Clinical Trial Protocol
Iranian Registry of Clinical Trials

07 Nov 2026

Comparison of the Effects of Different Doses of Combined Aerobic-Resistance Exercise on Neuroaxonal Injury and Clinical Outcomes in Patients With Relapsing-Remitting Multiple Sclerosis

Protocol summary

Study aim

The aim of this study is to determine the effects of different doses of combined aerobic-resistance exercise on neuroaxonal injury, inflammatory biomarkers, and clinical outcomes in patients with relapsing-remitting multiple sclerosis. The primary objective is to identify the exercise intensity threshold associated with reductions in serum neurofilament light chain (sNfL) as a biomarker of neuroaxonal injury.

Design

A phase II, randomized, three-arm, parallel-group clinical trial with blinded outcome assessment in 120 patients with RRMS. Participants will be allocated in a 1:1:1 ratio using stratified variable block randomization based on sex and EDSS.

Settings and conduct

The study will be conducted in specialized MS centers. After baseline assessment, participants will be randomly assigned to groups and complete a 16-week exercise program. Outcome assessors and laboratory personnel will remain blinded to group allocation.

Participants/Inclusion and exclusion criteria

Patients with RRMS; age 25–45 years; EDSS 1–4.5; no relapse or corticosteroid treatment during the previous 3 months; stable therapy ≥6 months; ability to exercise. Exclusion criteria: progressive MS; medical contraindications to exercise; severe mobility limitations; severe cognitive impairment; pregnancy; recent treatment changes.

Intervention groups

Three groups will perform combined aerobic-resistance exercise with low, moderate, and high doses. Low-dose: 50–60% HRR and 50–60% 1RM; moderate-dose: 65–75% HRR and 60–70% 1RM; high-dose: 80–85% HRR and 70–80% 1RM. All groups will train for 16 weeks, three sessions per week.

Main outcome variables

Changes in serum neurofilament light chain (sNfL) levels; aerobic capacity (VO_2peak); disease-related fatigue; walking performance; cognitive function; and health-related quality of life.

General information

Reason for update

Acronym

IRCT registration information

IRCT registration number: **IRCT20241205063953N6**
Registration date: **2026-08-01, 1405/05/10**
Registration timing: **registered_while_recruiting**

Last update: **2026-08-01, 1405/05/10**
Update count: **0**

Registration date

2026-08-01, 1405/05/10

Registrant information

Name

akram jafari

Name of organization / entity

Country

Iran (Islamic Republic of)

Phone

+98 912 547 9267

Email address

jafari.akm@gmail.com

Recruitment status

Recruitment complete

Funding source

Expected recruitment start date

2026-08-01, 1405/05/10

Expected recruitment end date

2026-11-01, 1405/08/10

Actual recruitment start date

empty

Actual recruitment end date

empty

Trial completion date

empty

Scientific title

Comparison of the Effects of Different Doses of Combined Aerobic-Resistance Exercise on Neuroaxonal Injury and Clinical Outcomes in Patients With Relapsing-Remitting Multiple Sclerosis

Public title

Effect of Different Doses of Combined Aerobic-Resistance Exercise on Neuroaxonal Injury and Clinical Outcomes in Patients With Multiple Sclerosis

Purpose

Supportive

Inclusion/Exclusion criteria

Inclusion criteria:

Patients with relapsing-remitting multiple sclerosis according to the 2017 McDonald criteria Age between 25 and 45 years Expanded Disability Status Scale score between 1 and 4.5 No relapse during the previous three months No corticosteroid treatment during the previous three months Stable disease-modifying therapy for at least six months Ability to perform exercise testing and participate in the training program No participation in structured regular exercise training during the previous three months

Exclusion criteria:

Progressive multiple sclerosis phenotype Cardiovascular disease or medical contraindications to exercise

Age

From **25 years** old to **45 years** old

Gender

Both

Phase

N/A

Groups that have been masked

- Outcome assessor

Sample size

Target sample size: **120**

Randomization (investigator's opinion)

Randomized

Randomization description

Eligible participants will be randomly allocated in a 1:1:1 ratio to low-dose, moderate-dose, or high-dose exercise groups after completion of baseline assessments. Individual randomization will be performed using variable block randomization. Stratified randomization will be applied according to sex (female/male) and baseline disability level based on the Expanded Disability Status Scale (EDSS ≤3.5 and >3.5) to minimize potential confounding effects. The random allocation sequence will be generated by an independent researcher using statistical software. Group allocation will be concealed using sequentially numbered, opaque, sealed envelopes prepared by a researcher who is not involved in participant recruitment or intervention delivery.

Blinding (investigator's opinion)

Single blinded

Blinding description

Participants and exercise trainers will not be blinded due to the nature of the exercise intervention. The principal investigator and intervention staff will be aware of group allocation. However, outcome assessors, laboratory personnel responsible for biomarker analyses, and the statistician will remain blinded to treatment allocation. Biological samples will be analyzed using coded identifiers, and group assignments will remain concealed until completion of the primary statistical analysis.

Placebo

Not used

Assignment

Parallel

Other design features

This study is a three-arm randomized controlled trial with blinded outcome assessment investigating the effects of different doses of combined aerobic-resistance exercise on a neuroaxonal injury biomarker (sNfL) and clinical outcomes in patients with multiple sclerosis.

Secondary Ids

empty

Ethics committees

1

Ethics committee

Name of ethics committee

Islamic Azad University Shahrekord Branch

Street address

Rahmatieh, Islamic Azad University Shahrekord

City

Shahrekord

Province

Chahar-Mahal-va-Bakhtiari

Postal code

8817630003

Approval date

2026-06-10, 1405/03/20

Ethics committee reference number

IR.IAU.SHK.REC.1405.110

Health conditions studied

1

Description of health condition studied

Relapsing-remitting multiple sclerosis (RRMS)

ICD-10 code

G35

ICD-10 code description

Multiple sclerosis

2

Description of health condition studied

Multiple sclerosis

ICD-10 code

G35

ICD-10 code description

Multiple sclerosis

Primary outcomes

1

Description

Change in serum neurofilament light chain concentration

Timepoint

Measurement at baseline before intervention and after completion of the 16-week exercise intervention

Method of measurement

Blood sampling and measurement of serum neurofilament light chain concentration using the Single Molecule Array method

Secondary outcomes

1

Description

Change in maximal cardiorespiratory fitness

Timepoint

Measurement at baseline before the intervention and after completion of the 16-week exercise intervention

Method of measurement

Using an incremental cardiopulmonary exercise test on a treadmill with respiratory gas analysis

2

Description

Change in disease-related fatigue severity

Timepoint

Measurement at baseline before the intervention and after completion of the 16-week exercise intervention

Method of measurement

Using the Modified Fatigue Impact Scale

3

Description

Change in walking performance

Timepoint

Measurement at baseline before the intervention and after completion of the 16-week exercise intervention

Method of measurement

Using the Six-Minute Walk Test

4

Description

Change in cognitive function

Timepoint

Measurement at baseline before the intervention and after completion of the 16-week exercise intervention

Method of measurement

Using the Symbol Digit Modalities Test

5

Description

Change in health-related quality of life

Timepoint

Measurement at baseline before the intervention and after completion of the 16-week exercise intervention

Method of measurement

Using the Multiple Sclerosis Quality of Life questionnaire containing 54 items

6

Description

Change in serum brain-derived neurotrophic factor level

Timepoint

Measurement at baseline before the intervention and after completion of the 16-week exercise intervention

Method of measurement

Using enzyme-linked immunosorbent assay

7

Description

Change in serum glial fibrillary acidic protein level

Timepoint

Measurement at baseline before the intervention and after completion of the 16-week exercise intervention

Method of measurement

Using the Single Molecule Array method

8

Description

Change in serum interleukin-6 level

Timepoint

Measurement at baseline before the intervention and after completion of the 16-week exercise intervention

Method of measurement

Measurement of serum interleukin-6 level using enzyme-linked immunosorbent assay

9

Description

Change in serum tumor necrosis factor-alpha level

Timepoint

Measurement at baseline before the intervention and after completion of the 16-week exercise intervention

Method of measurement

using enzyme-linked immunosorbent assay

Intervention groups

1

Description

Intervention Low-dose Combined Aerobic-Resistance Exercise group: Participants will complete a 16-week combined aerobic-resistance exercise program. Training will be performed three sessions per week. Aerobic exercise will be prescribed at 50–60% of heart rate reserve, and resistance exercise will be performed at

50–60% of one-repetition maximum. Each session will include warm-up, aerobic training, resistance training, and cool-down.

Category

Behavior

2

Description

Intervention moderate-dose Combined Aerobic-Resistance Exercise group: Participants will complete a 16-week combined aerobic-resistance exercise program. Training will be performed three sessions per week. Aerobic exercise will be prescribed at 65–75% of heart rate reserve, and resistance exercise will be performed at 60–70% of one-repetition maximum. Each session will include warm-up, aerobic training, resistance training, and cool-down.

Category

Behavior

3

Description

Intervention high-dose Combined Aerobic-Resistance Exercise group: Participants will complete a 16-week combined aerobic-resistance exercise program. Training will be performed three sessions per week. Aerobic exercise will be prescribed at 80–85% of heart rate reserve, and resistance exercise will be performed at 70–80% of one-repetition maximum. Each session will include warm-up, aerobic training, resistance training, and cool-down.

Category

Behavior

4

Description

Control group: The control group will receive usual care and will not participate in any structured exercise program during the study period. Participants will be instructed to maintain their usual daily physical activity level.

Category

Behavior

Recruitment centers

1

Recruitment center

Name of recruitment center

Islamic Azad University Shahrekord Branch

Full name of responsible person

Mehrdad Yadegari Dehkordi

Street address

Rahmatieh, Islamic Azad University Shahrekord Branch

City

Shahrekord

Province

Chahar-Mahal-va-Bakhtiari

Postal code

8817630003

Phone

+98 38 3336 1001

Email

Yadagari_mehrdad@yahoo.com

Sponsors / Funding sources

1

Sponsor

Name of organization / entity

Islamic Azad University

Full name of responsible person

Mehrdad Yadegari Dehkordi

Street address

Rahmatieh, Islamic Azad University Shahrekord

City

Shahrekord

Province

Chahar-Mahal-va-Bakhtiari

Postal code

8817630003

Phone

+98 38 3336 1001

Email

Yadagari_mehrdad@yahoo.com

Grant name

Grant code / Reference number

Is the source of funding the same sponsor organization/entity?

Yes

Title of funding source

Islamic Azad University

Proportion provided by this source

100

Public or private sector

Private

Domestic or foreign origin

Domestic

Category of foreign source of funding

empty

Country of origin

Type of organization providing the funding

Academic

Person responsible for general inquiries

Contact

Name of organization / entity

Islamic Azad University

Full name of responsible person

Akram Jafari

Position

Associate professor

Latest degree

Ph.D.

Other areas of specialty/work

Sport Physioligy

Street address

Rahmatieh, Islamic Azad University Shahrekord

Branch
City
Shahrekord
Province
Chahar-Mahal-va-Bakhtiari
Postal code
8817630003
Phone
+98 38 3336 3001
Email
Jafari.akm@gmail.com

Person responsible for scientific inquiries

Contact
Name of organization / entity
Islamic Azad University
Full name of responsible person
Akram Jafari
Position
Associate professor
Latest degree
Ph.D.
Other areas of specialty/work
Sport Physiology
Street address
Rahmatieh, Islamic Azad University Shahrekord Branch
City
Shahrekord
Province
Chahar-Mahal-va-Bakhtiari
Postal code
8817630003
Phone
+98 38 1336 1001
Email
Jafari.akm@gmail.com

Person responsible for updating data

Contact
Name of organization / entity
Islamic Azad University
Full name of responsible person
Akram Jafari
Position
Associate professor
Latest degree
Ph.D.
Other areas of specialty/work
Sport Physiology
Street address
Rahmatieh, Islamic Azad University Shahrekord Branch
City
Shahrekord
Province
Chahar-Mahal-va-Bakhtiari
Postal code
8817630003
Phone
009838133361001
Email
Jafari.akm@gmail.com

Sharing plan

Deidentified Individual Participant Data Set (IPD)
Yes - There is a plan to make this available
Study Protocol
Yes - There is a plan to make this available
Statistical Analysis Plan
Yes - There is a plan to make this available
Informed Consent Form
No - There is not a plan to make this available
Clinical Study Report
Yes - There is a plan to make this available
Analytic Code
Yes - There is a plan to make this available
Data Dictionary
Yes - There is a plan to make this available
Title and more details about the data/document
De-identified individual participant data, study protocol, statistical analysis plan, analysis codes, and data dictionary will be made available to qualified researchers after publication of the primary study results. Requests will be reviewed by the research team based on scientific and ethical considerations.
When the data will become available and for how long
Access to data and documents will begin 6 months after publication of the primary study results and will remain available for 5 years.
To whom data/document is available
Academic researchers, scientists from research institutions, and qualified investigators submitting a valid scientific request will be eligible for access.
Under which criteria data/document could be used
Data will be available for scientific research purposes, valid analyses, and advancing knowledge in multiple sclerosis and exercise science. Data reuse must comply with research ethics principles and must not attempt participant re-identification.
From where data/document is obtainable
Requests for data access should be submitted to the corresponding investigator through the official email address of the research center. Final contact information will be provided after publication of the primary study results.
What processes are involved for a request to access data/document
Requests will be reviewed by the research team. After scientific and ethical approval, a data use agreement will be completed and access to de-identified data will be provided.
Comments