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REVIEW

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Effectiveness of exercise-based interventions in patients with anorexia nervosa: A systematic review

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Abstract

Objective: This study aimed to conduct a systematic review of research that has evaluated the outcomes of exercise-based interventions in anorexia nervosa (AN) patients.

Method: We searched for studies in the MEDLINE, Embase, Web of Science, PsycInfo, Scopus and SPORTDiscus databases. We followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines throughout the selection process, and used Cochrane tools to assess the risk of bias in the primary studies. In cases where sufficient information was available, outcomes were pooled using meta-analytic techniques.

Results: Ten studies were included in the review. Results showed similar changes in body mass index in both experimental and control conditions (difference in mean changes of −0.53, 95% CI −1.52 to 0.46). We found no differences in depression or anxiety as a result of implementing exercise programmes. Studies using resistance or strength exercise programmes reported an increase in lower and upper body strength and in skeletal muscle mass in the intervention groups.

Conclusion: The incorporation of a supervised physical exercise programme to the usual treatment may be appropriate for AN patients. Exercise interventions should only be performed when they are safe for AN patients and should be focused on resistance/strength or flexibility exercises. The results from this systematic review should be interpreted with caution because the studies reviewed showed serious methodological problems.

KEYWORDS
anorexia, exercise, physical activity, systematic review

1 | INTRODUCTION

Anorexia nervosa (AN) is a serious mental illness characterised by the restriction of energy intake, leading to significantly low body weight. It is often accompanied by an intense fear of gaining weight or becoming fat and disturbances in the way in which one's body weight or shape is experienced (American Psychiatric Association, 2013). A recent review of epidemiological studies showed that the prevalence of AN is <1%–4% among European women (Keski-Rahkonen & Mustelin, 2016). Somatic complications occasioned by undernourishment

Abbreviations: AN, anorexia nervosa; BMI, body mass index; RCTs, randomised control trials.

and/or weight control strategies as well as psychiatric comorbidities and neuropsychological features (such as cognitive rigidity or poor central coherence) have been observed as recurring features of this pathology (Harper, Brodrick, van Enkenvort, & McAdams, 2017; Solmi, Collantoni, Meneguzzo, Tenconi, & Favaro, 2018). Because of comorbid physical and psychiatric conditions, AN is one of the most difficult psychiatric conditions to treat. Mortality in AN is considerably higher than that of other eating disorders and mental illnesses, with an estimated standardised mortality ratio of 5.35 (Fitcher & Quadflieg, 2016). The most important physical consequences of AN are bradycardia, amenorrhoea, decreased bone integrity (osteopenia leads to osteoporosis), weak proximal muscles, axial hypotonia (at very severe stages of malnutrition), gastrointestinal symptoms, dizziness and syncope (Hudson, Hiripi, Pope, & Kessler, 2007). AN also appears with psychiatric comorbidity. The most common comorbid disorders are anxiety disorders (generalised anxiety disorder, specific phobias, obsessive-compulsive disorder, social anxiety and post-traumatic stress disorder), mood disorders (including major depression) and, to a lesser extent, substance use disorders (Keski-Rahkonen & Mustelin, 2016; O'Brien & Vincent, 2003).

Excessive physical activity has long been identified amongst AN patients. Previous studies have shown that AN patients use physical activity as a common weight and shape control strategy (Le Grange & Eisler, 1993) and as a coping strategy to compensate, remove, or alleviate negative affective states (anxiety, depression and stress) and eating disorders symptoms (including weight preoccupation, drive for thinness, body dissatisfaction and restrictive profile; Meyer, Tarnis, Goodwin, & Haycraft, 2011; Rizk et al., 2015). Physical activity also has a positive reinforcement function in these patients, which is reflected in the positive addiction model of exercise dependence. According to this model, exercise dependence is attributable to exercise-induced euphoric states that are highly enjoyable (Glasser, 1976). Finally, physical activity has also been linked with obsessive-compulsive personality traits (such as perfectionism, inflexibility and rigidity) in AN patients (Meyer et al., 2011; Peñas-Lledo, Vaz Leal, & Waller, 2002).

Estimates of individuals with AN who have exercised excessively at some point during the course of their illness range from 40% (Shroff et al., 2006) to 81% (Davis et al., 1997). AN patients have an intense aversion of fat, and one of their main reasons to exercise is to influence their body weight and shape. Exercise often implies a compulsive pattern in AN patients: rigid exercise schedules are strictly adhered to; distress appears if the routine is altered and it is restarted if interrupted (Naylor, Mountford, & Brown, 2011). This type of exercise is associated with poorer clinical and therapeutic outcomes. It makes nutritional rehabilitation difficult and increases the probability of physical complications and the risk of dropout during treatment and relapses. Excessive exercise is also associated with a poorer quality of life (El Ghoch et al., 2013; Steinhausen, Grigoroiu-Serbanescu, Boyadjieva, Neumärker, & Winkler, 2008). This is why exercise has been considered a problematic behaviour that should be limited or even completely forbidden, especially during the acute phase of the disorder. Exercise in this phase can contribute to the development of serious clinical consequences, such as osteoporosis, risk of stress fracture, hydro-electrolytic imbalance and lack of muscle mass. In this context, current approaches for dealing with problematic exercise (compulsive, excessive and with the purpose of losing weight) during hospital treatment are characterised by exercise restriction and control. The engagement in problematic exercise during treatment could compromise goals and therapeutic commitment (Strober, Freeman, & Morrell, 1997).

Physical exercise has traditionally been excluded from treatment guidelines for these patients. AN treatment recommendations from the American Psychiatric Association and the National Institute for Health and Clinical Excellence Eating Disorders Guideline include nutritional rehabilitation, psychosocial interventions, family interventions and pharmacotherapy (although there is limited evidence supporting the use of

HIGHLIGHTS

- This systematic review highlights the paucity of data to make decisions about the relevance of structured and supervised exercise as a treatment in patients with anorexia nervosa (AN)
- Supervised physical exercise interventions were not associated with weight loss in patients with AN
- Physical exercise interventions focused on resistance/strength or flexibility have no additional effect on anthropometry, but they might improve vital signs, muscle function and strength, and eating disorder symptomatology
- Physical exercise programmes have not shown significant effects on psychological variables such as anxiety and depression

medication to treat chronic AN or to restore weight and prevent relapse).

However, a substantial body of evidence supports the implementation of exercise interventions for people with mental illnesses (Stanton & Happell, 2013; Zschucke, Gaudlitz, & Strohle, 2013), including eating disorders (Hausenblas, Cook, & Chittester, 2008; Vancampfort et al., 2013) and AN in particular (Fernández del Valle et al., 2010; Fernández del Valle, Larumbe, Morandé, & Perez, 2016; Moola, Gairdner,& Amara, 2013; Ng, Ng, & Wong, 2013; Noetel et al., 2016; Rizk et al., 2019). For example, Fernández del Valle et al. (2016) analysed the effects of short-term resistance training on body composition and muscle function in AN restrictive-type patients. The results showed that skeletal muscle mass and relative strength increased. Noetel et al. (2016) studied the effect of physiotherapy sessions on the psychological effect of AN inpatients and found that anxiety and depression affect decreased. In another study with adolescent inpatients with AN, high-impact low-frequency exercise shortened time to vital-sign stabilisation (Martin, Bachrach, & Golden, 2016). By contrast, other studies have not shown any benefits of exercise training. For example, Fernández del Valle et al. (2010) showed that low-to-moderate intensity strength training did not add major benefits to conventional psychotherapy and refeeding treatments in young anorexic patients. A systematic review of exercise interventions for women with AN found limited evidence of a positive correlation between physical activity and weight restoration (Zunker, Mitchell, & Wonderlich, 2011).

Another review of exercise interventions in AN patients was conducted by Ng et al. (2013). Their meta-analytic study conducted randomised controlled trials (RCTs) and quasi-randomised trials, which showed that, regardless of the type of exercise, supervised exercise training did not affect anthropometry (body weight, body fat and body mass index [BMI]) in patients with AN. They concluded that including supervised exercise training in the treatment of AN patients is safe, as it did not result in additional weight loss and may have benefits in the areas of strength and psychological well-being, but they noted study design limitations and heterogeneity of exercise training programmes.

Further research is required to determine what frequency, type and intensity of exercise is beneficial for AN patients and to establish a guideline for exercise training. RCTs allow a more extensive evaluation of the effects of supervised exercise training in AN patients. The present study provides an up-to-date systematic overview and an addition to the available body of evidence regarding the effectiveness of implementing structured exercise interventions in AN patients. Results could be exploited to provide directions for further research in this area as well as guidelines for the clinical management of individuals with AN.

2 | METHOD

The protocol for this systematic review was submitted to PROSPERO on the 26th of November 2019 (acknowledgement of receipt: 160046) and was registered in the Open Science Framework (date 10 April 2020; https://osf.io/dkvnz/). The current systematic review was reported according to the PRISMA statement (Liberati et al., 2009; Moher, Liberati, Tetzlaff, & Altman, 2009; Urrutia & Bonfill, 2010). The review was carried out by two researchers (Yolanda Quiles Marcos and Eva León Zarceño).

2.1 | Literature search

We carried out a comprehensive literature search of the MEDLINE, Embase, Web of Science, PsycInfo, Scopus and Sport Discuss databases. We also checked the clinical registries ClinicalTrials.gov, Current Controlled Trials, PROSPERO and the WHO Clinical Trials Registry Search Portal to identify ongoing and recently completed research in the field. Moreover, the references of all included articles were also screened. We limited the search to articles in Spanish and English published from January 1970 to December 2019.

2.2 | Eligibility criteria

We used the following descriptors in combination across all databases: eating disorders, anorexia, physical activity, exercise, treatment and intervention. For this study, we selected published articles referring to the use of physical exercise as part of treatment in anorexia. We divided the descriptors into three groups. Group 1: eating disorders or anorexia; Group 2: physical activity or exercise and Group 3: treatment or intervention. In the first phase, key words from Group 1 and Group 2 were used and then crossed with the descriptors from Group 3. For their inclusion in our study, we followed the modified Participants, Interventions, Comparator/Control group, Outcomes, Study design (PICOS) criteria (Liberati et al., 2009; Table 1).

RCTs and prospective non-randomised trials examining one or more exercise interventions in patients with AN or who used physical exercise as part of a treatment were included.

A wide range of physical and psychological variables, including BMI, strength, agility, markers of

TABLE 1 Applied inclusion and exclusion criteria according to the PICOS dimensions (Liberati et al., 2009)

PICOS dimensions	Inclusion	Exclusion
(P)articipants	Patients with anorexia nervosa	Other diagnoses
(I)nterventions	Any intervention that used physical exercise as a treatment	Compulsive physical exercise Exercise interventions that were not part of the treatment of anorexia
(C)omparator/ control group	No control group With control group in which traditional treatment has been applied	
(O)utcomes	BMI, psychological variables (depression/anxiety), bone mineralisation, eating disorder symptoms	
(S)tudy design	Randomised and prospective non-randomised trials	

Abbreviation: BMI, body mass index.

bone turnover, eating disorder symptoms and internalising symptoms were considered.

2.3 | Data extraction and risk of bias assessment

First, our team of two researchers (Yolanda Quiles Marcos and Eva León Zarceño) screened studies based on their titles and abstracts. They excluded duplicate references and assessed studies based on the research questions and inclusion/exclusion criteria. After this screening phase, they reviewed the full text of the remaining articles using a pre-specified piloted proforma. In case of any unresolved discrepancies, a third party (JALL) was consulted (this applied to all stages of the systematic review).

The details of design, sample size, population characteristics, interventions and outcome assessments were extracted for each included study.

We assessed the risk of bias in each study using the Cochrane tool (Higgins et al., 2019), assigning different judgements for each domain and outcome. We used different tools for randomised and non-randomised studies. The two reviewers (Yolanda Quiles Marcos and Eva León Zarceño) independently assessed the risk of bias in each study and resolved disagreements via discussion with a third colleague (JALL).

2.4 | Integration of results

First, we reviewed the evidence reported in the primary studies on the effectiveness of exercise-based interventions for each outcome domain. We extracted the numerical information provided in the papers and examined these results in the context of each outcome category. Wherever possible, we calculated effect sizes from the data provided using the Campbell Collaboration calculator (Wilson, 2020).

In cases where several studies reported results that were deemed combinable, we calculated effect sizes and carried out a statistical integration using meta-analysis. All outcomes were continuous and most studies reported both baseline and post-intervention measures, hence, we used the raw difference in mean changes as the main effect measure. Some studies did not report the standard deviations of the change scores, so we imputed these values using information from fully reporting studies (Higgins et al., 2019). To assess the impact of imputation on the results, we conducted a sensitivity analysis using a standardised measure that only required a measure of variability at baseline, which was the difference in standardised mean changes (Rubio-Aparicio, Marin-Martinez, Sanchez-Meca, & Lopez-Lopez, 2018, eq. 10).

We fitted random-effects meta-analytic models because we expected heterogeneity among the effect estimates from different studies. We graphically examined heterogeneity with forest plots, the Q statistic, and the I2 index (Cooper, Hedges, & Valentine, 2019). We planned moderator analyses via meta-regression models and funnel plots to examine potential reporting biases (such as publication bias). Finally, we performed sensitivity analyses using the leave-one-out strategy to explore the influence of extreme results. We performed all analyses in R v3.6.2 (R Core Team, 2019) using the 'metafor' package (Viechtbauer, 2010).

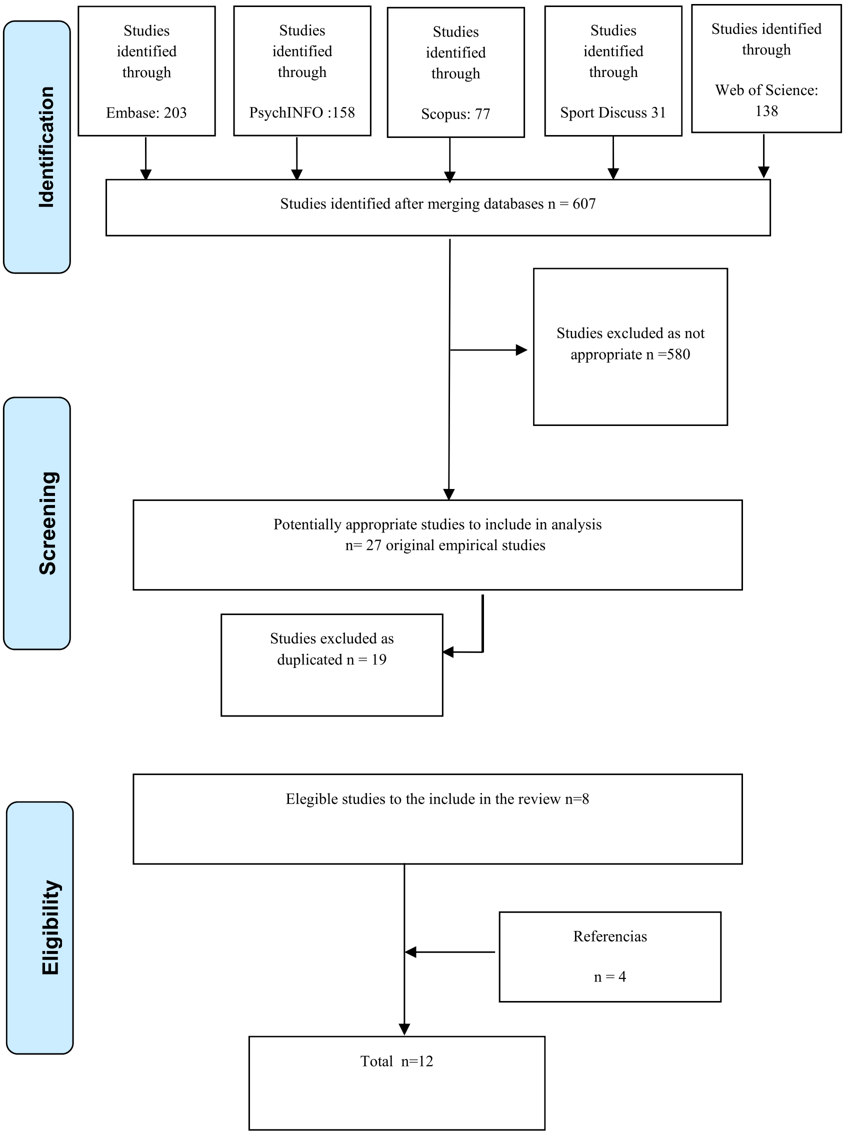


FIGURE 1 Flow chart summarising the search process and results [Colour figure can be viewed at wileyonlinelibrary.com]

3 | RESULTS

3.1 | Study selection

The first examination of retrieved records focussed on the information derived from the title, summary, and keywords ($n = 607$). We excluded articles that did not report original research, conference abstracts not published as full-text publications, studies that used non-human samples or case reports, review studies and studies that did not differentiate patients with AN from other eating disorders ($n = 580$). Articles relevant to the objective of this review were retained ($n = 27$). In the second phase, we used the aforementioned inclusion criteria for the final article selection; we selected eight articles (see Figure 1). In addition, we included articles obtained from the reference lists of the selected articles ($n = 4$), reaching 12 articles. We should highlight that the publications by Fernández del Valle et al. (2016) and Fernández del Valle et al. (2014) originated from the same study. The same happened with publications by Chantler, Szabo, and Stuttgart (2006) and Szabo and Green (2002).

3.2 | Descriptive characteristics of the included studies

We retrieved ten studies that reported results on at least one of the relevant outcomes of the review met our inclusion criteria. Table 2 provides some key characteristics of the included studies.

In our search, the year of publication parameter for studies ranged from 1993 to 2017. Although most studies were conducted in North America and Spain, research was also conducted in Australia, Japan, and South Africa. Most of the studies referred to inpatient treatment

TABLE 2 Summary of study characteristics

Author (s), year, country	Type of study, assessments	Setting and duration	Sample size, diagnostic, gender	Age mean ± SD, range)	BMI	Protocol	Measures
Martin et al. (2016) USA	RCT Baseline 4–6 days 7–9 days	Hospital 9 days	IG $N = 20$ AN DSM-V 95.23% females CG $N = 21$ AN DSM-V BMI = N/A 95.23 % females	16.8 ± 2.4 (12–21) 16.8 ± 2.3 (12–21)	BMI = N/A BMI = N/A	IG TAU + 20 jumps twice daily After a 24-h monitoring period of bed rest, the IG participated in high-impact, low-frequency exercises consisting of 20 vertical jumps to a height of 5 inches off the ground twice a day for 9 days CG TAU	Bone density Mean percentage weight gain BMI Hospitalisation stay length Time to stabilisation of vital signs (heart rate, blood pressure)
Fernándezdel Valle et al. (2016) Fernández del Valle et al. (2014) Spain	RCT Baseline Post-intervention (8 weeks) Following (4 weeks)	Structured daily intra-hospital care program 8 weeks	IG $N = 18$ AN-R DSM-IV 100% females CG $N = 18$ AN-R DSM-IV 100 % females	13 ± 0.6 (12–16) 12.6 ± 0.6 (12–16)	BMI > 14 17.28 ± 2.55 BMI > 14 18.12 ± 2.11	IG TAU + Resistance training programme + calorie intake adjustment The supervised training programme was performed over 8 weeks, 3 days per week. Each session lapsed 50–60 min and started and ended with warm-up and cool-down periods of 10–15 min. The core session included eight strength exercises engaging the major muscle groups followed by stretching exercises CG TAU	BMI Skeletal muscular mass Agility Strength: Bench press Strength: Leg press Strength: Lateral row

TABLE 2 (Continued)

Author (s), year, country	Type of study, assessments	Setting and duration	Sample size, diagnostic, gender	Age mean ± SD, range)	BMI	Protocol	Measures
Fernández del Valle et al. (2010) Spain	RCT Baseline Post-intervention (12 weeks)	Structured daily intra-hospital care programme 12 weeks	IG $N = 11$ AN-R N/A 90.9% females CG $N = 11$ AN-R N/A 90.9 % females	14.7 ± 0.6 (14–16) 14.2 ± 1.2 (12–16)	BMI > 14 18.7 ± 1.7 BMI > 14 18.2 ± 1.5	IG TAU + training programme Two training sessions per week for 12 weeks. Each session lasted 60–70 min Each session started and ended with a low-intensity warm-up and cool-down period (10–15 min each), each consisting of stretching exercises involving all major muscle groups: The core portion of the session 11 strength exercises engaging the major muscle groups and isometric contractions of large muscle groups using their own body weight or barbells for upper body CG TAU + Requirement to maintain their level of physical activity during the study period	BMI Muscle mass % body fat Functional capacity Strength: Bench press Strength: Leg press Seated rowing Quality of life (SF-36)
Carei et al. (2010) USA	RCT Baseline Post-intervention (8 weeks)	Adolescent hospital outpatient 8 weeks	IG $N = 15$ AN DSM-IV 100% femalesCG $N = 11$ AN DSM-IV 81.8 % females	17 ± 2.5 (11–21) 16 ± 1.9 (11–21)	17.9 17.8	IG TAU + individualised yoga Participants received 1 h of yoga twice a week for 8 consecutive weeks CG TAU	BMI Eating disorder symptomatology (EDE) Depression (BDI) Anxiety (STAI)

(Continues)

TABLE 2 (Continued)

Author (s), year, country	Type of study, assessments	Setting and duration	Sample size, diagnostic, gender	Age mean ± SD, range)	BMI	Protocol	Measures
Chantler et al. (2006) Szabo and Green (2002) South Africa	RCT Quasi-randomised trial Baseline Post-intervention (8 weeks)	Eating disorder unit 8 weeks	IG $N = 7$ AN DSM-IV 100% females CG $N = 7$ AN DSM-IV 100 % females	20 ± 5 (15–36) 22 ± 6 (15–36)	15.1 ± 1.1 16.5 ± 1.3	IG TAU + calorie intake + training programme The exercises were performed twice a week for 1 hr each for 8 weeksThe programme consisted of a series of exercises targeting a wide range of muscle groups throughout the body (using 2.5 kg dumbbells for the upper body and therapeutic elastic bands for the lower body, as well as body weight) CG TAU + calorie intake	BMI % Body fat Lean body mass Depression (BDI) Eating disorder symptomatology (EDI)
Calogero and Pedrotty (2004) USA	Quasi-randomised trial Baseline Post-intervention (2.5–5 weeks)	Residential eating disorders 2.5–5 weeks	IG $N = 63$ (AN-R = 43 AN-P = 20) DSM-IV 100% females CG $N = 52$ (AN-R = 39 AN-P = 13) DSM-IV 100 % females	22.49 ± 7.9 23.14 ± 8.72	AN-R = 15.85 AN-P = 16.67 AN-R = 15.85 AN-P = 16.67	IG TAU + exercise programme Exercise groups were held four times per week for 60 min The exercises consisted of a warm-up, exercise activities, cool-down, and time to process the experience Exercise activities included some combination of the following based on the exercise level: Stretching, posture, yoga, pilates, partner exercises, strength training, balance, exercise balls, aerobic activity (e.g., walking, skipping), recreational games, or other activities they enjoyed CG TAU	BMI

TABLE 2 (Continued)

Author (s), year, country	Type of study, assessments	Setting and duration	Sample size, diagnostic, gender	Age mean ± SD, range)	BMI	Protocol	Measures
Tokumura et al. (2003) Japan	Quasi-randomised trial Baseline Post-intervention (1 year)	Inpatient treatment 6–12 months, mean 10	IG $N = 9$ AN-R N/A 100% females CG $N = 8$ AN-R N/A 100 % females	14 median (12–17) 14 median (12–16)	18.8 ± 0.5 19.6 ± 0.7	IG TAU + training programDuring the convalescent phase: 30 min of supervised stationary bicycle exercise at their individual anaerobic threshold (AT) level, five times a week CG TAU	BMI
Thien et al. (2000) Canada	RCT Baseline Post-intervention (3 months)	Eating disorder outpatients follow-up clinic 3 months	IG $N = 5$ AN DSM-IV 100% females CG $N = 7$ AN DSM-IV 86 % females	29 ± 4.4 36.1 ± 7.9	20.3 ± 1.8 17.2 ± 1.6	IG TAU + training programme Graded exercise protocol (seven levels), the level of activity was dependent on the patient's percent ideal body weight and percent body fat Level 1 is stretching exercises in sitting and lying position Level 7 is stretching exercises, resistive strengthening and low impact cardiovascular exercises Three times per week CG TAU	BMI Quality of life (SF-36)

(Continues)

TABLE 2 (Continued)

Author (s), year, country	Type of study, assessments	Setting and duration	Sample size, diagnostic, gender	Age mean ± SD, range)	BMI	Protocol	Measures
Russell et al. (1993) Australia	Single group study Baseline (12 days after admission) Post-intervention (After refeeding)	Patients following a hospital programme for eating disorders (10 to 15 weeks)	IG $N = 28$ AN DSM-III 100% females	18.8 ± 41 (14–34)	15.4 ± 1.3	IG Graded, structured exercise programmes contingent upon a satisfactory rate of weight gain and reasonable compliance Combinations of aerobic and non-aerobic activity which was planned, supervised and documented by an exercise therapist	BMI Lean body mass Fat weight
Touyz et al. (1993) Australia	Quasi-randomised trialBaseline Post-intervention (4 weeks) Following (6 weeks)	Inpatient treatment (4 weeks)	IG $N = 19$ AN DSM-III-R CG $N = 20$ AN DSM-III-R	15.94 ± 2.45 20 ± 5.28	14.82 ± 1.01 14.28 ± 1.32	IG Behavioural program + exercise program Anaerobic exercise program consisting of stretching, posture enhancement, weight training and occasional social sport or aerobic activity 3 h per week CG Behavioural program	BMI Weight gain

Abbreviations: AN, anorexia; AN-R, anorexia restricting type; AN-P, anorexia nervosa purgative type; BDI, Beck Depression Inventory; BMI, body mass index; CG, control group; EDE, eating disorder examination; EDI, Eating Disorder Inventory; IG, intervention group; N/A, no available; RCT, randomised control trial; SF-36, Medical Outcomes Survey SF-36; STAI, State-Trait Anxiety Inventory; TAU, treatment as usual.

settings. Regarding the design of the study, six of them were RCTs, three were quasi-randomised trials, and one was a single group study. The sample size of the RCTs ranged from 12 to 41 patients and the sample size of the quasi-randomised trials ranged from 17 to 115 patients. Articles were very heterogeneous and covered a 24-year time span; different diagnostic criteria for AN were applied. Participants in these studies were predominantly Caucasian females suffering from AN of restricting and binging, and purging subtypes, with an age range from 11 to 36 years. All the articles reported a mean BMI higher than 14 and lower than 21.

Interventions varied substantially among studies. Five of the 10 studies used resistance/strength training (Chantler et al., 2006; Fernández del Valle et al., 2010, 2014, 2016; Martin et al., 2016; Szabo & Green, 2002; Tokumura, Yoshiba, Tanaka, Nanri, & Watanabe, 2003). Four studies carried out a combination of physical activities: flexibility, anaerobic and resistance/strength exercises (Calogero & Pedrotty, 2004; Russell et al., 1993; Thien, Thomas, Markin, & Birmingham, 2000; Touyz, Lennerts, Arthur, & Beumont, 1993). One study performed relaxation and flexibility activities such as yoga (Carei, Fyfe-Johnson, Breuner, & Brown, 2010). Exercise interventions ranged in duration from 9 days to 12 months, and most of the participants were assessed only at the end of the programme. Activity frequency and intensity varied from low to high.

The most common outcome measures were physical. Most studies assessed anthropometric variables, such as BMI, muscle strength, agility and bone density. Eating symptomatology, depression and quality of life were reported in two studies, and anxiety in one.

3.3 | Risk of bias

We judged most studies to be at a low risk of bias for random sequence generation, attrition bias and selective reporting. Conversely, most studies were at high or unclear risk of bias for allocation concealment, blinding of participants and personnel and blinding of outcome assessment. A more detailed description of risk of bias assessments appears in Figure 2.

3.4 | Physical outcomes

Five studies compared changes in BMI between anorexic patients who underwent an exercise-based intervention and those who did not. Figure 3A presents results on the natural scale. Random-effects' overall estimate was −0.53 (95% CI −1.52 to 0.46), suggesting there was no difference among groups. We found evidence of substantial between-study heterogeneity ($Q_4 = 14.24$, $p = 0.007$; $I^2 = 72.66\%$). However, such heterogeneity was largely due to extreme results reported by Tokumura et al. (2003). In fact, results from a sensitivity analysis excluding this study suggested that all variability was due to random sampling error ($Q_3 = 3.11$, $p = 0.375$; $I^2 = 0\%$). Results on the standardised scale followed the same trend (Figure 3B).

Consistent with meta-analytic results, studies conducted by Calogero and Pedrotty (2004), Carei et al. (2010), and by Martin et al. (2016) also mentioned that exercise and non-exercise groups showed similar changes in BMI after the intervention period. However, none of these studies provided numerical estimates comparable to those combined and presented in Figure 3.

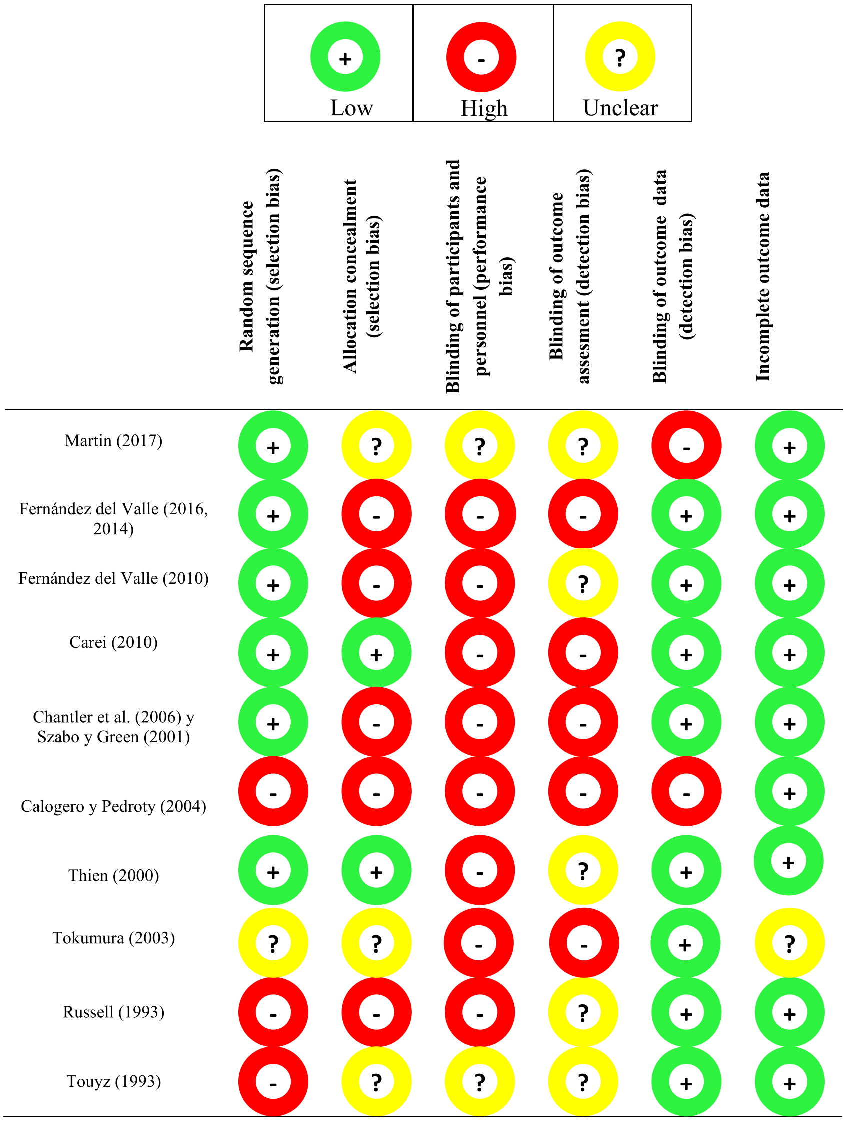
Regarding other physical outcomes, the trial by Martin and colleagues also reported that vital sign stabilisation time was significantly shorter among exercisers. This finding was confirmed by the results of the standardised mean difference calculated in the present study ($d = 0.63$, 95% CI 0.00 to 1.26). A shorter hospitalisation period was found in the intervention group with an effect size of $d = 0.54$ (−0.08 to 1.16), but no difference was found in the markers bone turnover between the two groups (range of d indices for different markers at post-intervention was 0–0.08).

Finally, three studies examined a number of strength and agility indicators and found mixed results. Fernández del Valle et al. (2010) used a group × time Analysis of variance with one factor (ANOVA) model and found a significant interaction for seated rowing ($p = 0.009$), but not for bench press ($p = 0.634$), leg press (0.683) or functional capacity (range of p-values for interaction effects was 0.143–0.964). Fernández del Valle (2016) also reported group × time interactive effects when examining strength-to-body weight ratios using several standard exercises (range of p-values was 0.001–0.046), and also reported significant skeletal muscle mass gain in the intervention group ($p = 0.045$), although no group × time interaction effect was found. Moreover, Chantler et al. (2006) reported a significant increase in the peak torque of knee extensors ($p < 0.001$), knee flexors ($p < 0.0001$) and elbow flexors ($p < 0.01$) for the intervention group, whereas no such differences were found for the control group at the end of the intervention period.

3.5 | Eating disorder symptoms and psychological outcomes

Two studies used scales to measure eating disorder symptomatology. Szabo and Green (2002) used the Eating

FIGURE 2 Results of risk of bias assessments using the Cochrane tools [Colour figure can be viewed at wileyonlinelibrary.com]



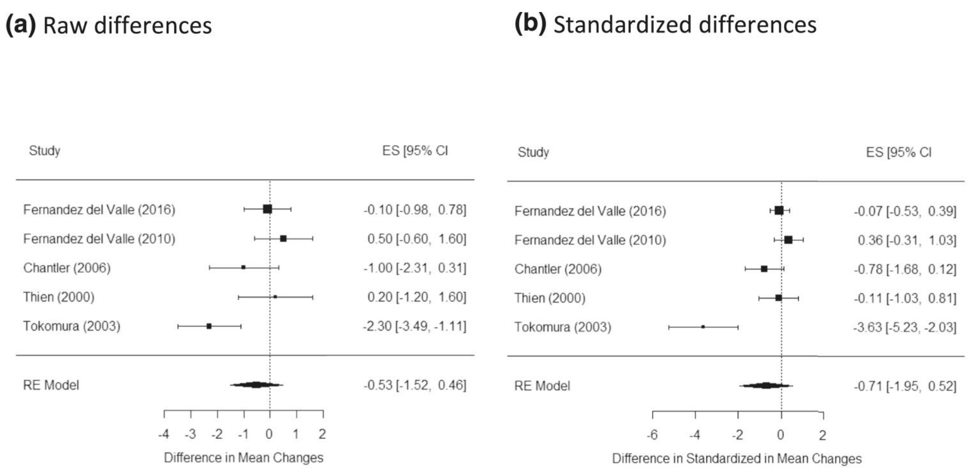


FIGURE 3 Forest plots for body mass index results

Disorder Inventory and reported descriptive results before and after the intervention period for patients undergoing exercise-based therapy and patients who did not. The difference in standardised mean changes was computed and obtained a value of $d = 0.93$ (95% 0.002 to 1.863), suggesting a clinically significant effect of the exercise programme. Similarly, the study by Carei et al. (2010) found a group × time interaction effect suggesting a score decrease for exercisers in the Eating Disorder Examination scale ($p = 0.05$, $\varpi^2 = 0.16$). These studies also used the Beck Depression Inventory. They calculated an effect size measure, which yielded an estimate of $d = 0.16$ (−0.68 to 0.99), suggesting no intervention effect.

Similarly, Carei et al. (2010) reported a decrease during the intervention period ($p = 0.01$, $\varpi^2 = 0.26$), but this was based on both groups (exercisers and non-exercisers) and no intervention effect was found. Regarding anxiety, Carei et al. (2010) also reported a decrease of state anxiety ($p = 0.02$, $\varpi^2 = 0.20$) and trait anxiety scores ($p < 0.001$, $\varpi^2 = 0.38$) for all participants, but no group × time interactions were found.

4 | DISCUSSION

In this systematic review, we examined the effectiveness of exercise interventions in AN patients by comparing it with a control condition. Moreover, we examined evidence of physical and psychological outcomes following exercise intervention.

Regarding the effectiveness of exercise intervention for weight gain, results showed similar changes in BMI after the intervention period in exercise and non-exercise groups. This indicates that supervised physical exercise interventions are not associated with weight loss in these patients. However, these results should be considered with caution. It is very important to point out that in three of the 10 studies, physical activity interventions were conducted in AN patients at normal weight (BMI ≥ 18.5), and in two studies with a BMI > 17. It is worth reminding that the practice of supervised physical exercise at low BMI or in the presence of complications is dangerous. There are real risks associated with undertaking exercise in a malnourished and medically unstable state, especially when activity is not nutritionally supported (Moola, Gairdner, & Amara, 2013). The extreme fragility of AN patients and severe physical (especially muscular-skeletal) complications invoke extreme prudence and contraindicate physical exercise at severe stages of malnutrition (El Ghoch et al., 2013).

Similar results have been reported in studies implementing resistance and strength training programmes at different intensity levels (Chantler et al., 2006; Fernández del Valle et al., 2010, 2016; Martin et al., 2016; Tokumura et al., 2003) and also in studies in which the training programme was based on flexibility exercises (Carei et al., 2010) or combined flexibility and cardiovascular exercises (Calogero & Pedrotty, 2004; Thien et al., 2000). Furthermore, in the specific case of studies by Fernández del Valle et al. (2016, 2010) and Chantler et al. (2006), calorie intake was also adjusted in the intervention group.

Regarding other physical outcomes, the trial by Martin et al. (2016) found that a 9-day intervention programme for AN adolescents involving jumping improved their vital signs rapidly and shortened their hospitalisation period. However, the programme failed to produce significant increases in biochemical markers of bone turnover. They suggested that prolonged bed rest itself may lead to orthostatic pulse and blood pressure changes and that increased physical activity may have a positive effect on vital signs (Martin et al., 2016).

The protein-energy malnutrition associated with AN can result in metabolic and skeletal muscle myopathy, which has a negative impact on muscle function and strength (McLoughlin et al., 1998). In studies using resistance or strength exercise programmes, lower and upper body strength and skeletal muscle mass increased in intervention groups. These results suggest that resistance-training programmes could induce an increase in strength and could be adequate for AN treatment (Chantler et al., 2006; Fernández del Valle 2016, 2010, 2014). This suggests that improvements in muscular mass and function are associated with reduced dependence and institutionalisation and lead to a better prognosis in chronic diseases (Fernández del Valle et al., 2014).

Regarding eating disorder symptomatology and psychological outcomes, two studies showed that AN symptoms decreased in the exercise group (Carei et al., 2010; Szabo & Green, 2002). These results are similar in studies on the benefits of exercise on health in the general population and clinical patients. A substantial body of evidence supports the implementation of exercise interventions as treatment for people with mental illness (Stanton & Happell, 2013; Zschucke et al., 2013), including eating disorders (Cook, Hausenblas, Crosby, Cao, & Wonderlich, 2015; Vancampfort et al., 2013).

Studies that assessed the effectiveness of exercise on depression and anxiety found no significant effects, as all participants improved over time in both groups (Carei et al., 2010; Szabo & Green, 2002). In Szabo and Green's study, the exercise programme consisted of performing strength and resistance exercises, while Carei's programme consisted of two yoga sessions per week. Practice of physical exercise, such as yoga or resistance/strength exercises, is effective in improving self-esteem (Yook, Kang, & Park, 2017) and reducing stress and anxiety in the general population. Thus, exercise is a useful resource as an exercise therapy component (Ross, Friedmann, Bevans, & Thomas, 2013). It is possible that for an exercise programme to have effects on anxiety and depression its duration needs to be longer. In both studies included in our review, the training programme lasted only 8 weeks.

A previous literature review on AN and exercise concluded that nutritionally-supported exercise interventions for patients with AN did not compromise weight gain and were associated with improvements in strength, quality of life and psychological well-being (Moola et al., 2013). These last two results were not found in our study. Compared to our study, Moola's review was less rigorous with study selection (case study and qualitative studies were also considered) and did not calculate effect sizes for intervention effects.

Our systematic review study has implications for clinical practice. Incorporating a supervised physical exercise programme to the usual treatment may be appropriate for AN patients. However, exercise interventions should only be performed when they are safe for these patients. Supervised appropriate-intensity exercise in the last phases of hospitalisation or stabilisation could be beneficial for patients. These exercise programmes should be based on resistance/strength or flexibility exercises. Although exercise programmes do not have a significant effect on anthropometry or psychological conditions (such as anxiety and depression), they can improve AN patients' vital signs, muscle function and strength and eating disorder symptomatology.

4.1 | Strengths and limitations

The present study applied a rigorous methodology and provided a critical and up-to-date overview of the available body of evidence regarding the effectiveness of implementing structured exercise interventions in AN patients. It highlights the paucity of available data concerning exercise-based interventions in the AN context.

While results from the primary studies provide some encouragement for using exercise interventions in AN patients, there are several reasons why the findings from this study should be interpreted with caution. Unfortunately, very few rigorous primary studies have examined the effects of implementing structured exercise interventions with AN patients receiving treatment, and these interventions have been very heterogeneous. There are also few RCTs, and available studies suffer from methodological problems, such as small sample sizes, short duration, high risk of bias for allocation concealment, blinding of participants and personnel and blinding of outcome assessment.

One of the limitations of this research is that it was not able to achieve the objective of providing physical activity guidelines for the clinical management of individuals with AN. The paucity of data and the heterogeneity of the reviewed studies have made this objective impossible. Primary studies were very heterogeneous; there were differences in patients' BMI, the phase in which the intervention was applied (some studies were conducted in convalescent phase while others at earlier stages of resident treatment), in the setting (inpatient/outpatient) and patients' age (from 11 to 36 years). Physical exercise programs differed in terms of duration, content and type of exercise. This heterogeneity made it difficult to compare results and make generalisations, so it was not possible to establish a safe exercise-based intervention guideline for all these patients.

Even though systematic review and meta-analysis are considered the best evidence for getting a definitive answer to a research question, there are certain inherent limitations associated with it, such as heterogeneity (that we have previously pointed out) and the location and selection of studies. This study was limited because we only reviewed articles published in English language. And other limitation of this research may be related to the well-known ‘publication bias’. Publication bias results in it being easier to find studies with a ‘positive’ result. This may have conditioned our selection of studies and generated biased results.

4.2 | Guidelines for future research

This review identifies some future challenges in the field of AN treatment. Among them is the design and implementation of RCTs with intervention programmes that include physical exercise components guided by interdisciplinary teams of health professionals (physical trainers, psychologists, psychiatrists and nutritionists). Other challenges include the need to design detailed and individualised exercise programmes for anorexic patients and the monitoring of physical parameters in patients before and after evaluation. Because safety is the ultimate concern when applying exercise programmes, it is very important to focus our attention on the patients' medical needs to assess possible contraindications and their nutritional state, and to examine their attitudes towards exercise (e.g., compulsions and exercise dependence).

Since restricting exercise does not seem to bring satisfaction to anorexic patients, future studies should focus on a combination of treatments (medical, nutritional, psychological and physical) with the aim of achieving a balance between guided exercise performance and compulsory exercise. While malnourished patients with AN are at risk while performing physical activity, it is important to keep working towards a positive conceptualisation of the helpful role that physical activity programmes can play in AN patients.

Finally, future studies in this field should adopt the highest standards in terms of methodological rigour. They should ensure a random allocation of treatment groups, that comparators are appropriate, that sample sizes large are enough to guaranty adequate statistical power of the tests (ideally examining the protocols before carrying out a study), and that follow-up periods are long enough to examine the effects of these programmes in a variety of physical and psychological outcomes.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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