

# The Safety of Exercise Training in Multiple Sclerosis: A Systematic Review

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## Introduction

- Relapses are a hallmark feature of multiple sclerosis (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, with concerns that exercise may trigger the onset or worsening of neurological symptoms and relapse. There is also uncertainty regarding other possible adverse events (AEs) associated with exercise training in MS.
- There is evidence for the benefits of exercise training in MS, but the safety of exercise training has yet to be systematically quantified.
- Information on rates of relapse and AEs are important for making informed decisions and recommendations regarding the safety of exercise training for people with MS in research and clinical settings.

## Aim

- To provide a quantitative synthesis of randomized controlled trials examining the effect of exercise training on relapses and AE's in persons with MS.

## 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 "exercise training" or "training" or "fitness" or "aerobic" or "resistance" or "strength" AND "multiple sclerosis."
- Studies were included in the review based on three criteria: sample of participants with MS, exercise training intervention, and RCT designs that included a no-treatment control condition.

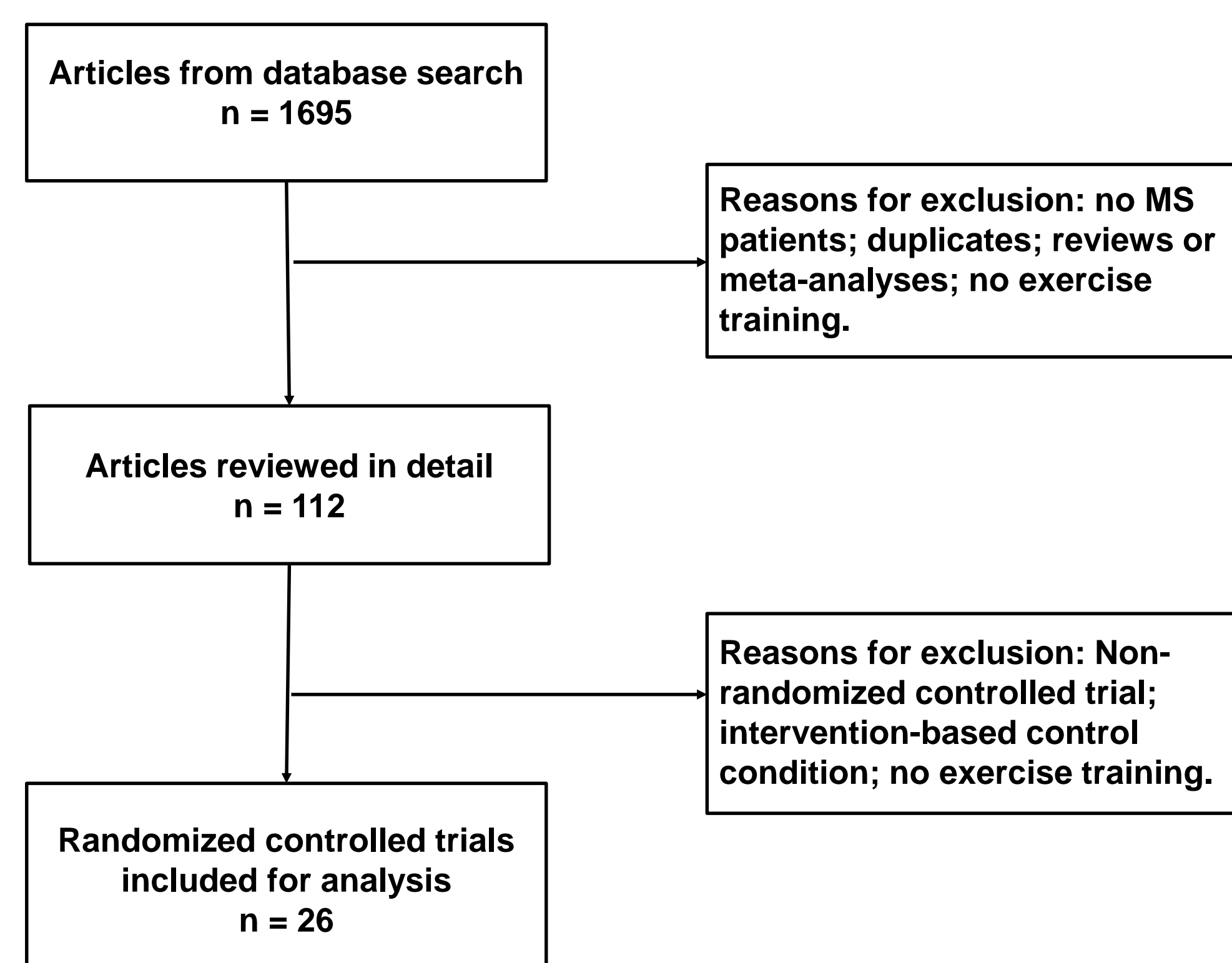


Figure 1: Flow diagram of study selection

## Methods (continued)

- We quantified the number of relapses and the number and type of AE(s) in the exercise training and control conditions separately.
- The rate of relapses and AEs 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.
- The overall relative risk of relapse and AEs 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) [2].
- Only studies that directly reported on the presence or absence of relapses and adverse events were included in the overall risk analysis.
- Study quality was assessed using the Physiotherapy Evidence Database (PEDro) criteria for randomized controlled trials [3]. 22 of the 26 studies reviewed were considered high quality (i.e., PEDro score  $\geq 6.0$ ).

Table 1: Number and rate of relapses and adverse events reported per study.

Study	n (CON/EX)	Exercise mode	Relapse				Adverse Events				Type	
			CON	EX	CON	EX	CON	EX	CON	EX	CON	EX
Ahmadi et al. (2010)	10/11	yoga	NR	NR	-	-	0	0	0.0	0.0		
Bjarnadottir et al. (2007)	10/8	combined	1	1	10.0	12.5	1	1	10.0	12.5	Illness	Illness
Broekmans et al. (2011)	14/11	resistance	1	0	7.1	0.0	0	1	0.0	4.6		Stroke
Cakt et al. (2010)	15/30	combined	3	3	20.0	10.0	0	0	0.0	0.0		
Carter et al. (2013)	13/15	combined	1	0	7.7	0.0	0	0	0.0	0.0		
Dalgas et al. (2009)	19/19	resistance	NR	NR	-	-	0	1	0.0	5.3		Low back pain
DeBolt et al. (2004)	18/19	resistance	0	1	0.0	5.0	NR	NR	-	-		
Doulatabad et al. (2013)	30/30	yoga	NR	NR	-	-	NR	NR	-	-		
Garrett et al. (2013)	71/243	combined; yoga	6	7	8.5	2.9	1	5	1.4	2.1	Ankle sprain	Sacro-iliac joint pain; low back pain; hernia; RA flare up; metatarsal fracture
Geddes et al. (2009)	6/9	aerobic	NR	NR	-	-	0	0	0.0	0.0		
Golzari et al. (2010)	10/10	combined	NR	NR	-	-	0	0	0.0	0.0		
Harvey et al. (1999)	5/14	resistance; other	0	1	0.0	7.1	0	1	0.0	7.1		Low back pain
Hebert et al. (2011)	13/13	aerobic	0	0	0.0	0.0	1	0	7.7	0.0	Ankle sprain	
Kargarfard et al. (2012)	16/16	aquatic	0	0	0.0	0.0	0	0	0.0	0.0		
Learmonth et al. (2012)	12/20	combined	NR	NR	-	-	0	2	0.0	10.0		Trigeminal neuralgia; illness
McCullagh et al. (2008)	13/17	combined	0	2	0.0	11.8	NR	NR	-	-		
Mostert et al. (2002)	18/15	aerobic	2	0	11.1	0.0	0	0	0.0	0.0		
Negahban et al. (2013)	12/12	combined	NR	NR	-	-	0	0	0.0	0.0		
Nilsagard et al. (2013)	42/42	combined	0	1	0.0	2.4	0	0	0.0	0.0		
Oken et al. (2004)	22/47	aerobic; yoga	0	2	0.0	4.3	0	0	0.0	0.0		
Petajan et al. (1996)	25/21	aerobic	3	4	12.0	19.1	NR	NR	-	-		
Romberg et al. (2004)	48/47	combined	6	5	12.5	10.6	1	2	2.1	4.3	Knee pain	Traffic accident; upper respiratory tract infection
Schulz et al. (2004)	13/15	aerobic	NR	NR	-	-	NR	NR	-	-		
Sosnoff et al. (2013)	14/13	combined	0	1	0.0	7.7	1	0	7.1	0.0	Fall	
Tarakci et al. (2013)	55/55	other	3	1	5.5	1.8	0	0	0.0	0.0		
van den Berg et al. (2006)	9/10	aerobic	NR	NR	-	-	NR	NR	-	-		

## Results

### Overall Risk of Relapse:

- There were 26 relapses reported in all control conditions (n=412), and 29 relapses reported in all exercise training conditions (n=626).
- This corresponds with 6.3% and 4.6% of participants in control and exercise training groups having relapse.
- The relative risk of relapse for exercise training versus control would be 0.73 (i.e., 27% lower risk of relapse with exercise training).

### Overall Risk of Adverse Events:

- There were 5 AEs reported in all control conditions (n=425), and 13 AEs reported in all exercise training conditions (n=650).
- This corresponds with 1.2% and 2.0% of participants in control and exercise training groups having AEs.
- The relative risk of AEs for exercise training versus control would be 1.67 (i.e., 67% higher risk of AEs with exercise training).

## Discussion & Conclusions

- Exercise training was associated with a slight decrease in the risk of relapse when compared to control.
- There were few AEs reported with exercise training, and the risk of AEs for exercise training in MS was higher than control conditions, but not higher than rates of AEs associated with exercise training in healthy populations [4].
- Overall, the evidence suggests exercise training is safe for persons with MS. Patients with MS should not be deterred from exercise participation for concern of experiencing a relapse or AE.
- Safety reporting recommendations:**
  - Detailed monitoring and reporting on relapses and AEs including timing of occurrence and whether the event was likely related to exercise participation.
  - CONSORT diagram with information on the number of drop-outs from each condition and reasons for drop-out.
  - Reporting on frequency and severity of temporary symptomatic changes with exercise.

## References

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