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Review article

The safety of exercise training in multiple sclerosis: A systematic review

Lara A. Pilutti [a,*], Matthew E. Platta [a], Robert W. Motl [a], Amy E. Latimer-Cheung [b]

[a] Department of Kinesiology and Community Health, University of Illinois at Urbana-Champaign, Urbana, USA
[b] School of Kinesiology and Health Studies, Queen's University, Kingston, Canada

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ABSTRACT

There are many reviews documenting the benefits of exercise training among persons with multiple sclerosis (MS). To date, we are unaware of a review that summarizes the risks of relapse and other adverse events (AEs) associated with exercise training, yet this is critical for informing decisions and recommendations regarding the safety of this behavior. We conducted a systematic review of relapse and other AEs reported in randomized controlled trials (RCTs) of exercise training in MS. We searched electronic databases for RCTs of exercise training in MS. We calculated the rate of relapse and AEs, and the relative risk of relapse and AEs for exercise training versus control. Twenty-six studies were reviewed that included 1295 participants. We determined that the rate of relapse was 6.3% and 4.6% for control and exercise, respectively. The rate of AEs was 1.2% and 2.0% for control and exercise, respectively. The relative risk of relapse for exercise training was 0.73, whereas the relative risk of AE for exercise training was 1.67. Exercise training was not associated with an increased risk of relapse, and risk of AEs was not higher than in healthy populations. This evidence should alleviate uncertainty regarding the safety of exercise training in MS.

Contents

1. Introduction

Multiple sclerosis (MS) is a disease of the central nervous system characterized by inflammation, axonal demyelination and transection, and neurodegeneration. Relapses are a hallmark feature of MS disease activity and are defined as an acute onset of new or worsening neurological symptoms [1]. There has been uncertainty regarding the effect of exercise training on MS disease activity, with particular concerns that exercise may trigger the onset or worsening of neurological symptoms and relapse. There is further uncertainty regarding the range of other possible adverse events (AEs) associated with exercise training in MS. To our knowledge, no literature reviews have systematically examined the rates of relapse and other AEs associated with exercise training in persons with MS. This is critical considering the evidence for benefits of exercise training in MS [2] combined with the development of guidelines for broad-scale promotion of exercise training in this population [3]. To that end, we systematically reviewed the literature to quantify the rate of relapses, AEs, and dropout reported in randomized controlled trials (RCTs) of exercise training in persons with MS. Such information is important for making informed decisions and recommendations regarding the safety of exercise training for people with MS in research and clinical settings.

2. Methods

We searched electronic databases (PubMed and Web of Science) for English language articles published up until November 2013. The following search terms were used: "exercise" or "physical activity" or

* Corresponding author at: Department of Kinesiology and Community Health, University of Illinois, 213 Freer Hall, Urbana, IL 61801, USA. Tel.: +1 217 333 6126; fax: +1 217 244 0702.
E-mail address: lpilutti@illinois.edu (L.A. Pilutti).

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"exercise training" or "training" or "fitness" or "aerobic" or "resistance" or "strength" AND "multiple sclerosis." We further searched the references from a previous systematic review of exercise training benefits in persons with MS as well as articles from our personal libraries. Initial article retrieval was performed by one of the authors (M.E.P.). A secondary search was conducted by another author (L.A.P.) to ensure all articles were captured from electronic databases and personal libraries. Fig. 1 provides a flow diagram of the studies reviewed for inclusion. The initial search retrieved 1695 articles, and 112 were reviewed in detail. Studies were included in the review based on three criteria: sample of participants with MS, exercise training intervention (i.e., not rehabilitation-based interventions such as physiotherapy), and RCT designs that included a no-treatment control condition. Studies not reporting on outcomes of interests (i.e., relapses, AEs, or dropout) were not excluded from the review in order to quantify the reporting of these events. The final decision for study inclusion was made by three of the authors (M.E.P., L.A.P., R.W.M.) based on a discussion and collective agreement. There were 26 studies that met the criteria for inclusion in the review [4–29].

We first determined the reporting of relapses, AEs, and dropouts, as well as inclusion CONSORT diagram per study. We then determined study quality using the 11-item Physiotherapy Evidence Database (PEDro) scale [30]. Scores on the PEDro scale range between 0 and 11, whereby higher scores indicate superior methodological quality. This scale has been used previously in systematic reviews of exercise training in persons with MS [2,31]. We then quantified the number of relapses (or exacerbations), the number and type of AE(s), and the number of dropouts in the exercise training and control conditions separately. Only relapses, AEs, and dropouts occurring during the intervention period of the RCTs were recorded as this provided a more direct link between the events and exercise training; we did not include events during follow-up after the cessation of exercise training, and there were only five studies with follow-up periods [8,12,15,19,29]. The rates of relapses, AEs, and dropouts were calculated per study as the number of events reported per condition (i.e., control and exercise) divided by the number of participants per condition, expressed as a percentage.

We computed an overall risk of relapse, AEs, and dropout for exercise training compared with control conditions. To do this, we computed the overall rate of relapse, AEs, and dropout as the total number of events in the exercise and control conditions across all studies, divided by the total number of participants in the exercise and control conditions across all studies, respectively. The overall relative risk of relapse, AEs, and dropout for exercise training was calculated using standard risk estimate procedures (i.e., the ratio of patients in a treatment group who experience an illness or condition to those in a control group who experience the same illness or condition) [32]. Relative risk was calculated by dividing the overall rate of relapse, AEs, or dropout for exercise by the overall rate of relapse, AEs, or dropout, respectively, in the control condition. A relative risk of 1.0 would indicate no difference in risk between exercise and control conditions. A relative risk above 1.0 would indicate higher risk of events with exercise training, and a relative risk below 1.0 would indicate lower risk of events with exercise training. Only studies that directly reported on the presence or absence of events were included in the overall risk analysis; we did not assume that the lack of reporting coincided with the lack of such events.

3. Results

Characteristics of the 26 studies included in the review are presented in Table 1. Overall, participants had mild-to-moderate MS disability. There was a considerable variation in the type and prescription of exercise training. The exercise sessions were performed between 1 and 5 days/week for between 20 and 90 minutes/day. The duration of the exercise program was between 4 and 24 weeks. There were a variety of exercise modes including aerobic, resistance, combined (i.e., aerobic and resistance), and other modalities (e.g., yoga, aquatics). Fifteen

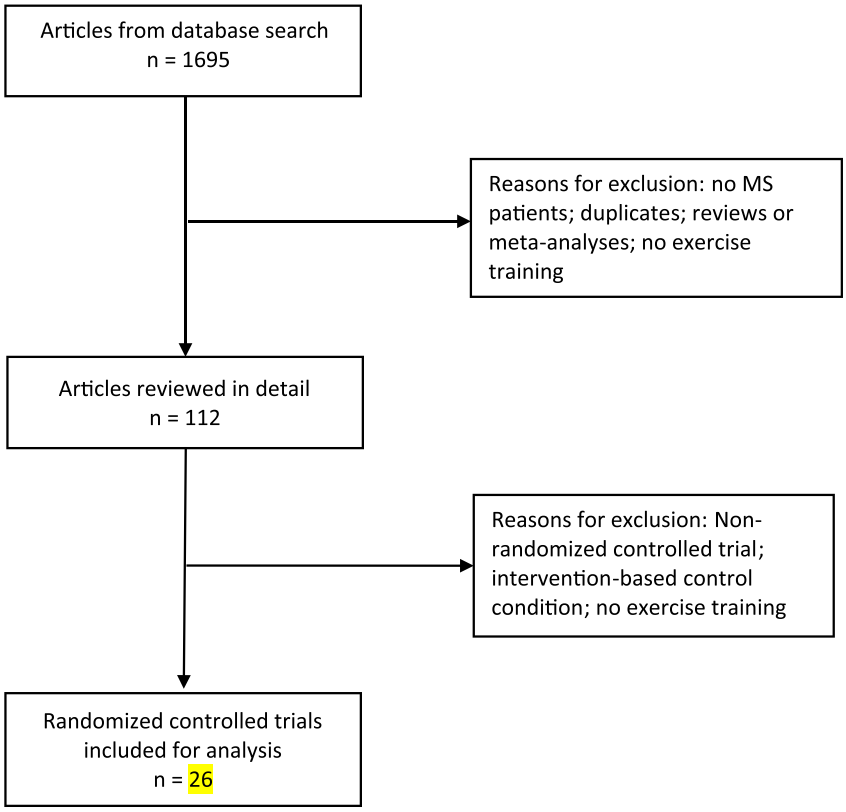

Fig. 1. Flow diagram of study selection.