Effect of Exercise Interventions on Anxiety in People with Multiple Sclerosis

A Systematic Review and Meta-analysis

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Background: Evidence suggests that exercise can alleviate symptoms associated with multiple sclerosis (MS). However, it is unclear whether exercise alleviates symptoms of anxiety, present in one-third of people with MS. This systematic review and meta-analysis investigates whether exercise interventions are effective in reducing anxiety in people with MS.

Methods: CINAHL, Embase, MEDLINE, PsycINFO, and the Cochrane Controlled Clinical Trials Register were searched to identify relevant randomized controlled trials (RCTs) published up to March 30, 2018. The primary outcome was postintervention difference in anxiety scores between intervention and control groups. Using a restricted maximum likelihood random-effects model, standardized mean differences were pooled and heterogeneity was estimated. Risk of bias was assessed using an a priori modified Cochrane Risk of Bias 2.0 tool.

Results: Four RCTs with 133 participants were included. Exercise type included walking, aerobic activities, and cycling. Intervention duration ranged from 8 to 26 weeks. The pooled standardized mean difference in anxiety score was –0.16 (95% CI, –0.50 to 0.19), without heterogeneity. Two studies had high risk of bias, and two had some risk of bias.

Conclusions: Based on available RCT data, exercise does not seem to have an effect on anxiety in people with MS. These results should be interpreted with caution because studies had concerns of bias and small sample sizes, and anxiety was not the primary outcome measure. Future studies should exhibit sufficient reporting standards, alongside publishing protocols. There is opportunity to investigate the effect of exercise in people with MS experiencing clinically relevant levels of anxiety rather than in the general MS population. ***Int J MS Care.*** **2020;22:103-109.**

Approximately 34% of people with multiple sclerosis (MS) have clinically significant anxiety symptoms,[1] which is approximately three times that of the general population.[2] Alongside other mental health issues, such as depression, anxiety has been associated with greater burden and severity of MS symptoms[2,3] as well as greater level of disability.[4] It is also speculated that anxiety often precedes depression in most comorbid cases.[5] Yet experiences of anxiety are often overlooked.[6] Only approximately 11% of those with anxiety are treated,[2] leaving most at greater risk of depression and exacerbated symptoms. Although there is some evidence that mindfulness-based interventions are effective for anxiety in people with MS,[7] one potential reason that so many do not receive treatment for their anxiety is that few existing treatments for anxiety in people with MS have shown efficacy.[8,9] Furthermore, because anxiety and depression often co-occur and have similar prevalence in people with MS,[10] they are frequently handled as similar constructs, although psychotherapy interventions designed to treat depression do not reduce anxiety in people with MS.[8] Insufficient knowledge of effective treatments for anxiety specific to this population means that psychiatric, psychological,

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and medical therapies are used in the same manner as for the general population.[2] These treatments are often lacking in accessibility, acceptability, and cost-effectiveness[11] and, therefore, do not meet the needs of people with MS experiencing symptoms of anxiety. It is evident that there is an urgent need for effective treatments for anxiety in people with MS.

Due to common symptoms of MS, such as heat sensitivity and fatigue, exercise was initially thought to aggravate such symptoms[12]; however, this perspective has shifted. Exercise can improve symptoms of fatigue[13] and depression[14] in people with MS, alongside a variety of other benefits to muscle strength,[15,16] balance,[17] quality of life,[18,19] and overall well-being.[20] However, people with MS are substantially less physically active compared with the general population.[21,22]

Exercise can alleviate anxiety symptoms in the general population and has a range of other mental health benefits, including a decrease in depressive symptoms as well as improved cognition and overall life satisfaction.[23-26] For people with MS, recent investigations identify exercise as a mode through which psychological symptoms can be remedied.[27] Yet, to our knowledge, this effect has not yet been reviewed in this population. This provides the basis for the research aim of the present study, wherein the effect of exercise on anxiety symptoms in people with MS was investigated through a systematic review and meta-analysis of randomized controlled trials (RCTs).

Methods

Registration

This systematic review was planned, conducted, and reported with adherence to the standards of quality for reporting systematic reviews and meta-analyses (PRISMA [Preferred Reporting Items for Systematic Reviews and Meta-Analyses]). The methods were planned a priori, and this systematic review was registered on the International Prospective Register of Systematic Reviews (PROSPERO; ID CRD42018091240).[28] Ethical approval was not required given that this study is a review of existing literature.

Search Strategy

The search strategy included multiple different iterations of the terms *multiple sclerosis, exercise, anxiety,* and *randomized controlled trials* to create a highly sensitive search strategy and was developed with the assistance of a librarian. The full search strategy can be found in Appendix S1, which is published in the online version of this article at ijmsc.org.

On March 30, 2018, we searched the following five databases: MEDLINE, Embase, CINAHL, PsycINFO, and the Cochrane Controlled Clinical Trials Register. No language or date restrictions were applied. Bibliographic citations of relevant review articles[8,29-31] were also searched to ascertain articles not identified through the database search.

Eligibility Criteria

To be selected for this systematic review and meta-analysis, the study needed to 1) be published in English, 2) study a sample of people with MS, 3) be an RCT, 4) include anxiety as an outcome, 5) include supervised exercise in the intervention, 6) exclude any other additional therapies in the intervention, 7) include a nonactive control, and 8) have full text of the manuscript available (ie, we excluded conference abstracts).

We defined exercise as "a subset of physical activity that is planned, structured, and repetitive and has as a final or an intermediate objective the improvement or maintenance of physical fitness."[32(p126)]

A study was considered to include a measure of anxiety if it used the anxiety subscale of the Hospital Anxiety and Depression Scale (HADS), the Beck Anxiety Inventory (BAI), the state anxiety subscale of the State-Trait Anxiety Inventory (STAI), the tension-anxiety subscale of the Profile of Mood States (POMS), or other validated tools that measure a similar construct of anxiety, as defined by the STAI: "a transitory psychobiological emotional state or condition that is characterised by subjective, consciously experienced thoughts and feelings relating to tension, apprehension, nervousness, and worry that vary in intensity and fluctuate over time."[33(p70)] In cases in which more than one measure of anxiety was used, a decision was made by consensus with all authors, considering the validity and reliability of the measures, as well as the reporting standards of the outcome measures.

We required that the study participants were older than 18 years, with a diagnosis of any type of MS, of any sex, and experiencing disability at any level. To avoid contamination of effects, multimodal interventions that included additional therapies that did not meet our definition of exercise and were seen as potentially contributing to the outcome of anxiety (eg, meditation, cognitive behavioral therapies, or acupuncture) were excluded. Studies without repetitive exercise sessions (single-bout) were excluded because they did not fit our definition of exercise. Studies without a nonactive control were excluded because we were interested in assessing the effect on anxiety of exercise compared with no exercise, rather than to evaluate the effect on anxiety of different types of exercise or therapeutic interventions.

Data Extraction

Duplicate articles based on title, abstract, journal, volume, issue, pages, and year of publication were removed before two researchers (C.G. and T.D.) independently screened the resulting articles initially based on abstract and then full text. Articles were excluded based on predefined eligibility criteria (see previously herein), with discrepancies resolved by consensus. Two researchers (C.G. and A.K.) independently extracted data from the included studies using a standard form. The type of data that were extracted included general information regarding the study design, study population, intervention, and outcome measurements, as well as information relating to the assessment of risk of bias and overall study quality. Full details can be found in Table S1. Where data were not available, the authors of these studies were contacted to request the data.

Assessment of Risk of Bias

Risk of bias was assessed using the Cochrane Collaboration Risk of Bias 2.0 tool for individually randomized parallel group trials.[34] Risk of bias for each individual study was assessed by two of us (C.G. and A.K.), with discrepancies resolved in consultation with a third author (C.M.). A decision was made a priori to exclude the subdomains where it was not feasible to avoid risk of bias due to the nature of the studies under investigation. This included subdomains 2.1 to 2.3, which addressed whether trial personnel and the individuals measuring the outcome (ie, the participants themselves) were aware of the assigned interventions of the participants, and domain 4, which addressed bias in measurement of the outcome. The remaining domains that were used included bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, and bias in selection of the reported results. Studies were assessed to have low risk, some concerns, or high risk of bias.

Statistical Analysis

The primary outcome measure was defined as the standardized mean difference (SMD) in anxiety scores between the intervention and comparator groups measured immediately after the intervention. The secondary outcome measure was the SMD in anxiety scores measured 3 to 6 months after the end of the intervention, data permitting. The SMDs were pooled using a restricted maximum likelihood random-effects meta-analysis, which assumes that there would be some variation in true effect between studies.

Statistical heterogeneity between studies was quantified using the I^2 and τ^2 statistics. These statistics describe the proportion of variability due to true differences rather than sampling variation. Meta-regression models were planned to explore the outcome of the heterogeneity assessment using the following characteristics: 1) risk of bias, 2) duration of intervention (total weeks), 3) intensity of intervention (minutes of exercise per week), and 4) type of intervention (exercise type), data permitting.

Finally, we planned to investigate small study effects using a funnel plot and the Egger regression asymmetry test if sufficient studies were found (ie, ≥10 studies).[35] All the analyses were conducted using Stata, version 13.0 (StataCorp, College Station, TX).[36]

Results

Study Selection

The database search strategy identified 2849 records, and an additional five records were identified through relevant review papers. After removal of duplicates and nonrelevant articles, four studies were included in the systematic review (Figure S1). Further details of the screening process, including reasons for exclusion, are provided in Figure S1. Given the small number of studies, the planned meta-regression, funnel plot, and Egger regression asymmetry test were not conducted.

Study Characteristics

The study characteristics are summarized in Table 1. Two studies were performed in the United States,[37,38] one in Scotland,[39] and one in Iran.[40] All the studies measured anxiety at baseline and immediately after the intervention, with either no information on whether this was the primary outcome or an indication that this was the secondary outcome. None of the studies selected participants based on anxiety level. Only one study measured anxiety 3 to 6 months after the intervention,[39] preventing analysis of the effect of the long-term outcome. Intervention types included treadmill walking,[40] cycling,[38] and arm and leg cycling.[37] One study had a combination of aerobic, resistance, and balance activities delivered in a circuit module.[39] Further intervention and outcome characteristics, including outcome data, are described in Table 2.

Results of Individual Studies

None of the studies observed a statistically significant change in anxiety symptoms after the intervention, with all CIs crossing the null value of zero. No harmful or adverse effects of the intervention were reported, and any observed attrition was reported to be unrelated to the nature of the intervention.

Risk of Bias

Two studies had some concerns of risk of bias overall,[37,40] and two studies had high risk of bias overall (Figure 1).[38,39] The weaknesses regarding bias arising from the randomization process were primarily due to lack of reporting. Stating that participants were randomized is not sufficient to fulfill the subdomain requiring that the allocation sequence was random. The issues regarding bias arising from selection of the reported results stemmed from a complete lack of prepublished or recorded study protocols from all included studies.

Table 1. **Baseline characteristics of the four included studies with 133 participants**

Study	Country	Age, y	MS type	MS duration, y	EDSS score	Sample size	Female sex
Petajan et al,[37] 1996	United States	40.0 ± 12.5	NS	7.6 ± 9.0	3.3 ± 0.3	46	31 (67)
Oken et al,[38] 2004	United States	49.1 ± 9.0	NS	NS	3.1 ± 1.8	35	33 (94)
Learmonth et al,[39] 2012	Scotland	51.6 ± 8.1	NS	13.1 ± 7.0	6.0 ± 0.4	32	23 (72)
Ahmadi et al,[40] 2013	Iran	35.2 ± 9.0	NS	5.1 ± 4.1	2.2 ± 1.2	20	20 (100)

Note: Values are given as mean ± SD, number, or number (percentage).
Abbreviations: EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; NS, not specified.

Table 2. Intervention characteristics of the four included studies and primary outcome measurements at baseline and immediately after intervention

Study	Intervention duration, wk	Exercise duration per week, h	Type of exercise	Anxiety measure	Anxiety primary outcome?	Intervention group[a]		Control group[a]	
						Baseline	Post-intervention	Baseline	Post-intervention
Petajan et al,[37] 1996	15	2.0	Arm/leg cycle	POMS	NS	39.4 ± 7.8	37.2 ± 9.2	37.0 ± 5.0	36.6 ± 7.0
Oken et al,[38] 2004	26	1.0	Cycling	STAI	No	32.1 ± 8.1	30.7 ± 10.9	38.4 ± 15.9	36.0 ± 13.7
Learmonth et al,[39] 2012	12	1.7	Mixed[b]	HADS-A	No	8.0 ± 4.1	6.2 ± 3.3	7.9 ± 5.2	6.5 ± 4.0
Ahmadi et al,[40] 2013	8	1.5	Treadmill walking	BAI	NS	6.1 ± 5.0	6.1 ± 5.0	7.5 ± 6.8	8.2 ± 7.4

Abbreviations: BAI, Beck Anxiety Inventory; HADS-A, Hospital Anxiety and Depression Scale, Anxiety subscale; NS, not specified; POMS, Profile of Mood States; STAI, State-Trait Anxiety Inventory.
[a]Anxiety scores are presented as mean ± SD and differ in scale depending on anxiety measure used.
[b]Mixed exercise refers to multiple exercise types, including aerobic, motility, resistance, and balance exercises, delivered in a circuit module, with all participants engaging in same exercise.

Given that intended measurement of outcomes and intended analyses cannot be verified, we were not able to rule out whether selective reporting was occurring. One study reported anxiety and depression (as measured by HADS) as a combined score rather than as individual scores.[39] In this instance, the author was contacted to retrieve raw data of the subscales that described depression and anxiety as separate constructs. This contributed to risk of bias in domain 5 of the Cochrane risk-of-bias tool, given that the outcome was potentially selectively reported as a single construct rather than as two independent constructs.

A second study did not present outcome data for anxiety, although this was measured as stated in the abstract of the article,[38] which contributed to risk of bias in domain 5 of the Cochrane risk-of-bias tool. The author was contacted to retrieve these data. For this same study, high risk of bias in domain 2 was due to intervention class attendance of only 65%.

Synthesis of Results

A random-effects meta-analysis including four studies with 133 participants found that there was no difference in anxiety between the intervention and control groups immediately after the intervention was completed (pooled SMD, –0.16; 95% CI, –0.50 to 0.19) (Figure 2).

Given that we identified only four studies relevant to the research question, we did not investigate small study effects. In addition, because there was no heterogeneity to explain, the planned meta-regression analyses were not conducted.

Discussion

This systematic review and meta-analysis including four RCTs with 133 participants with MS found that exercise does not have an effect on anxiety symptoms in this population. However, these results should be interpreted with caution due to the quality and design of the included studies.

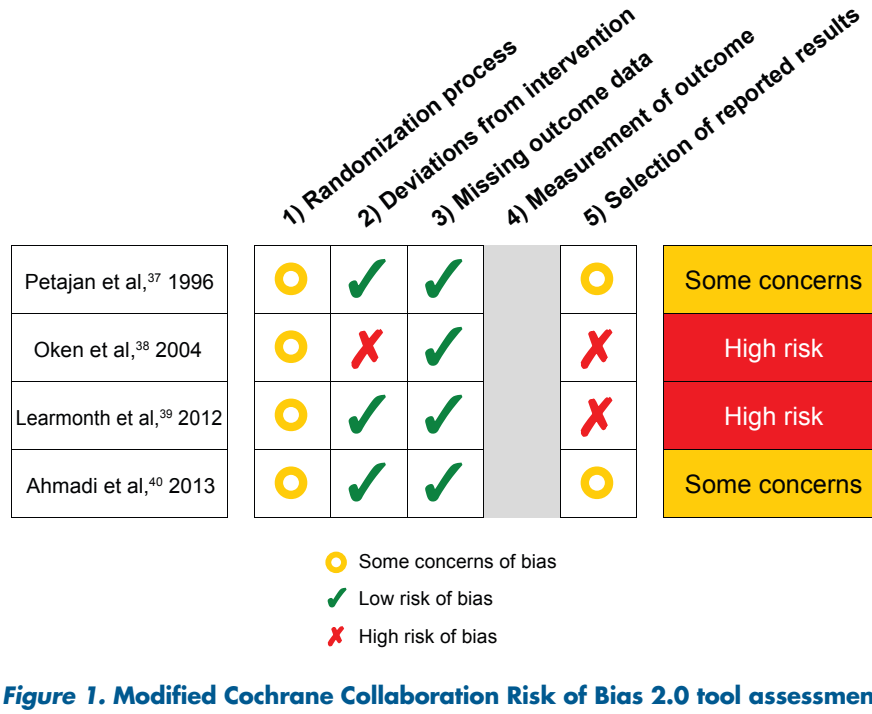

Figure 1. Modified Cochrane Collaboration Risk of Bias 2.0 tool assessment

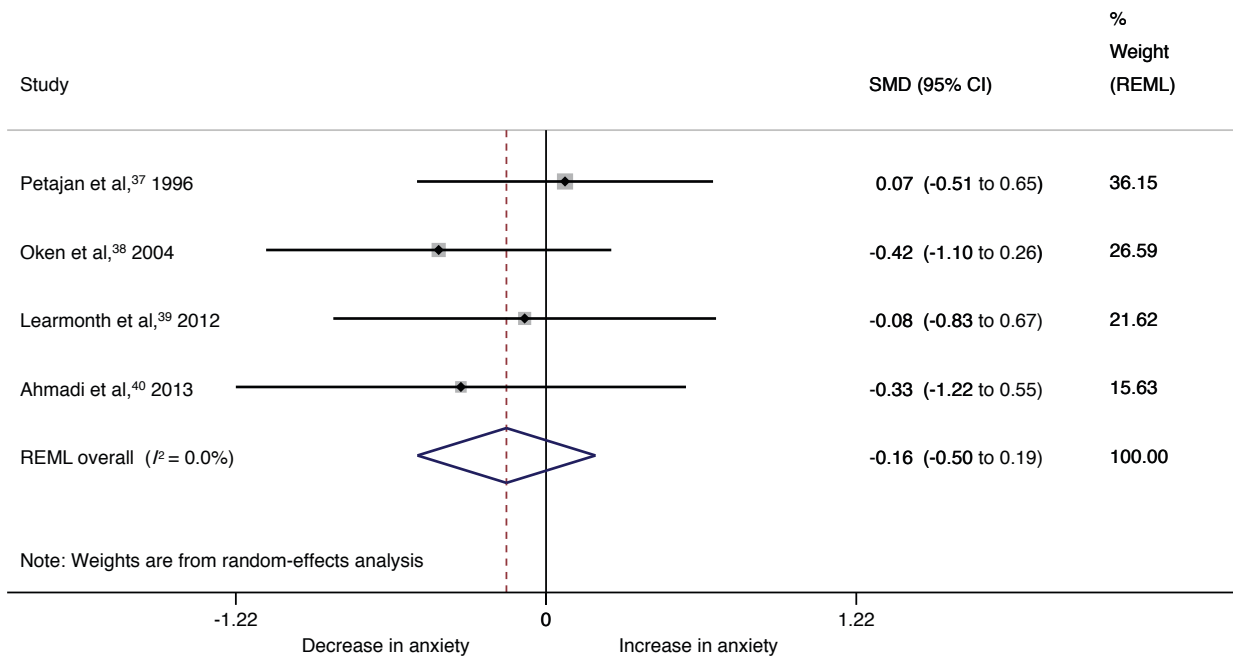

Figure 2. **Forest plot of standardized mean differences (SMDs) in anxiety scores between intervention and control groups generated using a random-effects meta-analysis**

Dotted red vertical line, pooled estimate; blue diamond, 95% CI of pooled estimate; black vertical line, no effect (ie, SMD = 0); black diamonds, individual study effects; black horizontal lines, 95% CI of individual study effects; grey box, relative weights of each study. REML, restricted maximum likelihood.

Quality of Individual Studies

The quality of the included studies was limited due to a lack of study protocols and poor reporting. Findings are also limited by the inadequate power of the four studies, potentially introducing type II error.[41] Two studies verified with a priori sample size calculations that the studies were, indeed, underpowered.[38,39] Similar reviews have also noted a large proportion of studies in this population with inadequate power,[20,42] potentially due to difficulty recruiting participants for a study with an exercise intervention in a disabled population. Two studies stated that anxiety was not the primary outcome,[38,39] and two provided no indication of which measure was the primary outcome.[37,40] Hence, the included studies did not select participants based on anxiety level. Participants had mean baseline anxiety scores below a clinically significant level for three of the included studies (STAI < 40; HADS-A < 8; BAI < 10),[43] and a clinical cutoff score for Profile of Mood States has not yet been determined for a comparable population. In addition, none of the studies reported what proportion of participants met the criteria for clinical fatigue. Perhaps an effect of exercise on anxiety symptoms exists for people with MS who have clinically significant levels of anxiety, consistent with studies in the general population.[23,24]

Given these weaknesses, it is unsurprising that an effect of exercise on anxiety symptoms in people with MS was not observed despite evidence for an effect in the general population. This highlights a need for further studies on the effect of exercise for people with MS experiencing anxiety.

Strengths and Limitations

This study used a highly sensitive search strategy, producing four eligible studies from the original 2849 studies retrieved from the online database search. Given that RCTs are able to provide the best evidence of effect,[44,45] the search strategy and eligibility criteria required that only RCT studies were included in the review. It is possible that the inclusion of only English articles excludes relevant articles; however, no articles with relevant titles and abstracts were excluded based on language. Therefore, we believe that all relevant articles were captured, thus providing a comprehensive review of available research.

The modified risk-of-bias tool reflected the nature of the studies used in the meta-analysis. Because it is not possible to blind trial personnel and participants to

an exercise intervention, and because the outcome was self-reported by participants, we believe that the decision to a priori exclude these domains was justified. The self-report method used for measurement of the outcome may have led to bias; however, this weakness is unavoidable because there is arguably no existing objective measure for anxiety. Hence, the modification of the risk-of-bias tool allows studies to achieve a low risk-of-bias assessment in the event that all appropriate measures were taken to avoid bias.

Possible Mechanisms

One theory of effect mechanism in the general population suggests that because there is a positive association between anxiety and poor sleep quality[46] (such as sleep disturbances, nightmares, and daytime sleepiness) and a positive association between sleep quality and exercise,[47] an increase in sleep due to the physiological consequences of exercise (such as the depletion of energy stores and downregulation of body temperature[47]) may, therefore, be remedial for symptoms of anxiety.[23]

There is also evidence that exercise for people with MS can increase self-efficacy,[19] which is the belief that one has "capabilities to produce designated levels of performance that exercise influence over events that affect their lives."[48(p71)] Via this pathway, symptoms of anxiety can be relieved because an increased sense of self-efficacy or mastery over one's internal and external environment is associated with positive psychological outcomes.[49] Furthermore, exercise has a range of beneficial physiological effects on the sympathetic nervous system, the regulation of stress hormones, and brain health, including new neuronal growth, which may help alleviate stress and anxiety.[50]

Future Directions

Studies of higher quality need to be conducted to generate a valid assessment of the effect of exercise on anxiety symptoms in people with MS. This includes minimizing risk of bias through more comprehensive reporting standards and a priori publication or registration of study protocols. Selecting anxiety as the primary outcome may lead to adequately powered studies, and inclusion of participants with high levels of anxiety will increase the validity and quality of studies in this area. Symptoms of MS, such as heat sensitivity, fatigue, and pain, provide barriers to exercise.[51] Future studies should address these issues by designing interventions with greater sensitivity to the participants' needs and preferences. Suggestions include investigating the effect of aquatic exercises on anxiety symptoms because this type of exercise diminishes issues of heat sensitivity and aids individuals experiencing muscle weakness in achieving greater mobility.[52]

In summary, high-quality studies are warranted. These studies need to be designed specifically for people with MS, with their capabilities in mind, and should investigate whether 1) an effect exists in people with high levels of anxiety and 2) whether this effect is modified by factors such as level of disability or other disease characteristics.

Although there is currently insufficient evidence to conclude that exercise is an effective treatment for anxiety for people with MS, there is also no evidence to suggest that exercise causes harm in this population. Furthermore, people with MS should be encouraged to engage in exercise appropriate to their personal needs and abilities to remedy concurrent symptoms of MS, given the many benefits of physical activity to health and well-being.[13]

Conclusion

To our knowledge, this is the first systematic review and meta-analysis to assess the effect of exercise interventions on anxiety symptoms in people with MS. In contrast to findings in the general population, we found that in people with MS there is currently no evidence for an effect of exercise interventions on symptoms of anxiety. However, due to issues of study quality and design, these findings should be interpreted with strong caution. Above all, this review identified that there is a significant demand for high-quality studies of exercise and its potential to alleviate symptoms of anxiety in people with MS. □

PRACTICE POINTS

- There is a paucity of high-quality evidence assessing the effect of exercise on anxiety in people with MS.
- Based on available randomized controlled trial data, exercise does not seem to have an effect on anxiety in people with MS. These results should be interpreted with strong caution because studies had concerns of bias and participants were not selected based on clinical levels of anxiety.
- There is opportunity to investigate the effect of exercise in people with MS experiencing clinically relevant levels of anxiety rather than in the general MS population.

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