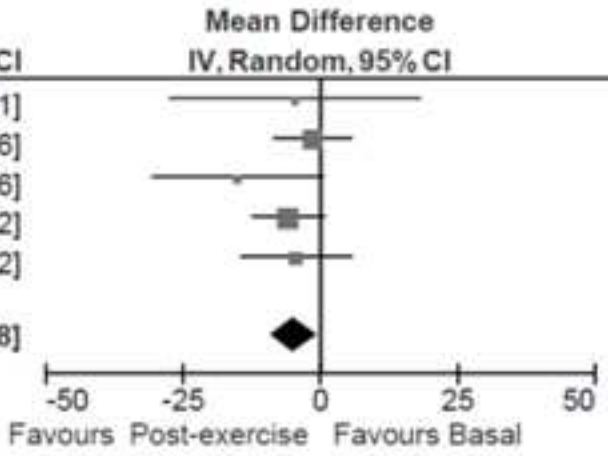


3A

Study or Subgroup	Basal Mean	Basal SD	Basal Total	Post-exercise Mean	Post-exercise SD	Post-exercise Total	Weight	Mean Difference IV, Random, 95% CI
AKERLUND 2021	61	30	12	65.625	27	12	3.3%	-4.63 [-27.46, 18.21]
ALLENDORFER 2019	51.5	6.6	9	52.85	8.65	9	33.9%	-1.35 [-8.46, 5.76]
HAFELE 2021	54.7	18.6	10	69.8	17.1	10	7.0%	-15.10 [-30.76, 0.56]
LUNDGREN 2008	51.3	7.9	10	57.2	7.2	10	39.1%	-5.90 [-12.52, 0.72]
McAULEY 2001	73	14.9	14	77.5	12.3	14	16.7%	-4.50 [-14.62, 5.62]
Total (95% CI)			55			55	100.0%	**-4.72 [-8.86, -0.58]**

Heterogeneity: Tau² = 0.00; Chi² = 2.67, df = 4 (P = 0.61); I² = 0%

Test for overall effect: Z = 2.24 (P = 0.03)



3B

Study or Subgroup	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
AKERLUND 2021	4.625	19.9	12	1.625	20.8	10	5.5%	3.00 [-14.12, 20.12]
ALLENDORFER 2019	1.35	5.6	9	1.25	5.2	8	33.2%	0.10 [-5.04, 5.24]
HAFELE 2021	15.1	12.4	10	0.9	12.6	10	12.0%	14.20 [3.24, 25.16]
LUNDGREN 2008	5.9	5.27	10	0.5	6.37	8	31.0%	5.40 [-0.09, 10.89]
McAULEY 2001	4.5	9.73	14	0.3	10.1	9	18.3%	4.20 [-4.14, 12.54]
Total (95% CI)			55			45	100.0%	**4.34 [0.15, 8.53]**

Heterogeneity: Tau² = 6.87; Chi² = 5.80, df = 4 (P = 0.21); I² = 31%

Test for overall effect: Z = 2.03 (P = 0.04)

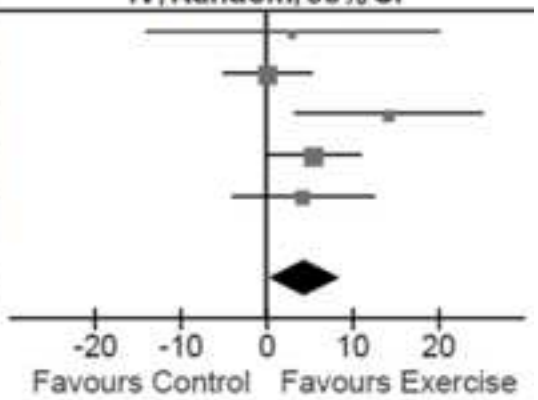
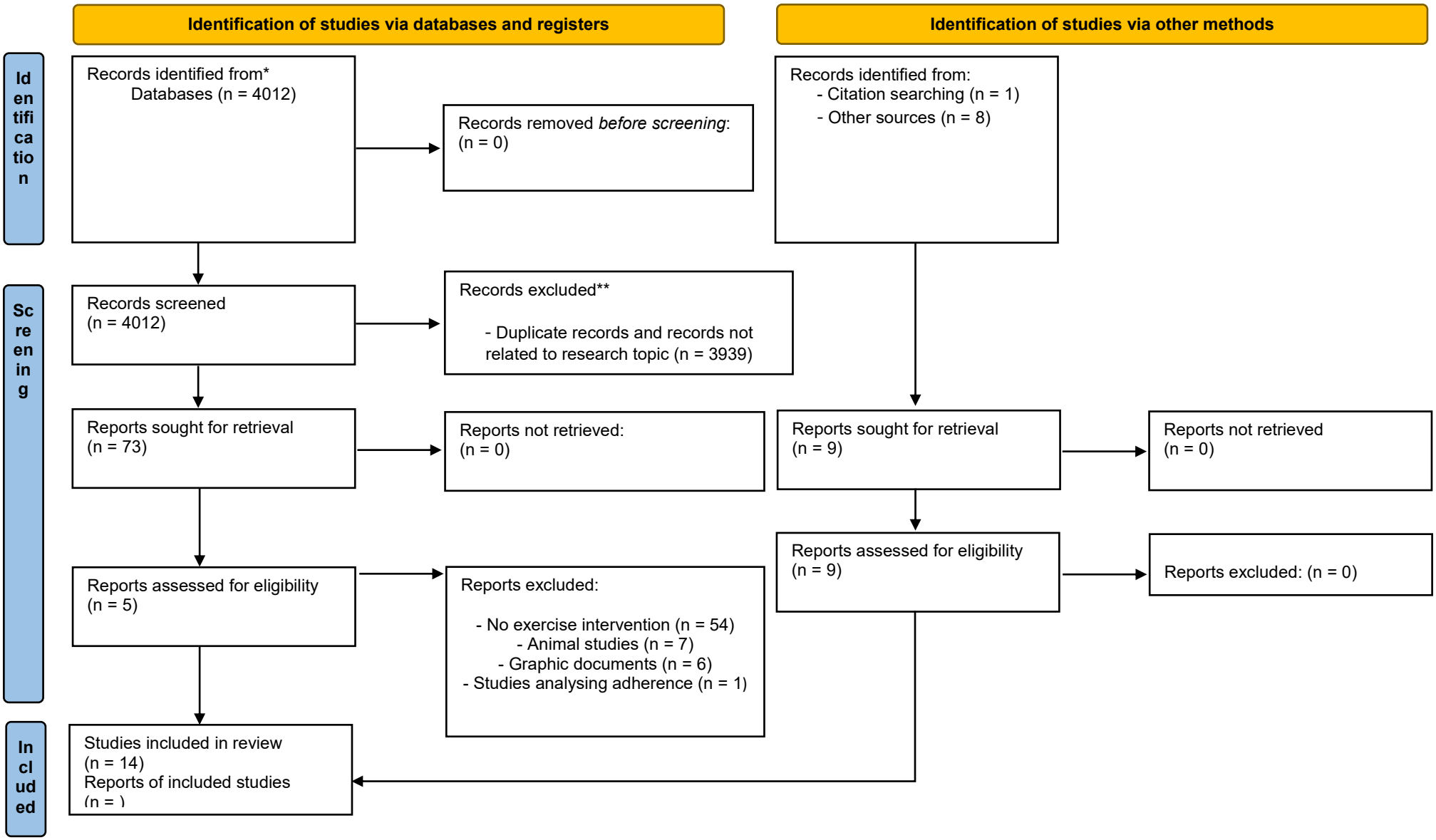


Figure 1

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources

Figure 1. Flow diagram of the search and selection process for the inclusion of articles.

Table 1. General characteristics of the included studies.

Reference	Study design	Participants	Inclusion and exclusion criteria	Intervention	Variables (tests)	Results	Compliance and Adverse Events
Åkerlund et al. (2021)	RCT	**Sample (male:female):** IG: n= 12 (5:7) CG: n= 9-10 (3:7) **Mean age (years):** IG: 48 CG: 41 **Average illness duration (years):** IG: 15.0 CG: 13.0 **Epilepsy:** DR **Type:** Focal: n=22 **AED or ASD information:** Yes	**Inclusion criteria:** • Age range: 16-65 years • Established diagnosis of focal epilepsy • Frequency of at least 3 focal seizures (including focal to bilateral tonic-clonic) during a 4-week-prospective baseline period despite ongoing treatment with one to 4 ASMs • Stable ASM treatment for at least 4 weeks • No expected need to modify current ASM treatment over the subsequent 6 months • Capability to follow instructions (or has a caretaker willing to help) • Keep a seizure calendar, ability to understand the purpose, procedures and potential risks and benefits associated with participation in the study • Signing a written informed consent	**Duration:** 4-week **Follow-up:** 6-month **IG:** Exercise group **Frequency:** 5 days/ week **Volume:** At least 150 min/week, preferably 30 min/day If patients already were training regularly then they were given a higher goal to achieve of 300 min/week. **Activity description:** Ergometric bicycle at home **Intensity:** Moderate intensity level using 12–13 on the Rated Perceived Exercise Scale (RPE-Scale, 6–20). The scale was introduced prior to the intervention, both verbally by the physiotherapist and in written form. **Conducted:** No **CG:** Relaxation group **Frequency:** At least 5 days/week **Volume:** 20 min **Activity description:** Muscular relaxation exercises sitting or lying down	**Quality of life:** • **Health status ratings:** RAND-36 **Psycho-affective outcomes:** • **Anxiety and depression:** Hospital Anxiety and Depression Scale (HADS) **Physical fitness:** • **Cardiorespiratory efficiency:** VO_{2max}: Ekblom-Bak test, a submaximal cycle ergometer test on a stationary bicycle **Physical activity:** • **Minutes of physical activity/week and sedentary time:** Questionnaire with questions about minutes per week in daily activities with lower intensity • **Self-efficacy for exercise (SEE):** Self-assessment form concerning the test subject's confidence in his/her ability to perform physical activity	**Significant differences ($p<0.05$):** **IG Intragroup (pre vs. post)** ↑VO_{2max} ↑Minutes of physical activity/week **Group x time interaction** Minutes of physical activity/week: IG>CG	**Recruitment:** 28% (28 out of 100 initially intended) **Completion rate:** 78.57 % (22 out of 28) IG:80% (12 out of 15) CG: 76.92% (10 out of 13) **Adherence:** NR **Adverse events:** One participant stopped the exercise intervention due to increase in seizure frequency

			Exclusion criteria: • Any associated condition contraindicating non-competitive physical exercise • Engaged in a regular daily physical exercise program of over 150 min/week • A history of seizures induced by exercise • A history of psychogenic nonepileptic seizures • Pregnancy or puerperium • Alcohol or substance abuse • Any condition (for example, an unstable or progressive medical condition) which, in the investigator's assessment, may interfere with the evaluation procedures or the objectives of the study	**Conducted:** No			
Allendorfer et al. (2019)	RCT	**Sample (male:female):** IG: n=9 (6:3) CG: n=8 (3:5) **Mean age (years):** IG: 28.0 CG: 28.0 **Mean age at epilepsy onset (years) :** IG: 15.0 CG: 16.0	**Inclusion criteria:** • EEG-confirmed diagnosis of epilepsy • Age range: 18-55 years • <4 seizures/month on average in the past 3 months • Being relatively healthy with no comorbid medical	**Duration:** 6-week **IG:** Exercise training group **Frequency:** 3-day/week, nonconsecutive **Number of sessions:** 18 **Volume:** 60-min/session **Activity description**: Warm-	**Quality of life:** • **Short Form-36 (SF-36)** **Psycho-affective outcomes:** • **Mood state:** Profile of Mood States (POMS) - Total mood disturbance (TMD) score - Standard trials 1–5 total Learning score **Physical fitness outcomes:**	**Significant differences (p<0.05):** **IG Intragroup (pre vs. post)** ↓ POMS, TMD score ↑1RM, Leg press ↑1RM, Knee extension ↑1RM, Chest press ↑CVLT-II, d′ ↓rsFC, Left hippocampus ↓rsFC, Paracingulate cortex ↑rsFC, Cerebellum	**Recruitment:** 32% (16 out of 55) **Completion rate:** 81.25% (13 out of 16) IG: 100% CG: 72.72% (8 out of 11)

		Epilepsy DR **Type (generalized:focal):** IG: 7:2 CG**:** 7:1 **AED or ASD information:** Yes	conditions • No suicidal ideation in the past 3 months • Fluent in English language • Not concurrently participating in a different intervention study **Exclusion criteria:** • Feel problems with the memory • Unsuccessful contacting • Pregnancy	up sets + endurance training + resistance training • *Endurance training:* 15 min of cycling on a stationary cycle ergometer at 65–85% of HRR and progressed up to 30-min by session 7 **Intensity:** 65–85% of HRR • *Resistance training:* 8 movements (biceps curl, triceps pushdown, leg press, calf press, chest press, knee extension, lateral pull-down, and seated cable row), with alternating upper-body and lower-body movements **Intensity:** Session 1-4: 1-3x8-12 rep. **Progression:** When the participant achieved 12 or more repetitions on 2 or more sets of a given movement **Safety precautions:** To ensure safety and head/face protection in the unlikely event of a seizure, participants who were not seizure-free for at least 6 months prior to the onset of intervention were required to wear safety headgear **Conducted:** Yes **CG:** No-exercise group	• **Cardiorespiratory efficiency:** $VO_{2\ max}$ Nondiagnostic maximal graded exercise test (GXT) on a cycle ergometer and CareFusion indirect calorimetry system • **Muscular strength:** 1RM - Leg press - Knee extension - Chest press **Neurocognitive outcomes:** • **Verbal learning and memory**: California Verbal Learning Test, 2nd Edition (CVLT-II) - Long-delay free recall score - Recognition discriminability (d′) **Physiological outcomes:** • **HRR:** Nondiagnostic maximal graded exercise test (GXT) on a cycle ergometer and CareFusion indirect calorimetry system • **Resting State Functional Connectivity (rsFC):** 3.0T Siemens Prisma scanner using a 20-channel head coil (neuroimaging): - Lateral cerebellum - Left hippocampus - Right hippocampus - Thalamus - Posterior Cingulate Cortex (PCC) - Left Inferior Parietal Lobule (IPL) - Right IPL - Paracingulate cortex **Physical activity:** • **Baecke Questionnaire (BQ)**	↑rsFC, Thalamus ↑rsFC, PCC ↑rsFC, Left IPL ↑rsFC, Right IPL **CG Intragroup (pre vs. post)** ↓rsFC, Left hippocampus ↑rsFC, Cerebellum **Group x time interaction** CVLT-II, Learning score: IG>CG CVLT-II, d′: IG>CG	**Adherence:** 100% (18 sessions) **Adverse events:** No
Feter et al. (2020)	RCT	**Sample size:** n=20 **Sample (male:female):**	**Inclusion criteria:** • Age range: 18-60 years	**Duration:** 12-week **IG:** Exercise group	**Physical fitness outcome:** • **Cardiorespiratory efficiency:** VO_{2max}: Maximum incremental protocol	**Significant differences ($p<0.05$):**	**Recruitment:** NR

		IG: n=11 (4:7) CG: n=10 (4:6) **Mean age ± SD (years):** IG: 37.1 ± 4.0 CG: 39.7 ± 3.0 **Epilepsy** DR/CR **Type:** NR **AED or ASD information:** Yes	• Both sexes • Sedentary • Diagnosed with epilepsy **Exclusion criteria** • Any physical impairment that did not allow physical exercise practice • Inability to draw or read on a piece of paper due to visual impairment • Pregnancy	**Frequency:** 2-day/week (no in row) **Volume*:*** 60 min/session **Activity description:** Structured and individually supervised combined training: • *Warm-up:* 5 min light activity (walking on a treadmill) • *Aerobic training*: On a treadmill - 1-4 week: 15 min - 5-8 week: 20 min - 9-12 week: 25 min **Intensity:** Rating of perceived exertion (RPE) using the 6-to-20 Borg scale with target intensity between 14 and 17 • *Strength training:* 35 min exercise machines and free weights: chest press, seated row, leg press, squat, shoulder press, sit-up, and plank **Intensity:** 90 seconds rest between sets - 1-4 week: 2x12-15 submaximal/maximal rep. - 5-8 week: 2x12-15 maximal rep. - 9-12 week: 3x10-12 maximal rep. Plank: - 1-4 week: 20 seconds - 5-8 week: 30	on a treadmill during stress test • **Muscular strength:** Dynamometer • **Anthropometry:** • Weight: Digital Filizola scale • Height: Stadiometer • Hip and waist circumferences: Inextensible tape **Neurocognitive outcomes:** • **Global cognitive function:** Montreal Cognitive Assessment (MoCA) • **Attention, visual search speed, speed of processing, mental flexibility, and executive function:** Trail Making Test (TMT) - Attention capacity: TMT-A - Executive domain: TMT-B • **Working memory:** Digit Span Test (DST) • **Executive function:** Stroop Color and WordTest (SCWT) • **Language domain of executive function:** Verbal fluency test	**IG Intragroup (pre vs. post)** ↑MoCA ↓TMT-A ↑SCWT ↑Verbal fluency test **Group x time interaction** TMT-A**:** IG>CG	**Completion rate:** 95.23% (20 out of 21) IG: 90.90% (10 out of 11) CG: 100% **Adherence:** NR **Adverse events:** No

				seconds - 9-12 week: 45 seconds • *Stretching exercises:* 5 min active exercises (3x10 seconds); shoulders, hamstrings, quadriceps, chest, triceps, lower back, and neck **Conducted:** Yes **CG:** Control group **Activity description:** Advised to maintain usual daily activities			
Häfele et al. (2021)	RCT	Same as above	**Inclusion criteria:** • Aye range: 18-60 years • Epilepsy diagnosed • Not exercising in the past 3 months **Exclusion criteria:** • Physical disabilities that hindered activities • Could not read/write	Same as above	**Seizures/symptoms:** • **Seizures:** The number of seizures in the past three months and seizure dairy (seizures during the intervention: date(s), time of day(s), type(s), and number(s) of seizures **Quality of life:** • **Quality of Life in Epilepsy Inventory (QOLIE-31)** - Seizure worry - Overall quality of life - Emotional well-being - Energy/fatigue - Cognitive function - Medication effects - Social function - Total score • **Quality of sleep:** Pittsburgh Sleep Quality Index (PSQI) **Psycho-affective outcomes:** • **Depression:** Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) • **Anxiety:** Short version of the State-Trait Anxiety Inventory (STAI) - Anxiety State	**Significant differences ($p<0.05$):** **IG Intragroup (pre vs. post)** ↓Seizures frequency ↑QOLIE-31, Total score ↑QOLIE-31, Seizure worry ↑QOLIE-31, Overall quality of life ↑QOLIE-31, Emotional well-being ↑QOLIE-31, Energy/fatigue ↑QOLIE-31, Cognitive function ↑QOLIE-31, Social function ↓AEP ↓PSS-10 ↑VO_{2max} ↑Muscular strength **CG Intragroup (pre vs. post)** ↓STAI, Anxiety Trait **Group x time interaction** QOLIE-31, Total score: IG>CG QOLIE-31, Seizure worry: IG>CG	**Recruitment:** NR **Completion rate:** 95.23% (20 out of 21) IG: 90.90% (10 out of 11) CG: 100% **Adherence:** NR **Adverse events:** NR

					- Anxiety Trait • **Adverse effects of antiepileptic drugs:** Adverse Effects Profile (AEP) • **Stress:** Perceived Stress Scale (PSS-10) **Physical fitness outcome:** Same as above **Physiological outcomes:** Same as above • **BP:** Stethoscope and the sphygmomanometer and contact closure • **HR:** Heart monitor **Clinical outcomes:** Same as above	QOLIE-31, Overall quality of life: IG>CG QOLIE-31, Energy/fatigue: IG>CG QOLIE-31, Cognitive function**:** IG>CG PSS-10: IG>CG VO_{2max}: IG>CG	
Lundgren et al. (2008)	RCT	**Sample (male:female):** IG: n=10 (7:3) CG: n=8 (5:3) **Mean age (years):** IG: 21.9 CG: 25.8 **Epilepsy:** DR **Type (generalized:focal):** IG:8:3 CG: 7:3 **AED or ASD information:** Yes	**Inclusion criteria:** • Ability and willingness to participate in the treatment program, • Minimum of 3 seizures during the past 3 months • EEG-verified diagnosis of epilepsy **Exclusion criteria:** • Ongoing progressive illness	**Duration:** 3-month **Follow-up:** 6- and 12-month **IG:** Acceptance and Committment Therapy (ACT) group **Activity description:** Build broader behavior repertoires in valued directions using such processes as values clarification, acceptance, defusion, mindfulness, commitment, functional analysis of seizure chains, and countermeasure. **Volume:** 12 hours/participant therapy time divided in: - **Number of sessions and volume:** 4 - 1 individual session, 90 min - 2 group sessions, 180 min/session - 1 individual session, 90 min - Booster sessions (90 min) occurred at 6- and 12-month	**Seizures/symptoms:** • **Seizure index** (seizure frequency x seizure duration): Seizure diary **Quality of life:** • **Satisfaction with Life Scale (SWLS)** • **World Health Organization Quality of Life instrument, short version (WHOQOL-BREF)**	**Significant differences ($p<0.05$):** **IG Intragroup (pre vs. post)** ↓Seizure index ↑WHOQOL-BREF **CG Intragroup (pre vs. post)** ↓Seizure index ↑SWLS **Intergroup (pre)** Seizure index: IG>CG **Group x time interaction** Seizure index: IG>CG	**Recruitment:** NR **Completion rate:** NR **Adherence:** NR **Adverse events:** NR

				Conducted: Yes **CG:** Yoga group **Activity description:** Respond to internal stimuli in a conscious way, to decrease seizure activity and increase quality of life • *Physical dimensions:* - Pranayama (''controlled deep breathing") - Asanas (''physical postures") - Dhyana (''meditation") • *Psychological dimensions:* - Yama (''harmony with others") - Niyama (''harmony with yourself") **Conducted:** Yes			
McAuley et al. (2001)	RCT	**Sample (male:female):** IG: n=14 (3:11) CG: n=9 (3:6) **Mean age (years):** IG: 40.0 CG: 37.2 **Epilepsy:** CR **Type (generalized:focal):** IG: 7:7 CG: 8:1 **AED or ASD information:** Yes	**Inclusion criteria:** NR **Exclusion criteria:** • Treatable causes of seizures • Diagnosis of a progressive neurological or systemic disorder • Linguistic or cognitive inability to complete study questionnaires • Clinical laboratory test results outside the acceptable range • Significant	**Duration:** 12-week **Follow-up:** 4-week **IG:** Supervised exercise group **Frequency:** 3-day/week **Volume:** 60 min/session **Activity description:** Supervised cardiovascular, strength, and flexibility training **Intensity:** • *Cardiovascular*	**Seizures/symptoms:** • **Seizure frequency:** Seizure diary **Quality of life:** • **Quality of Life in Epilepsy Inventory (QOLIE-89):** - Overall score - Overall quality of life - Physical function - Role limitations-physical - Energy/fatigue - Emotional well-being - Health perceptions **Psycho-affective outcomes:** • **Mood state**: Profile of Mood States (POMS) - Total score	**Significant differences (p<0.05):** **IG Intragroup (pre vs. post)** ↑QOLIE-89, Overall score ↑QOLIE-89, Physical function ↑QOLIE-89, Energy/fatigue ↑QOLIE-89, Health perceptions↑ ↓POMS, Total score (n=9) ↓POMS, Vigor (n=9) ↑PSDQ, Total score (n=12) ↑PSDQ, Physical activity (n=12) ↑PSDQ, Coordination (n=12) ↑PSDQ, Endurance (n=12) ↑PSDQ, Strength (n=12)	**Recruitment:** NR **Completion rate:** 82.14% (23 out of 28) IG: 82.35% (14 out of 17) CG: 81.81% (9 out of 11) **Adherence:** NR **Adverse events:** NR

			cardiovascular, pulmonary, orthopedic, or endocrinologic disease • Nonepileptic spells (pseudoseizures) • Medication noncompliance • Attend at least 28 of the 36 scheduled exercise sessions (80% attendance rate)	*training:* Started at 60% of VO_{2max} and progressed as tolerated • *Strength training*: Began at 1x10 rep. of 70% of 1RM **Conducted:** Yes **CG:** No planned intervention group **Activity description:** Continue their current level of activity with no planned interventions	- Tension - Depression - Anger - Vigor - Confusion • **Global self-esteem:** 10-item Rosenberg Self-Esteem Scale • **Physical self-concept** Physical Self-Description Questionnaire (PSDQ) - Total score - Physical activity - Appearance - Body fat - Coordination - Endurance - Flexibility - Health - Sport - Strength - Esteem - General physical **Clinical outcome:** • **AED concentrations:** Blood sample	**CG Intragroup (pre vs. post)** ↑QOLIE-89, Energy/fatigue **IG Intragroup (pre vs. follow-up)** ↑PSDQ, General physical (n=12)	
Heise et al. (2002)	RCT	**Sample (male:female):** IG: n=14 (4:10) CG: n=9 (2:7) **Mean age ± SD (years):** IG: 41 ± 13 CG: 32 ± 12 **Epilepsy:** CR **Type (generalized:focal):** IG: 7:7 CG: 8:1 **AED or ASD information:** No	**Inclusion criteria:** • Aye range: 16-60 years • Documented epilepsy • Be stabilized for at least 1 month on an AED regimen **Exclusion criteria:** • Noncompliance history • Cardiovascular, endocrinal or pulmonary disease • Pregnancy	**Duration:** 12-week **Follow-up:** 4-week **IG:** Exercise group **Frequency:** 3-day/week **Volume:** 60 min/session **Activity description:** • *Cardiovascular training:* Treadmill, upright and recumbent stationary cycle, and stairclimber **Intensity:** 60% peak VO_2 during 10-30 min (depending on fitness level). Increased 5% VO_2 peak every 3 weeks as tolerated (first achieve 30 min	**Seizures/symptoms:** • **Seizures frequency:** Seizure dairy **Physical fitness outcome:** • **Cardiorespiratory efficiency:** • Submaximal endurance time on a treadmill (at least 24 hours following the VO_{2amax} and body composition assessments) • **Muscular strength:** 1RM - Lateral pulldown - Leg press - Leg extension - Shoulder press - Leg curl - Chest press - Biceps curls • **Anthropometry:** • **Body fat:** 3 skinfold calipers **Physiological outcomes:** • **Lipid profile:** Blood sample - Total cholesterol	**Significant differences ($p<0.05$):** **IG Intragroup (pre vs. post)** ↑Submaximal endurance time ↑VO_{2max} ↓Body fat ↓Total cholesterol (IG: n=7) ↓LDL (IG: n=7) ↓Triglycerides (IG: n=7) ↑7-Day PAR, Very-hard ↑7-Day PAR, Strength ↑7-Day PAR, Flexibility **IG Intragroup (pre vs. follow-up)** ↑Submaximal endurance time ↑ Muscular strength ↓ Body fat ↑7-Day PAR, Very-hard **IG Intragroup (post vs. follow-up)**	**Recruitment:** NR **Completion rate:** 82.14% (23 out of 28) IG: 82.35% (14 out of 17) CG: 81.81% (9 out of 11) **Adherence:** NR **Adverse events:** NR

				continuous exercise to increase) • *Strength training*: 7 exercise; lateral pulldown, leg press, leg extension, shoulder press, leg curl, chest press, and biceps curls **Intensity:** 1x10 rep. 70%. Increased when 12 rep. were perform as given weight. Decreased if did not able to do 8 rep. • *Active cool-down:* 3-5 min walking/stretching **Conducted:** Yes **CG:** Control group **Activity description:** Maintain current level of activity	- Triglycerides - HDL - LDL **Physical activity:** • **7-day Physical Activity Recall interview (7-Day PAR)** - Strength - Flexibility • **CARDIA physical activity history questionnaire**	↓VO_{2max} ↓7-Day PAR, Strength ↓7-Day PAR, Flexibility	
SudhindraVooturi et al. (2020)	RCT	**Sample (male:female):** n = 90 (13:77) IG: n=48 CG: n=42 **Mean age ± SD (years):** 25.85 ± 9.62 **Mean age at onset ± SD (years):** 14.31 ± 9.71 **Average illness duration ± SD (years)**: 8.16 ± 6.89 **Epilepsy:** CR **Type**	**Inclusion criteria:** • Aye range: 18- 60 years • Epilepsy diagnosis • Seizure-free (including auras) on optimal medical management for the last 2 years • Normal physical and neurological examinations **Exclusion criteria:** • Cognitive or behavioral problems • Endocrine, cardiac, or	**Duration:** 12-week **IG:** Exercise group **Activity description:** Counseled in detail about importance of healthy weight (healthy and balanced diet by a certified nutritionist) and staying physically active + *home-based exercise* *Home-based exercise:* • **Frequency:** 4-day/week • **Volume:** 45 min/session	**Quality of life:** • **12-Item Short Form Survey (SF-12):** - Physical Health Composite Scores (PCS) - Mental Health Composite Scores (MCS) **Physical fitness outcomes:** • **Cardiorespiratory efficiency:** • 6-minute walk distance • 1-minute step test • **Anthropometry:** • Average change in weight **Physiological outcomes:** • **Lipid profile:** Blood sample - Total cholesterol - Triglycerides - HDL - LDL	**Significant differences ($p<0.05$):** **Group x time interaction** SF-12, PCS: IG>CG 6-minute walk distance: IG>CG Average change in weight: IG>CG	**Recruitment:** % 9.14 (110 out of 1203) **Completion rate:** 81.81% (90 out of 110) IG: 87.27% (48 out of 55) CG: 76.36% (42 out of 55) **Adherence:** NR **Adverse events:** No

		(generalized:focal): IG: 7:7 CG: 8:1 **AED or ASD information:** Yes	pulmonary disease, or musculoskeletal limitations • Conditions or existing treatment affected hormone or insulin concentrations (thyroid dysfunction, hepatosis, and glucocorticoid therapy) • Pregnancy • No consent to enroll into the study and randomization • Normal BMI	• **Activity description:** Exercise with videos that encompassed cardiovascular, endurance and flexibility training • **Intensity:** - *Cardiovascular exercise:* Moderate intensity aerobic exercises at 60% target HR - *Endurance training:* Beginning with 10 repetitions of 70% of 1RM • **Activity log**: Finish at least 35 of the prescribed 48 home-based exercise sessions • **Baseline visit:** Exercises were demonstrated in person by an experienced physiotherapist to both the participant and the caregiver **Conducted:** No **CG:** Control group **Activity description:** Advised about healthy weight and importance of physical activity to continue enrolled in any exercise program			
Sathyaprabha et al. (2008)	Comparative study	**Sample (male:female):** IG: n=18 (10:8) CG: n=16 (10:6) **Mean age ± SD (years):** IG: 33.1 ± 11.1	**Inclusion criteria:** • Aye range: 15-55 years • Normal intellectual function	**Duration:** 10-week **Frequency:** NR **Volume:** 60 min/day	**Seizures/symptoms:** • **Seizure frequency score** **Physiological outcomes:** • **Autonomic function test (AFT):** - *Parasympathetic dysfunction:* HR	**Significant differences (p<0.05):** **IG Intragroup (pre vs. post)** ↓Seizure frequency score ↑AFT, Deep breathing ratio	**Recruitment:** NR **Completion rate:** 85%

		CG: 31.4 ± 7.5 **Mean age at onset ± SD (years):** IG: 13.1 ± 8.9 CG: 11.3 ± 6.6 **Average illness duration ± SD (years):** IG: 9 ± 9.4 CG: 19.1 ± 7.2 **Epilepsy:** DR **Type (generalized:focal):** IG: 3:15 CG: 3:13 **AED or ASD information:** No	• Uncontrolled epilepsy **Exclusion criteria:** • Cardiorespiratory or neurological disorders • Diabetes mellitus • Chronic alcoholism and/or substance abuse • Symptomatic seizures due to underlying structural pathology • Pregnant or lactating	**IG:** Yoga group **Activity description:** 2-week training and 8-week actual yoga therapy: • 20 min pranayama (yogic breathing exercises; pranayama, om meditation, and cyclic meditation) • 40 min postural or yogic stances (yogasana; suryanamaskara, ardhakati chakrasana, bhujangasana, salabhasana, and savasana) **Conducted:** Yes **CG:** Exercise group **Activity description:** 20 min quiet sitting and 40 min simple physical exercise **Conducted:** NR	▪ Deep breathing ratio ▪ Valsalva ratio ▪ Max:min ratio - *Sympathetic dysfunction:* BP ▪ Standing ΔSBP ▪ Isometric ΔDBP	↑AFT, Max:min ratio **Group x time interaction** Seizure frequency score: IG<CG AFT, Max:min ratio: IG>CG	(34 out of 40) IG: 90% (18 out of 20) CG: 80% (16 out of 10) **Adherence:** NR **Adverse events:** NR
Eom et al. (2014)	Quasi-experimental study	**Sample (male:female):** n=10 (4:6) **Mean age ± SD (range):** 9.7 ± 1.42 years (8-12) **Mean age at onset (range):** 7.8 years (6.5-9.3) **Epilepsy:** CR **Type (generalized:focal):** Generalized: n=9 Focal: n=1 **AED or ASD**	**Inclusion criteria:** NR **Exclusion criteria:** NR	**Duration:** 5-week **Frequency:** 2-day/week **Number of sessions:** 10 **Activity description:** • *Supervised therapeutic exercises:* Basketball, soccer, table tennis, badminton, or jump rope and line dancing. At the last session, children's parents also joined the exercise program, completing a dance session together. **Volume:** 180	**Seizures/symptoms:** • **Seizure frequency** **Quality of life:** *Parents-completed questionnaires* • **Korea-Quality of Life in Childhood Epilepsy (K-QOLCE)** - Physical function ▪ Physical restriction ▪ Energy/fatigue - Well-being (mood) ▪ Depression ▪ Anxiety ▪ Control/helplessness ▪ Self-esteem - Cognition ▪ Attention/Concentration ▪ Memory ▪ Language	**Significant differences (p<0.05):** **Intragroup (pre vs. post)** ↑K-QOLCE, Well-being (mood) ↓K-QOLCE, Behaviors (n=8) ↓K-CBCL, Internalizing behavior problems (n=7) ↓K-CBCL, Social problems ↑Push-ups ↑CAT, Simple selective attention: visual (n=9) ↑CAT, Simple selective attention: auditory (n=9) ↑CCTT1 ↑CCTT2 (n=9)	**Recruitment:** NR **Completion rate:** 100% **Adherence:** 100% (10 sessions) **Adverse events:** NR

		information: Yes		min/session (2 different activities x 90 min) • *Home-based exercise:* Resistance exercises; own body weight sit-ups and push-ups. **Volume:** 15–20 min/ session • *Parent education program***:** Lectures by the therapeutic exercise team, including presentations about the efficacy of exercise and the relationship between exercise and seizures **Duration:** 5-week **Conducted:** Yes	▪ Other cognition - Social function ▪ Social activities ▪ Social interactions - Behaviors - General health - Quality of life - Overall Quality of Life **Psycho-affective outcomes:** *Child-completed questionnaires* • **Depression:** Children's Depression Inventory (CDI) • **Anxiety:** Revised Children's Manifest Anxiety Scale (RCMAS) *Parents-completed questionnaires* • **Children's behavioral problems:** Korea-Child Behavior Checklist (K-CBCL) - Competence ▪ General social competence ▪ Social competence ▪ School competence - Behavioral problems ▪ Total behavior problems ▪ Internalizing behavior problems ▪ Externalizing behavior problems ▪ Withdrawal ▪ Somatic complaints ▪ Anxiety/depression ▪ Social problems ▪ Thought problems ▪ Attention problems ▪ Delinquent problems ▪ Aggressive behavior **Physical fitness outcomes:** • **Cardiorespiratory efficiency:** • 50-m run • 1000-m run • **Muscular strength:** • Standing broad jump • Sit-ups • Push-ups • Sit and reach		

					Neurocognitive outcomes: • **Attention:** - Korea-Wechsler Intelligence Scales for Children—Third Edition (K-WISC-III) - Comprehensive Attention Test (CAT) ▪ Simple selective attention: visual ▪ Simple selective attention: auditory ▪ Working memory: forward ▪ Working memory: backward • **Executive function:** Children's Color Trails Test (CCTT) - CCTT1: Perceptual tracking, sustained attention, and psycho-motor speed - CCTT2: Attention, sequential processing, and inhibition–disinhibition **Physiological outcomes:** • **EEG**		
Eom et al. (2016)	Quasi-experimental study	**Sample (male:female):** n=10 (4:6) **Mean age (range):** 10.3 years (8.5-12.5) **Mean age of onset (range):** 7.8 years (6.5-9.3) **Epilepsy:** CR **Type:** NR **AED or ASD information:** No	**Inclusion criteria:** NR **Exclusion criteria:** NR	**Duration:** 35-week (5-week supervised therapeutic exercise + 30-week home-bases exercise) **Activity description:** • *Supervised therapeutic exercise:* Basketball, soccer, table tennis, badminton, jumping rope, and line dance **Frequency:** 2-day/week **Number of sessions:** 10 **Volume:** 180 min/session (2 different activities x 90 min) • *Home-based exercise:* Resistance exercises;	**Seizures/symptoms:** Same as above **Quality of life:** Same as above **Psycho-affective outcomes:** *Parents-completed questionnaires* • **Children's behavioral problems:** Same as above *For parents and children, 2 separated questionnaires* • **Satisfaction Surveys:** Questions about enjoyment, satisfaction, and emotional and thought change **Neurocognitive outcomes:** • **Attention:** Same as above • **Executive function:** Same as above **Physiological outcomes:** Same as above	**Significant differences ($p<0.05$):** **Intragroup (pre vs. post)** ↑K-QOLCE, General health (n=9) ↑K-QOLCE, General quality of life ↓K-CBCL, Internalizing behavior problems (n=8) ↑K-WISC-III, Symbol Search ↑CCTT1 ↑CCTT2 (n=9)	**Recruitment:** NR **Completion rate:** 100% **Adherence:** NR **Adverse events:** NR

				own body weight sit-ups and push-ups + 20-30 min aerobic exercise. Participants were provided with a pedometer and encouraged to walk more than 7000 steps per day. • *Children + parents 4 meetings* (during 30-week home-based exercise): Leisure activities (hiking and bowling) and education sessions. **Conducted:** Yes			
Eriksen et al. (1994)	Quasi-experimental study	**Sample:** n=13 female **Mean age (range):** 32 years (18-46) **Average illness duration (range):** 22 years (6-37) **Epilepsy:** DR **Type:** Generalized: n=1 Focal : n=12 **AED or ASD information:** No	**Inclusion criteria:** • Women • Age range: 18-50 years • Epilepsy without additional handicaps • At least 1 seizure a month in the previous year • AED treatment **Exclusion criteria:** NR	**Duration:** 15- week **Follow-up:** 15-week **Frequency:** 2 day/week **Volume:** 60 min/session **Activity description:** Standard physical exercise program (The Norwegian Aerobic Fitness model)*: • *Ergonomics* • *Warmup* • *Aerobic* • *Dancing* • *Cool down* • *Stretching* • *Strength* training • Relaxation *All accompanied by music **Intensity:** Individually adapted to meet the capability of each individual on the basis of baseline fitness measurements 70-80% maximum HR	**Seizures/symptoms:** **Seizure frequency:** Seizure diary **Psycho-affective outcomes:** • **Psychological and social problems:** Washington Psychosocial Seizure Inventory (WPSI) • **Anxiety:** Spielberger State-Trait Anxiety Inventory (STAI) • **Depression:** Beck's Depression Inventory (BDI) • **Locus of control (LOC) and The Multidimensional Health Locus of Control (MHLC)** • **Subjective somatic and psychological problems:** Ursin Health Inventory (UHI) - Anxiety and depression subindex - Cardiac subindex - Gastrointestinal subindex - Sleep-fatigue subindex - Muscle pain subindex - Headache/migraine subindex - Respiratory subindex - Constipation subindex - Diarrhoea subindex - Skin subindex - Overall health complaints	**Significant differences ($p<0.05$):** **Intragroup (pre vs. post)** ↓Seizures frequency ↓UHI, Muscle pain subindex ↓UHI, Sleep-fatigue subindex ↓UHI, Overall health complaints ↑VO_{2max} ↓Total cholesterol (n=11) ↓HDL ratio (n=11) ↓HDL **Intragroup (pre vs. follow-up)** ↓UHI, Muscle pain subindex↓ ↓Cholesterol ↓HDL	**Recruitment:** 10.71% (15 out of 140) **Completion rate:** 86.6% (13 out of 15) **Adherence:** 75% (range 30-100%) 11 patients had >60% compliance **Adverse events** No

				during aerobic dancing **Conducted:** Yes	**Physical fitness outcomes:** • **Cardiorespiratory efficiency:** VO_{2max}: O_2 analyzer + maximal running uphill on a motor-driven treadmill with 3°inclination **Physiological outcomes:** • **Lipid profile:** Blood sample - Total cholesterol - Triglycerides - HDL - LDL • **HR:** Resting HR with BP monitor • **BP:** BP monitor - Systolic BP (SBP) - Diastolic BP (DBP) • **Vital capacity:** Jaegers pneumoscope - FVC - FEV • **Lactate:** Lactate analyzer with 50 µl blood obtained from the fingertip • **Borg scale:** Borg 15-grade scale (6-to-20 scale)		
Nakken et al. (1990)	Quasi-experimental study	**Sample (male:female):** n=21 (10:11) **Mean age (range):** 29 years (18-39) **Average illness duration (range):** 20.5 years (0-32) **Epilepsy:** DR **Type:** Generalized: n=6 Focal: n=15 **AED or ASD information:** Yes	**Inclusion criteria:** NR **Exclusion criteria:** NR	**Duration:** 4-week **Frequency:** 6-day/week **Number of sessions:** 3-session/day **Volume:** 45 min/session **Activity description:** Aerobics, swimming, jogging, hiking, volleyball, horseback riding, table tennis, bicycling, and rowing **Intensity:** At least two daily sessions with a minimum intensity of 60% of VO_{2max}. HR controlled by the instructors. **Safety precautions**: • During water activities, one guard per patient,	**Seizures/symptoms:** • **Type** • **Frequency** • **Connection:** Possible connection between seizures and mode and intensity of the exercises or other circumstances of possible influence • **Psychosocial functioning:** Before the training period, all patients were asked about their experience regarding the influence of physical activity on their seizures. **Physical fitness outcome:** • **Cardiorespiratory efficiency:** • Maximal work capacity (W) (Åstrand method) • VO_{2max}: Åstrand method • **Anthropometry:** • Weight • Body fat: Skinfold thickness **Physiologic outcomes:**	**Significant differences ($p<0.05$):** **Intragroup (pre vs. post)** ↑W↑ ↑VO_{2max} ↓Weight	**Recruitment:** 47.7% (21 out of 44) **Completion rate:** 100% **Adherence:** NR **Adverse events** One participant had a minor cutaneous head injury while riding a bicycle. One participant had "exercise-induced" seizures.

				patients wore life jackets while boating, and an extra guard was available. • During horseback riding and bicycling helmets were used. **Conducted:** Yes	• **BP** • **Vital capacity:** FVC and FEV • **ECG**		
Conant et al. (2008)	Pilot study	**Sample (male:female):** n=9 (2:7) **Mean age (range):** 10.6 years (8-16) **Mean age of onset (range):** 5.0 years (0.1-8.33) **Epilepsy:** DR/CR **Type:** Generalized: n=2 Focal: n=5 NR: n=2 **AED or ASD information:** No	**Inclusion criteria:** NR **Exclusion criteria:** NR	**Duration:** 10-week **Frequency:** 1-hour/week **Volume:** 60 min/session **Activity description:** Kempo karate **Conducted:** Yes	**Seizures/symptoms:** • **Frequency** • **Number of AED** **Quality of life:** *Parents-completed questionnaires* • **Quality of Life in Childhood Epilepsy (QOLCE)** - Physical function ▪ Physical restriction ▪ Energy/fatigue - Well-being (mood) ▪ Depression ▪ Anxiety ▪ Control/helplessness ▪ Self-esteem - Cognition ▪ Attention/Concentration ▪ Memory ▪ Language ▪ Other cognition - Social function ▪ Social activities ▪ Social interactions - Behaviors - General health - Quality of life - Overall Quality of Life **Psycho-affective outcomes:** *Parents-completed questionnaires* • **Parental Stress Index Short Form Third Edition(PSI/SF)** - Parental distress - Parental-Child dysfunctional interaction - Difficult child - Total stress	**Significant differences ($p<0.05$):** **Intragroup (pre vs. post)** ↑ QOLCE, Memory	**Recruitment:** 60% (9 out of 15) **Completion rate:** NR **Adherence:** NR **Adverse events:** NR

					Child-completed questionnaires • **Piers-Harris Children's Self Concept Scale 1 (PH-1)** - Behavior - Intellectual and school status - Physical appearance and attributes - Anxiety - Popularity - Happiness and satisfaction - Total score		

IG: Intervention group, CG: Control/comparison group, 1RM: One repetition maximum, AED: Antiepileptic drug, ASM: Anti-Seizure Medication, BECTS: Benign Epilepsy with Centrotemporal Spikes, BMI: Body Mass Index, BP: Blood Pressure, CR: Controlled, DR: Drug-resistant, ECG: Electrocardiogram, EEG: Electroencephalogram, FVC: Forced Vital Capacity, FEV: Forced Expiratory Volume, GTC: Generalized Tonic-Clonic; HDL: High-Density Lipoprotein, HR: Heart Rate, HHR: Heart Rate Reserve, LDL: Low-Density Lipoprotein, MCS: Mental component scores, NR: Not Reported, VPA: Valproic Acid, PCS: Physical component scores, VO2max: Maximum Oxygen uptake.

Table 2. PEDro result of the methodological quality evaluation of the RCTs.

First author (year)	PEDro items										Score
	1	2	3	4	5	6	7	8	9	10	
Allendorfer (2019)	Yes	No	Yes	No	No	No	No	No	Yes	Yes	4/10
Åkerlund (2021)	Yes	No	Yes	No	No	No	No	No	Yes	Yes	4/10
Feter (2020)	Yes	No	Yes	No	No	Yes	Yes	No	Yes	Yes	6/10
Häfele (2021)	No	No	Yes	No	No	No	Yes	No	Yes	Yes	4/10
Heise (2002)	Yes	No	Yes	No	No	No	No	No	Yes	Yes	4/10
Lundgren (2008)	Yes	Yes	No	No	No	No	Yes	Yes	Yes	Yes	6/10
McAuley (2001)	Yes	No	Yes	No	No	No	No	No	Yes	Yes	4/10
SudhindraVooturi (2020)	Yes	No	No	No	No	No	No	No	Yes	Yes	3/10

Items: 1 = random allocation; 2 = concealed allocation; 3 = baseline comparability; 4 = blind subjects; 5 = blind therapists; 6 = blind assessors; 7 = adequate follow-up; 8 = intention-to-treat analysis; 9 = between-group comparisons; 10 = point estimates and variability.

Table 3. Methodological quality of the included non-randomized comparative studies.

First author (year)	MINORS items												Score
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
Sathyaprabha (2008)	2	2	2	2	2	2	2	0	2	2	2	2	22/24

Items: 1 = a clearly stated aim; 2 = inclusion of consecutive patients; 3 = prospective collection of data; 4 = endpoints appropriate to the aim of the study; 5 = unbiased assessment of the study endpoint; 6 = follow-up period appropriate to the aim of the study; 7 = loss to follow up less than 5%; 8 = prospective calculation of the study size; 9 = an adequate control group; 10 = contemporary groups; 11 = baseline equivalence of groups; 12 = adequate statistical analyses. The items are scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate).

Table 4. Methodological quality of the included Before-After (Pre-Post) Studies With No Control Group.

First author (year)	BEFORE-AFTER (PRE-POST) STUDIES WITH NO CONTROL GROUP items												Score
	1	2	3	4	5	6	7	8	9	10	11	12	
Eom (2014)	Yes	No	CD	NR	No	Yes	Yes	No	No	Yes	No	NA	Fair
Eom (2016)	Yes	No	CD	NR	No	Yes	Yes	No	No	Yes	No	NA	Fair
Eriksen (1994)	Yes	Yes	CD	Yes	No	Yes	Yes	No	No	Yes	No	NA	Fair
Nakken (1990)	Yes	No	CD	NR	No	Yes	Yes	No	No	Yes	No	NA	Fair
Conant (2008)	Yes	No	CD	No	No	No	Yes	No	No	Yes	No	NA	Poor

Items: 1 = study question; 2 = eligibility criteria and study population; 3 = study participants representative of clinical populations of interest; 4 = all eligible participants enrolled; 5 = sample size; 6 = intervention clearly described; 7 = outcome measures clearly described, valid, and reliable; 8 = blinding of outcome assessors; 9 = follow-up rate; 10 = statistical analysis; 11 = multiple outcome measures; 12 = group-level interventions and individual-level outcome efforts.