frontiers | Frontiers in Neurology

TYPE Systematic Review
PUBLISHED 26 November 2024
DOI 10.3389/fneur.2024.1494368

Check for updates

OPEN ACCESS

EDITED BY
Pasquale Calabrese,
University of Basel, Switzerland

REVIEWED BY
Cagla Ozkul,
Gazi University, Türkiye
Nancy R. Mejía-Domínguez,
National Autonomous University of Mexico,
Mexico

*CORRESPONDENCE
Ming-Da Li
✉ 100339@cdsu.edu.cn

RECEIVED 18 September 2024
ACCEPTED 14 November 2024
PUBLISHED 26 November 2024

Comparison of different exercise modalities on fatigue and muscular fitness in patients with multiple sclerosis: a systematic review with network, and dose–response meta-analyses

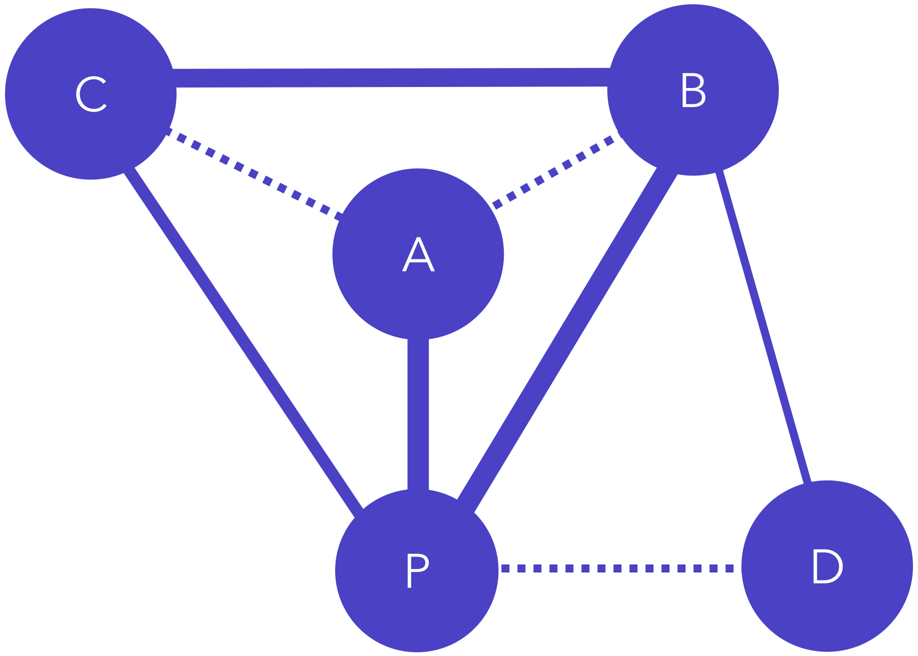
Xi-Nuan Zhang[1], Zhi-De Liang[2] and Ming-Da Li[1]*

[1]School of Sports Training, Chengdu Sport University, Chengdu, Sichuan, China, [2]Department of Physical Education, College of Physical Education, Qingdao University, Qingdao, China

Nantharat Apiwantanakul
PhD student in Clinical Epidemiology Program
07 November 2025

Network connectivity

- NMA provides a method to combine evidence on relative effects from comparative RCTs that form a connected network

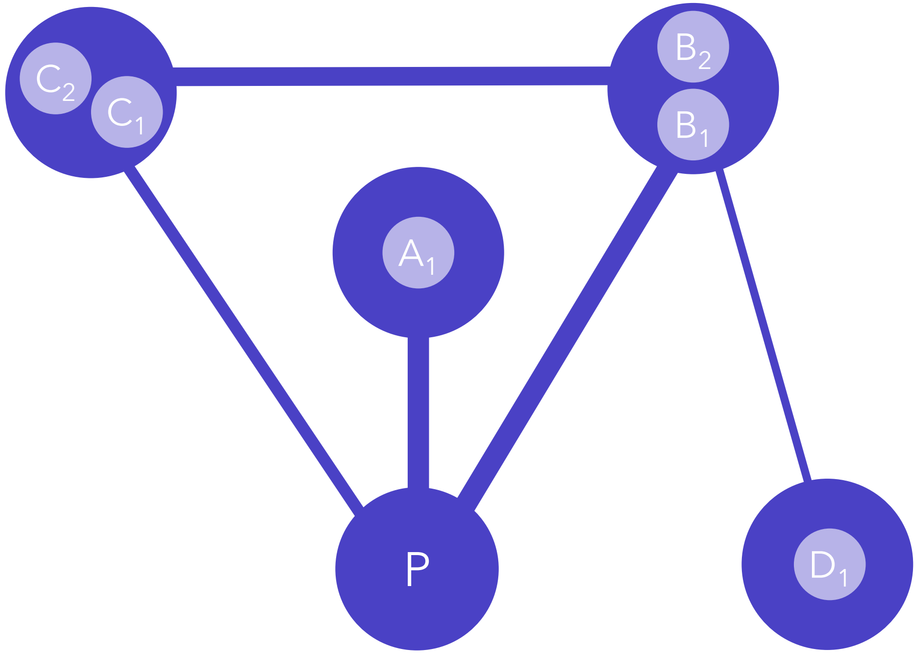


Lumped NMA

All doses are assumed to have the same efficacy

- Increases the between-study heterogeneity
- Increase the risk of inconsistency in the network

Unable to make prediction as a function of dose

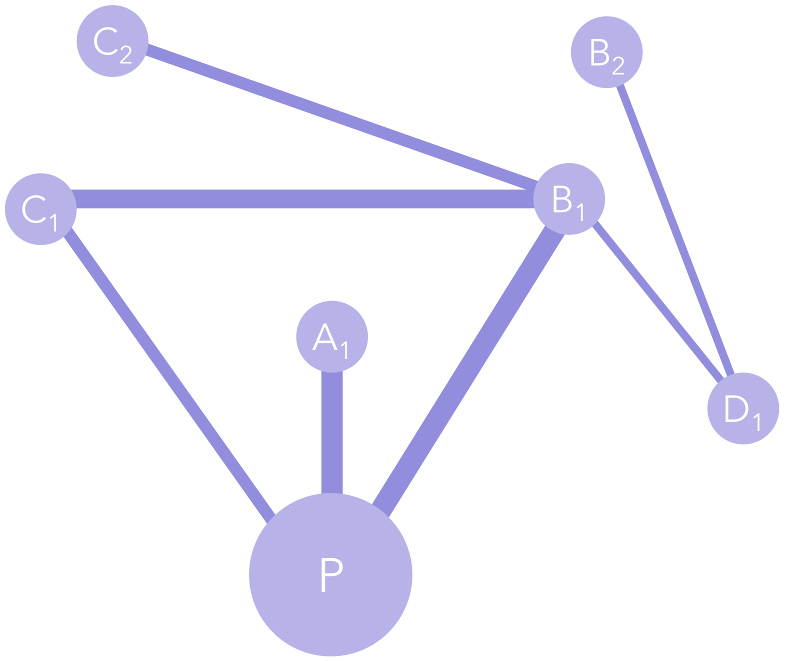


Split NMA

Each dose is considered as a separate treatment

- Smaller between-study heterogeneity
- Estimate effect size with lower precision because each contrast is informed by fewer trials

Can only be used to make prediction at trialed doses

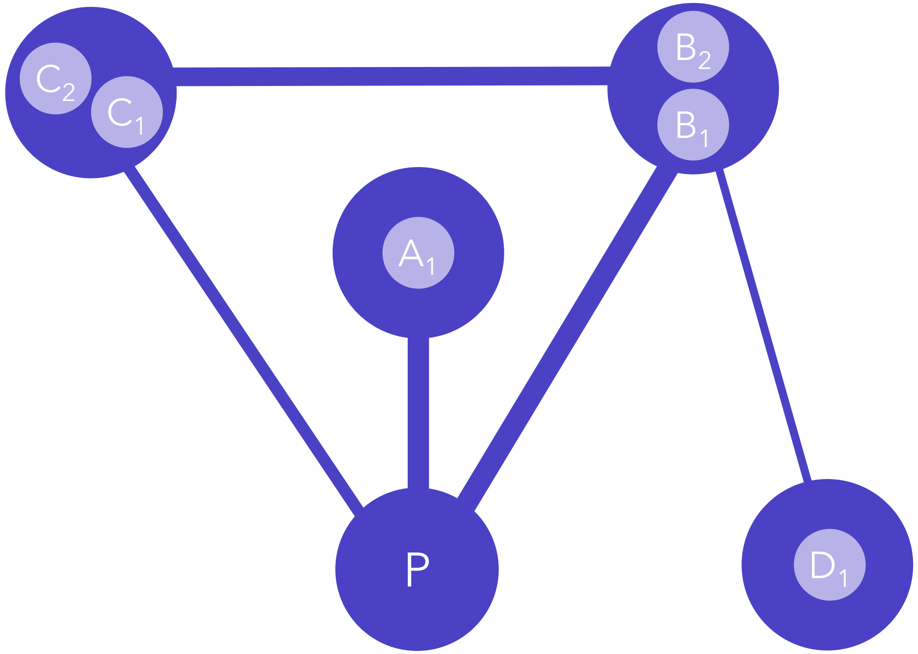


Lumped NMA

All doses are assumed to have the same efficacy

- Increases the between-study heterogeneity
- Increase the risk of inconsistency in the network

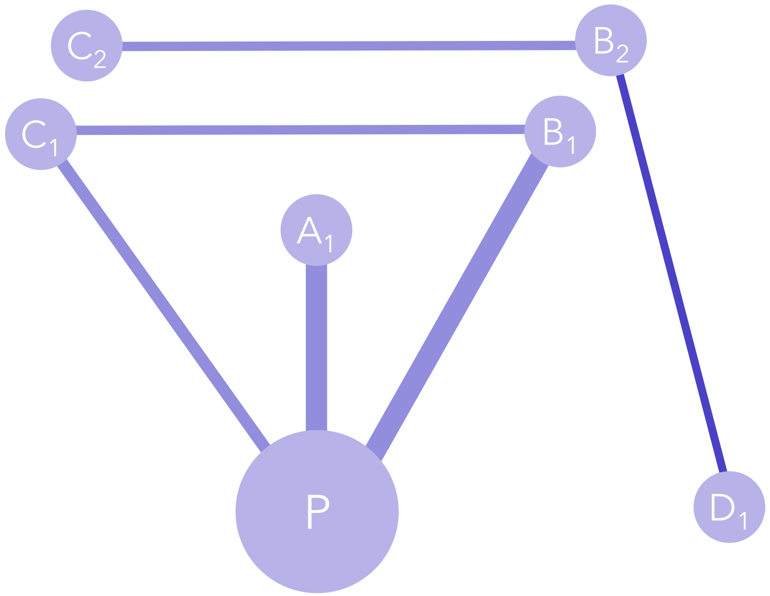
Unable to make prediction as a function of dose



Split NMA

Each dose is considered as a separate treatment
- Smaller between-study heterogeneity
- Estimate effect size with lower precision because each contrast is informed by fewer trials

Can only be used to make prediction at trialed doses

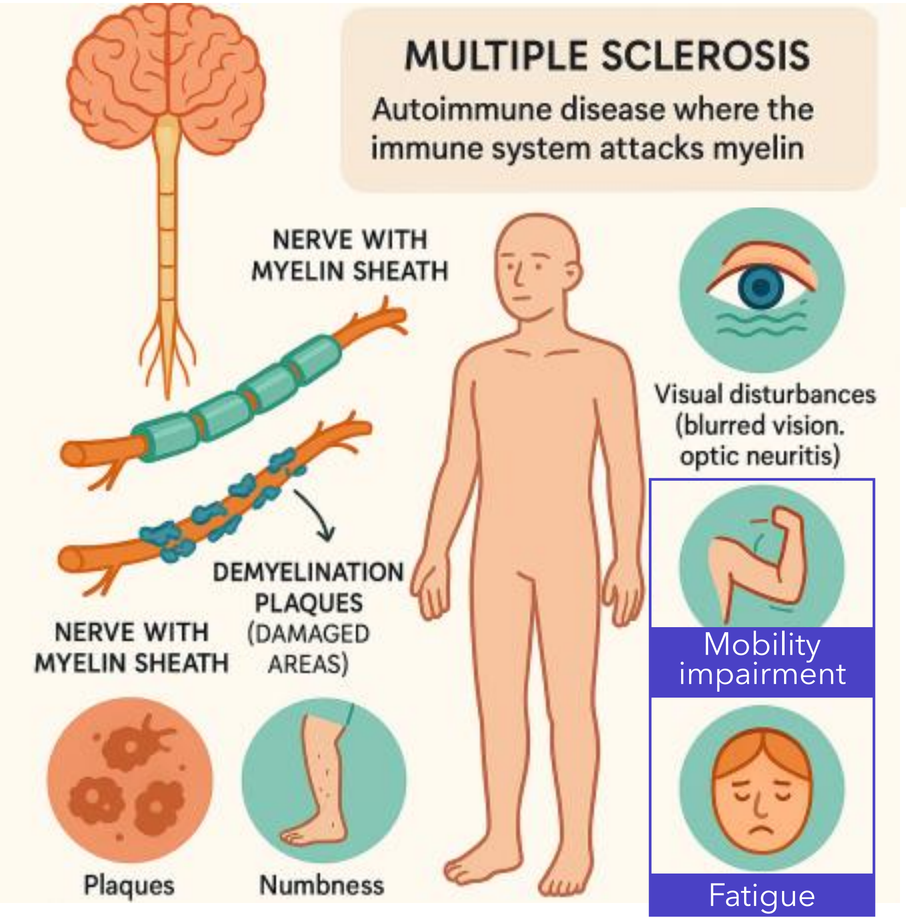


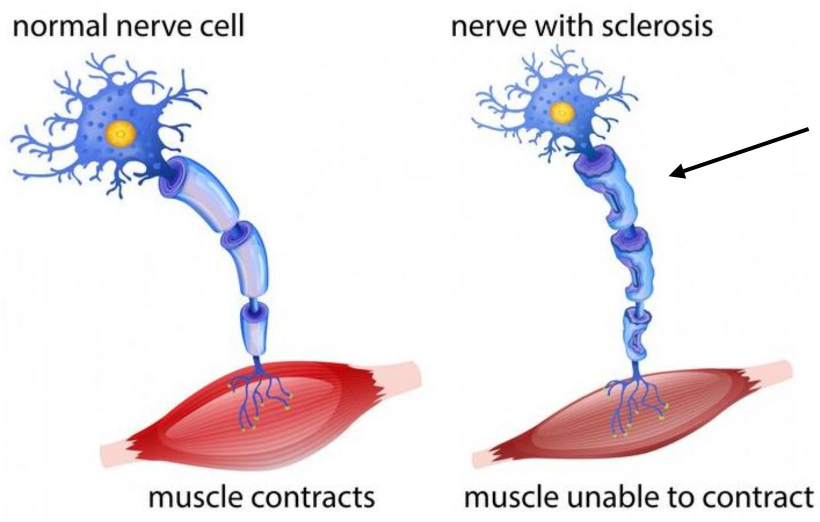
A split network may **become disconnected**, meaning that some treatments cannot be compared

Model-based NMA approach (MBNMA)

- Incorporate a dose response model into network meta-analysis
  - Help to connect the network of evidence, allowing a wider range of agents to be compared
  - Allow estimation and prediction of relative effects across a range of doses (including at doses that have not been trialed)
- The dose–response pattern can be modeled <u>using a variety of functional form</u>, such as maximum effect (Emax) and linear model
- MBNMA approach provides a more flexible modeling approach than lumped and split NMA

Multiple sclerosis (MS)





The **myelin** acts as the protective nerve coating and is essential for signal transmission

Treatment

- **Typically treated with disease modifying drugs**, which control inflammation but do not address neurodegenerative processes, leading to residual symptoms and dysfunction
- Among nonpharmacologic management, **exercise can be a beneficial rehabilitation approach for MS**, particularly, reducing fatigue and addressing mobility problems have received particular attention as ways to improve overall quality of life

Introduction

- Previous NMAs
  - Studied the effects of various exercise interventions on MS patients.
  - Research on exercise dose for MS patients is still underexplored.
  - The dose–response relationship has already been widely applied in the field of exercise interventions
- Guideline from WHO encourage MS patients to engage in exercise but <u>not provide clear recommendation regarding dose</u> and exercise modality.

Objective

- To determine the minimum effective dose, the optimal dose, and the maximum safe threshold of different exercise modalities
  - Providing more precise guidance for clinical practice in MS

PICOs

- **Population:** Patients with Multiple sclerosis
- **Interventions:** HIIT, COM, RT, AE, MBE
- **Comparator:** Control group (CG)
- **Outcome:** Fatigue, Muscular fitness
- **Study design:** Randomized controlled trials

Modality
High-intensity interval training (HIIT)
Combined exercise (COM) **RT+AE**
Resistance training (RT)
Aerobic exercise (AE)
Mind–body exercises (MBE)

Fatigue

Outcome: FSS (Fatigue Severity Scale); FSMC (Fatigue Scale for Motor and Cognitive Functions); MFIS (Modified Fatigue Impact Scale); FIS (Fatigue Impact Scale); Weimus (Würzburg Fatigue Scale for Multiple Sclerosis); PROMIS (Patient-Reported Outcomes Measurement Information System); POMS (Profile of Mood States)

Muscular fitness

Outcome: STS (Sit-to-Stand Test); CAR (Central Activation Ratio); CUT (Curl Up Test); Muscle fiber CSA (Muscle Fiber Cross-sectional Area); Strength MVC (Maximal Voluntary Contraction); MIT (Maximal Isometric Torque); Power MIVC (Maximum Voluntary Isometric Contraction); MPT (Modified Push-ups Test); MSL (Maximum Squat Load); Standing Test WST (Wall Squat Test); SCT (Stair-Climbing Test)
; MWD (Maximal Walking Distance); PHT (Plank-Hold Test)

Assessed the impact of exercise interventions by calculating the **standardized mean difference (SMD)** for changes observed between pre- and post-intervention periods.

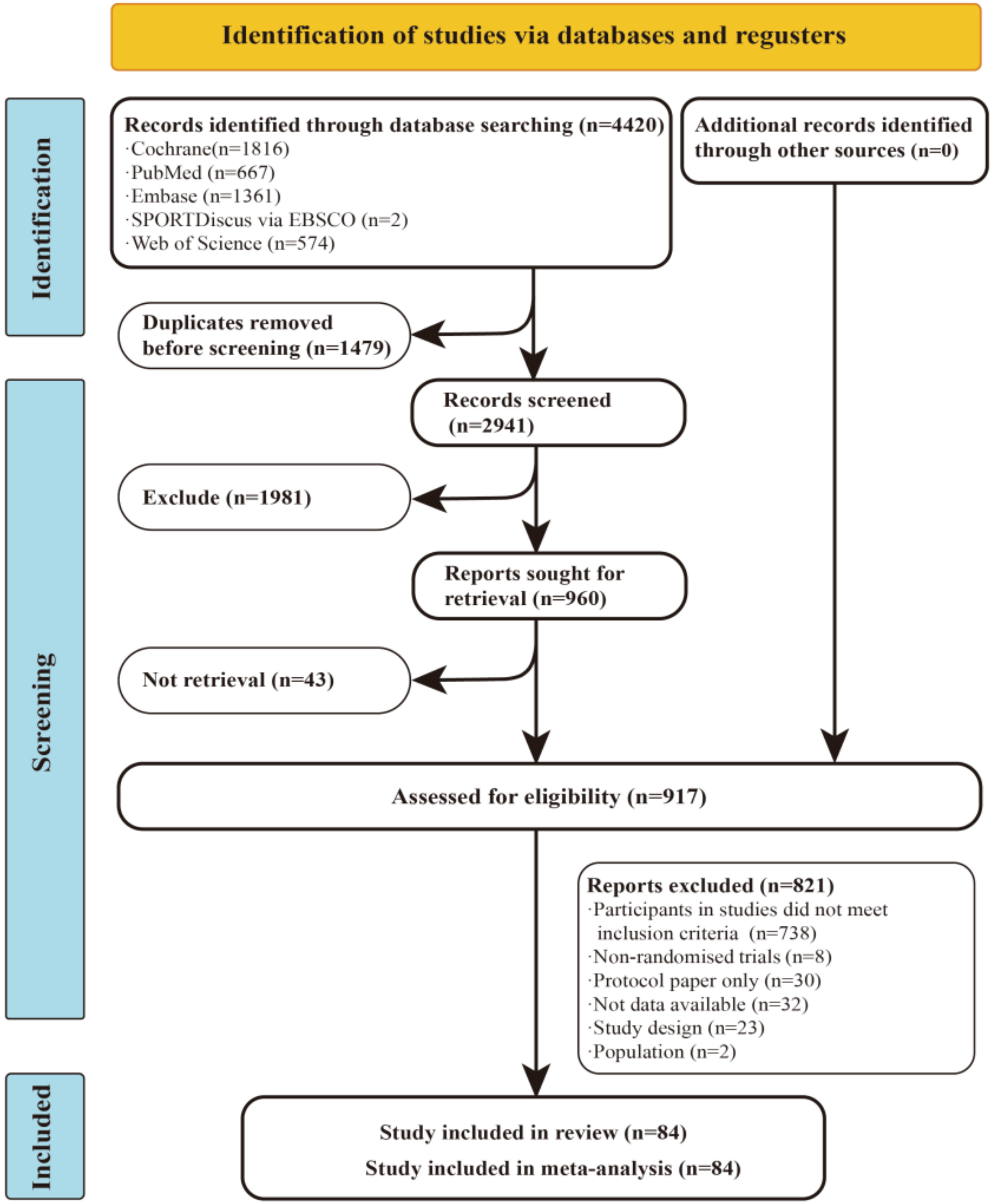


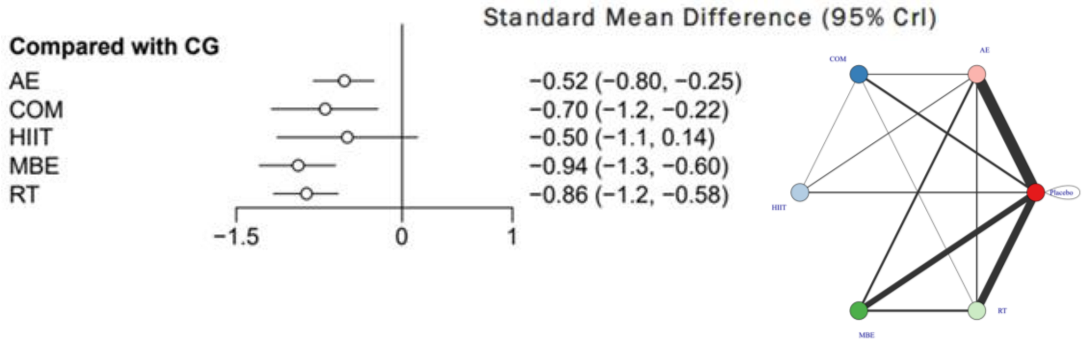
FIGURE 1
Literature review flowchart. RCT, randomized controlled trial.

Analysis

- Bayesian NMA using the “Metainsight” tool (version 6.1.0)
- Transitivity assumption
    - Examination of the key characteristics of each intervention and baseline participant data to ensure that the comparison across studies was valid
- Consistency assumption
    - Global inconsistency
    - Inconsistency between direct and indirect effect estimates within the network
- Rank the intervention – calculate SUCRA

Primary analysis

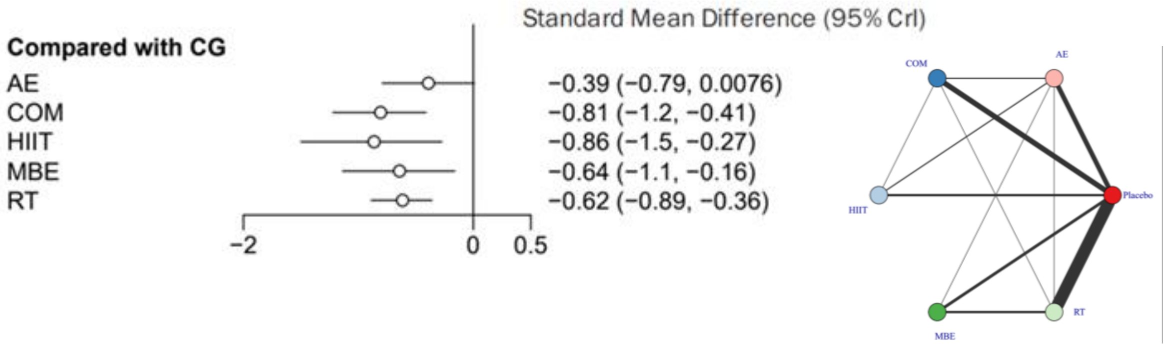
Fatigue



Compared to the control group

- **Most exercise interventions were effective in significantly reducing fatigue.**
- All yielded notable reductions. The only exception was **HIIT**, which did not show a statistically significant reduction in fatigue levels.

Muscular fitness

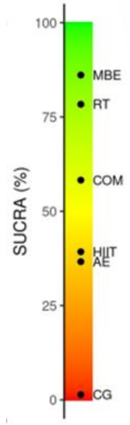


Compare to the control group

- **All found to significantly enhance muscular fitness**
- **AE** was the only intervention that fail to reach statistical significance when compared to controls

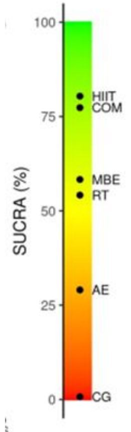
Primary analysis

TABLE 2 League table of network comparisons of the effects of different exercise interventions on fatigue and muscular fitness.



(A) Fatigue

MBE					
−0.07 (−0.47, 0.32)	RT				
−0.24 (−0.84, 0.33)	−0.17 (−0.71, 0.37)	COM			
−0.45 (−1.19, 0.27)	−0.38 (−1.09, 0.32)	−0.2 (−0.97, 0.55)	HIIT		
−0.42 (−0.83, −0.01)	−0.34 (−0.72, 0.02)	−0.17 (−0.7, 0.36)	0.03 (−0.64, 0.72)	AE	
−0.94 (−1.29, −0.6)	−0.87 (−1.17, −0.58)	−0.7 (−1.18, −0.21)	−0.49 (−1.14, 0.16)	−0.52 (−0.8, −0.25)	CG



(B) Muscular fitness

HIIT					
−0.06 (−0.78, 0.63)	COM				
−0.23 (−1.03, 0.54)	−0.17 (−0.81, 0.45)	MBE			
−0.25 (−0.95, 0.42)	−0.19 (−0.67, 0.29)	−0.02 (−0.52, 0.49)	RT		
−0.48 (−1.17, 0.15)	−0.42 (−0.96, 0.09)	−0.26 (−0.87, 0.35)	−0.23 (−0.72, 0.24)	AE	
−0.87 (−1.53, −0.27)	−0.81 (−1.24, −0.41)	−0.64 (−1.14, −0.15)	−0.62 (−0.92, −0.35)	−0.39 (−0.8, 0.02)	CG

The data shown in the table are mean differences and 95% credible intervals. Exercises are reported in order of surface under the curve cumulative ranking.
HIIT, High-intensity interval training; COM, Combined exercise; RT, Resistance training; AE, Aerobic exercise; MBE, Mind–body exercises.

There were **no significant differences in efficacy among the different exercise mobilities** for either fatigue or muscular fitness

Dose-response NMA

- To investigate the dose–response relationship between exercise and outcomes such as fatigue and muscular fitness in patients with MS
  - Extended the analysis by performing a dose–response network meta-analysis using a Bayesian **model-based NMA (MBNMA)**

Dose (Exercise intensity)

- The intensity of an activity is measured using Metabolic Equivalent of Task (METs)
- **One MET** is the energy expended while **sitting at rest**
- An activity with a MET value of 5
  - expending five times the energy than you would while at rest
- The higher the MET value, the greater the energy expenditure

MET values

Cycling (moderate)	7.5
Cycling (vigorous, eg up hill)	14
Jogging/brisk walking	6
Running	8
General gardening/housework	4
Skipping	11
Walking up stairs	5
Pilates/Tai chi	3
Resistance/weight training	5

Dose (Exercise intensity)

Total intensity of each exercise
MET-minutes per week

= Intensity of the specific activity (MET) x Duration of a single session (min) x The weekly frequency (session/week)

Coded according to the standards outlined in *the 2024 Compendium of Physical Activities and its expansion*

= exercise duration

= exercise frequency

The descriptions of the intervention details reported in the studies

Study	Treatment	Time/session	Frequency
Tue Kjølhede 2015	RT	60 min/session	2 sessions/week
	CG	-	-

→ **RT_600**
→ **Placebo_0**

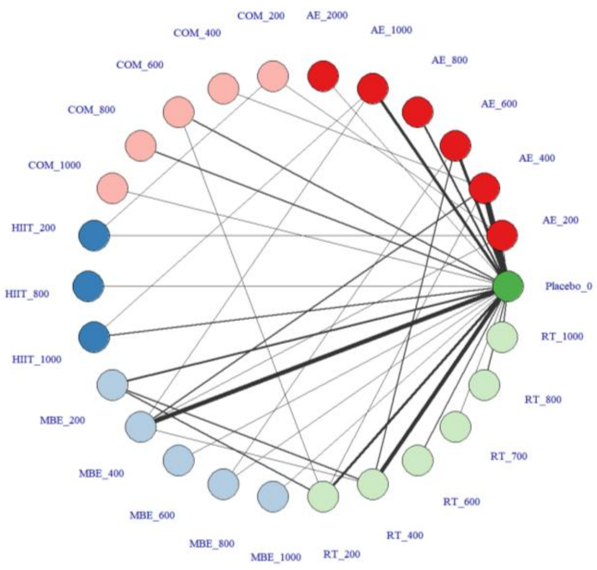
600
MET-minutes per week

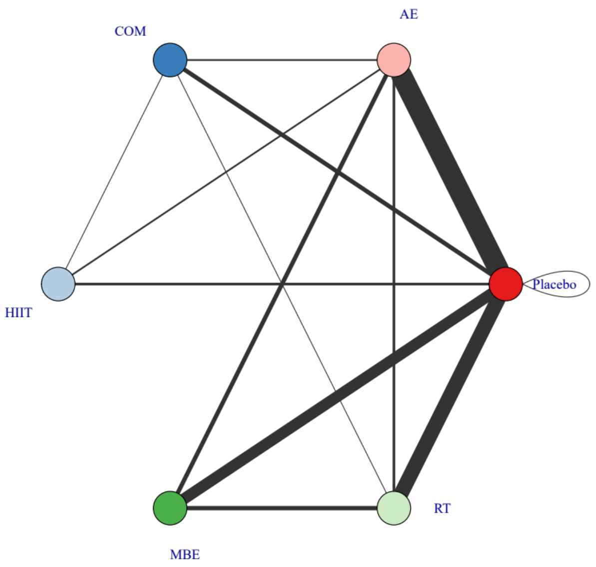
= 

x 60 min/session x 2 sessions/week

Dose-response NMA

- The estimated weekly MET-minutes were clustered into seven predefined categories to facilitate network connectivity and dose–response analysis
  - 0 (control), 200, 400, 600, 800, 1,000, and 2,000 MET-minutes/week





Treatment-level network

Agent-level network

Dose-response NMA

- Evaluate transitivity and consistency
- The entire MBNMA and dose–response analysis was performed using the "MBNMAdose" package in R (version 4.3.1), and the graphical representation of the dose–response curves was accomplished with the "ggplot2" package.

Model selection

- Perform a split NMA of the different doses of physical activity as separate and unrelated treatments

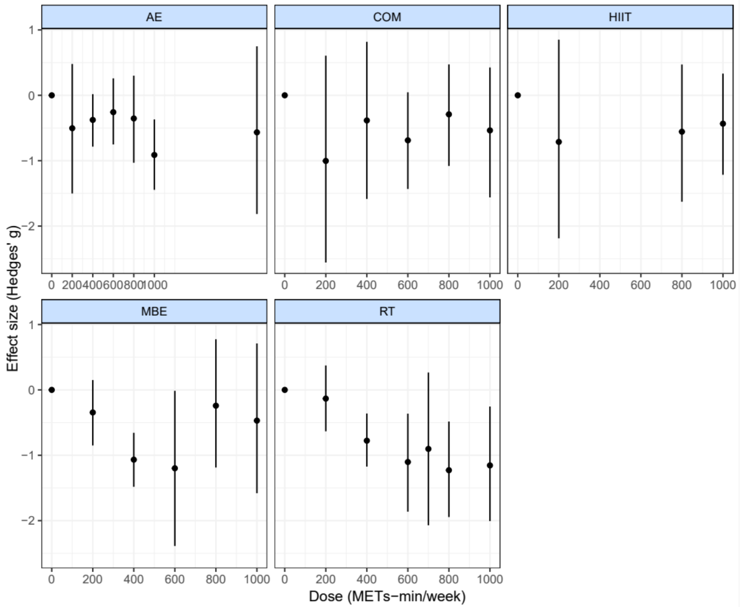


Figure a. Split NMA of different exercise agents.

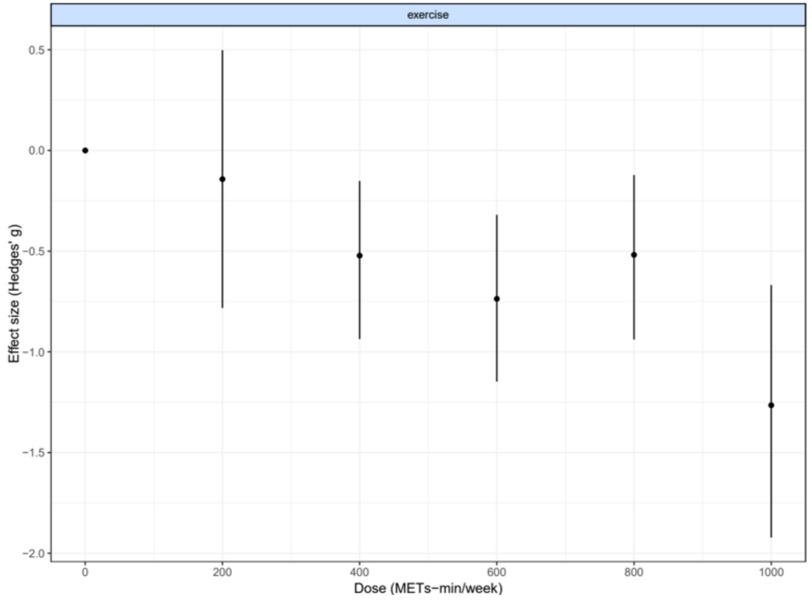


Figure b. Split NMA of overall exercise

- The <u>different responses of each dose</u> to overall and different types of exercise
- This step helps determine which function is more appropriate for the data and should be used in a model-based network meta-analysis

Model selection

- Applied several widely recommended functions to model the dose–response relationship
- Comparison of model fit index

(a) Fatigue

Model	DIC	SD	Deviance	Residual deviance	pD
Emax (common treatment effects)	19350.4	NA	19295.91	19391.066	55.1
Restricted cubic spline (common treatment effects; 3 knots)	18715.4	NA	18659.01	18754.174	57.4
Restricted cubic spline (random treatment effects; 3 knots)	133.2	6.181 (5.167, 7.477)	19.682	114.838	114.2
Non-parametric monotonically up (common treatment effects)	36988.5	NA	36935.990	37031.146	53.0
Quadratic (2nd degree polynomial, common treatment effects)	19302.7	NA	19248.141	19343.297	54.9
Quadratic (2nd degree polynomial, random treatment effects)	134.0	6.158 (5.172, 7.392)	19.924	115.079	115.1

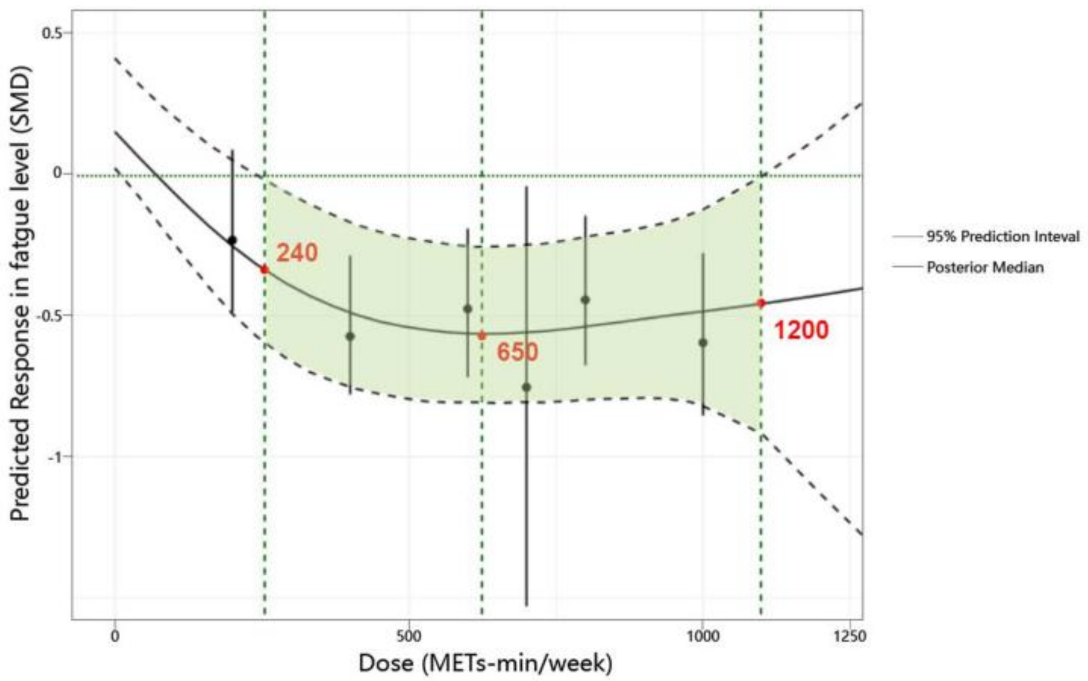
(b) Muscular fitness

Model	DIC	SD	Deviance	Residual deviance	pD
Emax (common treatment effects)	176.8	NA	131.353	179.205	46.2
Restricted cubic spline (common treatment effects; 3 knots)	169.2	NA	120.953	168.805	48.8
Restricted cubic spline (random treatment effects; 3 knots)	134.7	0.551 (0.331, 0.813)	60.499	108.351	75.4
Non-parametric monotonically up (common treatment effects)	254.7	NA	209.776	257.628	45.6
Quadratic (2nd degree polynomial, common treatment effects)	175.6	NA	128.936	176.788	47.3
Quadratic (2nd degree polynomial, random treatment effects)	135.6	0.576 (0.368, 0.819)	60.271	108.124	75.7

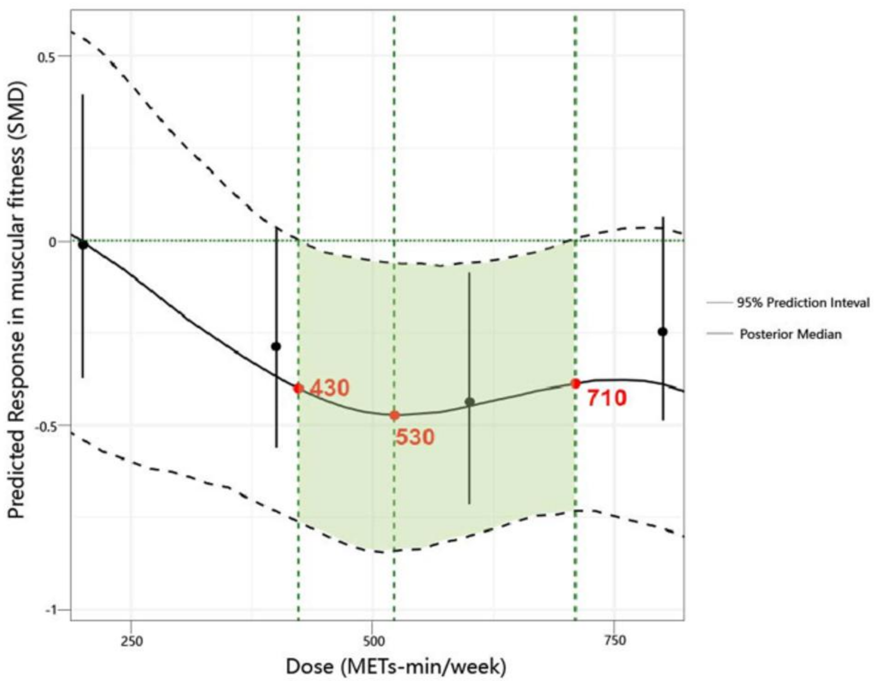
The **restricted cubic splines model showed superior fit**,
suggesting that it best captured the underlying dose-response relationship

Prediction dose-response relationship

- A **non-linear dose–response relationship** between the total exercise dose and fatigue levels as well as muscular fitness



(a) Fatigue



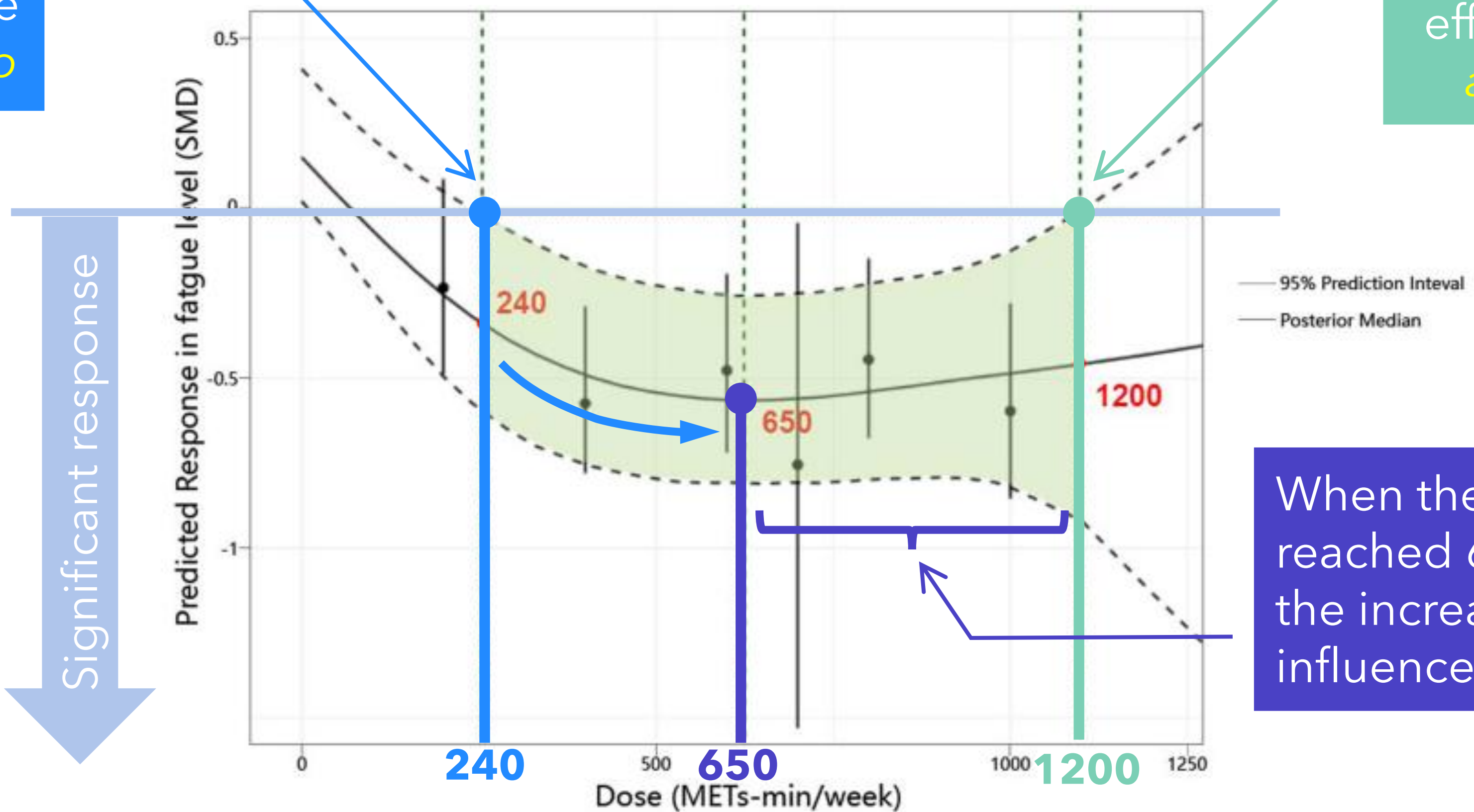
(b) Muscular fitness

Prediction dose-response relationship
Fatigue

The upper limit of the 95% CrI *less than zero*

a significant response was observed starting at 240 METs-min/week

The increase in the effect of its influence *approached zero*



When the exercise dose reached 650 METs-min/week, the increase in the effect of its influence became very slow

Minimum effective dose

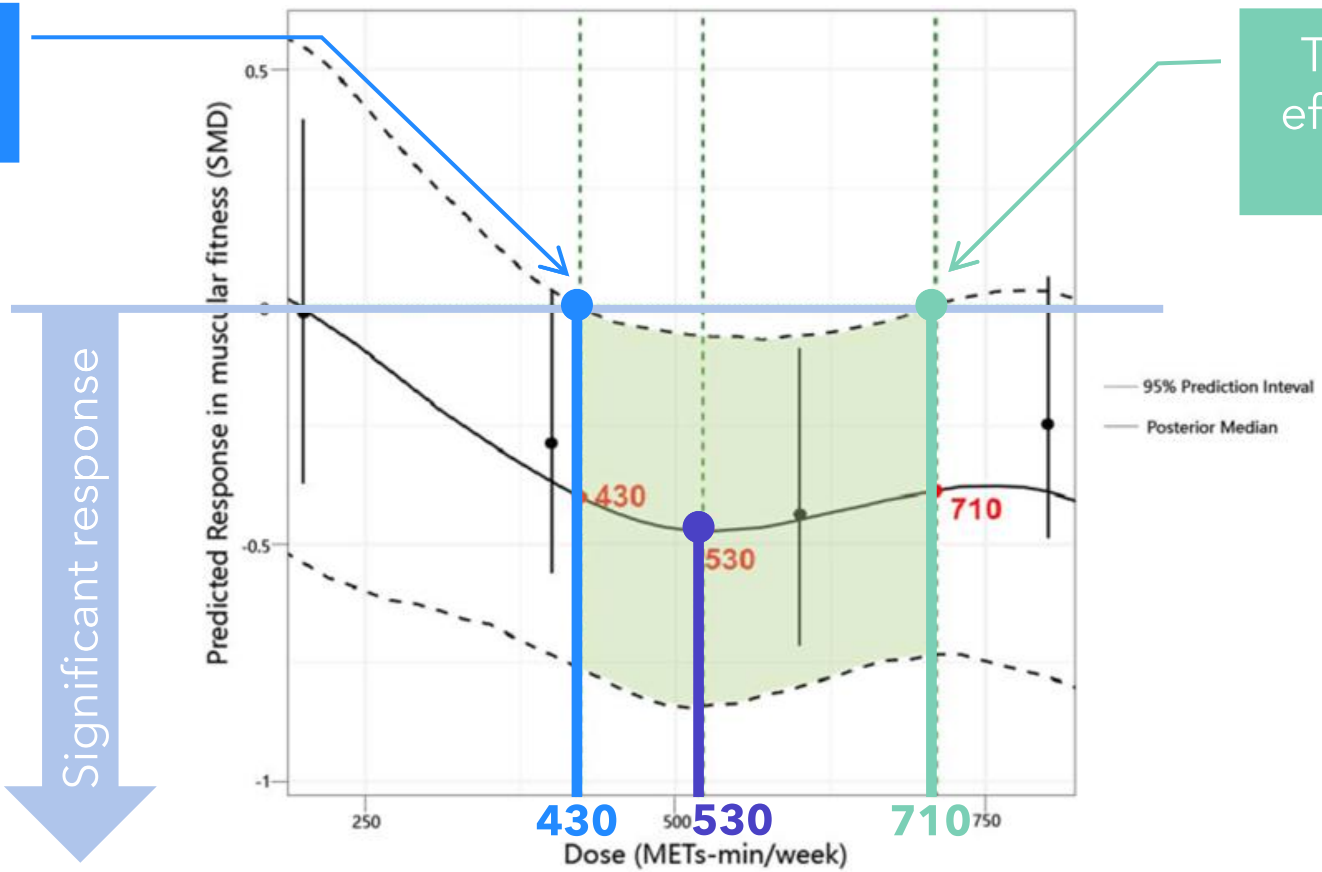
Optimal dose

Maximum safe dose

Prediction dose-response relationship
Muscular fitness

The upper limit of the 95% CrI *less than zero*

a significant response was observed starting at 430 METs-min/week



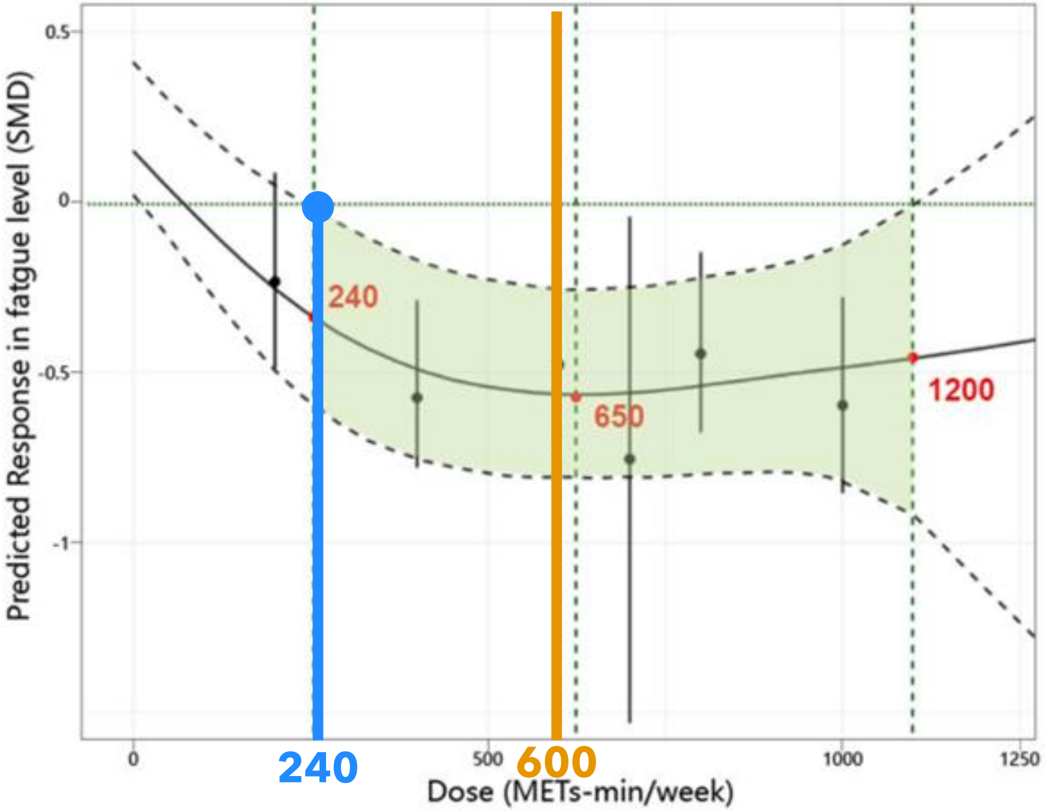
The increase in the effect of its influence *approached zero*

Minimum effective dose

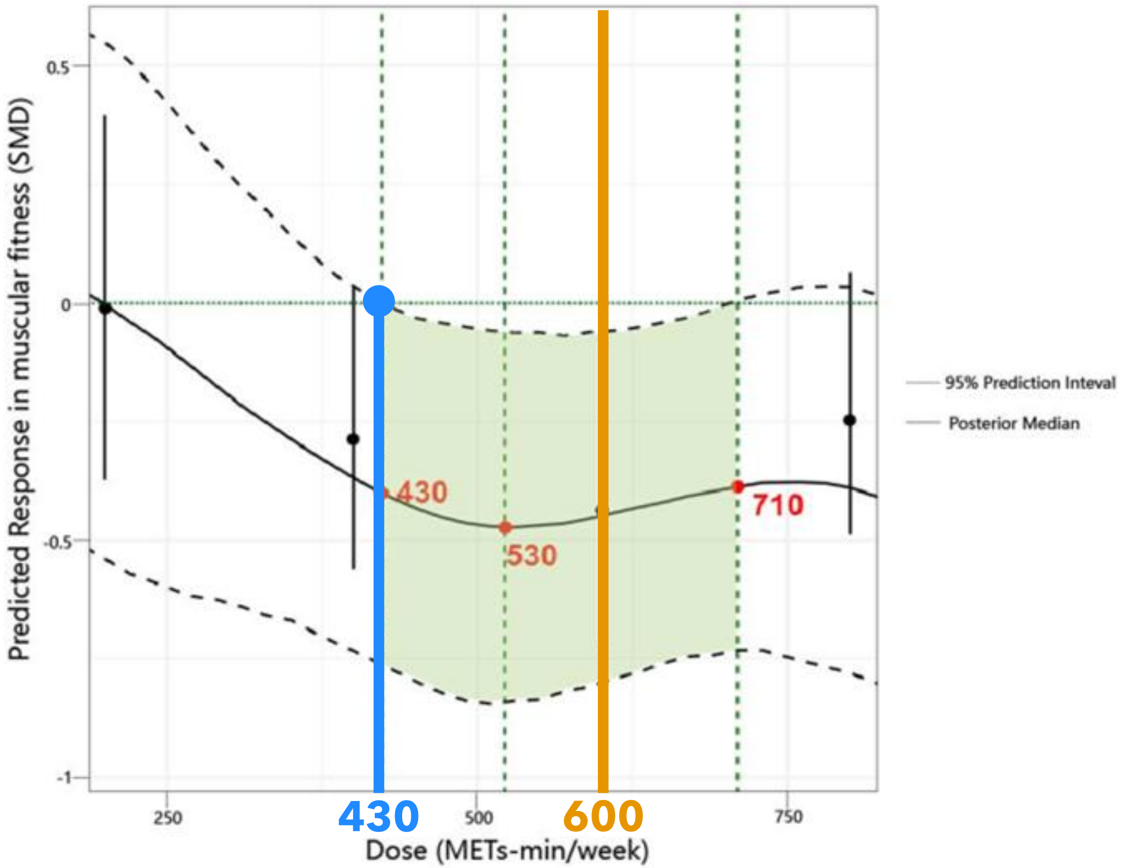
Optimal dose

Maximum safe dose

Current WHO guidelines = **600 – 1200 MET minutes** per week



Minimum effective dose



Minimum effective dose

In contrast to the WHO's recommended 600 METs-min/week, our findings indicate that a dose **as low as 240 METs-min/week** is *sufficient to improve fatigue* in patients, while **430 METs-min/week** can *enhance muscular fitness*.

Practical recommendation based on optimal dose

A. Exercise recommendations for reducing fatigue in patients with multiple sclerosis based on optimal dosage (650 METs-min/week).

Type of exercise	Intensity	Energy expenditure[a] (METs-min)	Optimal recommended accumulation[b] (min/week)	Minimum recommendations for exercise prescription[c] (sessions × min/per week)
MBE	Moderate	4 (code 02160)	~165	4 × ~40
				3 × ~55
RT	Moderate	3.5 (code 02054)	~190	4 × ~50
				3 × ~65
	Vigorous	6.5 (code 02057)	~100	4 × ~30
				3 × ~40
COM	Moderate	4.5 (mean of codes 01214, 02052)	~145	3 × ~50
	Vigorous	8 (mean of codes 01236, 02055)	~90	3 × ~30

The optimal dose for reducing fatigue = **650 METs-min/week**

Practical recommendation
based on optimal dose

B. Exercise recommendations for patients with multiple sclerosis to improve muscular fitness based on optimal dosage (530 METs-min/week).				
Type of exercise	Intensity	Energy expenditure[a] (METs-min)	Optimal recommended accumulation (min/ week)	Minimum recommendations for exercise prescription[b] (sessions x min/per week)
HIIT	Moderate	7 (code 02210)	~75	4 × ~20
				3 × ~25
	Vigorous	11 (code 02214)	~50	3 × ~20
				2 × ~25
COM	Moderate	4.5 (mean of codes 01214, 02052)	~120	3 × ~40
				2 × ~60
	Vigorous	8 (mean of codes 01236, 02055)	~70	3 × ~25
				2 × ~35
MBE	Moderate	4 (code 02160)	~135	3 × ~50
				2 × ~70

The optimal dose for improving muscular fitness = **530 METs-min/week**

Conclusion

- They confirmed the effectiveness of various exercise interventions in reducing fatigue levels and improving muscular fitness among patients with multiple sclerosis.
- There were no significant differences in efficacy among the different exercise modalities for either fatigue reduction or muscular fitness improvement.
- The findings revealed a nonlinear dose–response relationship between exercise and levels of fatigue as well as muscular fitness.

Conclusion

- The optimal dose
  - for reducing fatigue = 650 METs-min/week,
  - for improving muscular fitness = 530 METs-min/week
- Unlike the WHO's recommended 600 METs-min/week
  - A dose as low as 240 METs-min/week is sufficient to reduce fatigue
  - A dose as low as 430 METs-min/week is sufficient to enhance muscular fitness
- Future large-scale randomized controlled trials are needed to investigate the effects of different exercise doses on patients with MS.

Limitations

- The multidimensional nature of MS symptoms complicates its management. Cognitive and psychosocial dimensions could act as confounding variables or mediators in the associations.
  - However, they could not account for these confounding variables in their analysis.

Limitations

- The dose–response analysis for some exercises did not show significant effects.
  - This may be due to *the limitations of the exercises themselves*, or *an insufficient range of doses covered in the studies*, which may not have been enough to detect relevant and significant dose effects.
  - Should approach the results of dose predictions with caution and emphasize the need for future research to focus more on the impact of different exercise doses on MS patients.

Thank you