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Exercise and Multiple Sclerosis: Symptom Management or Disease Modification?

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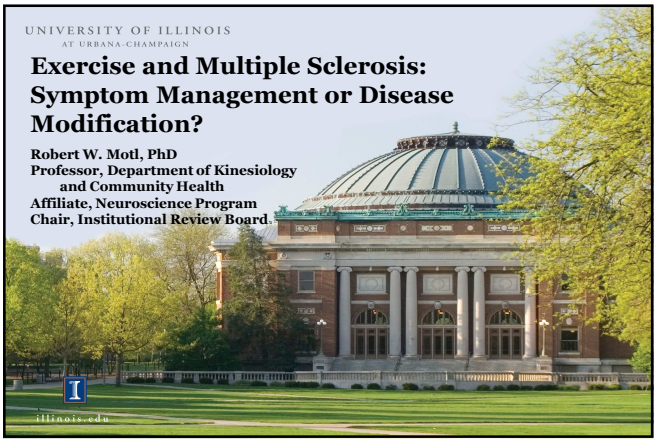

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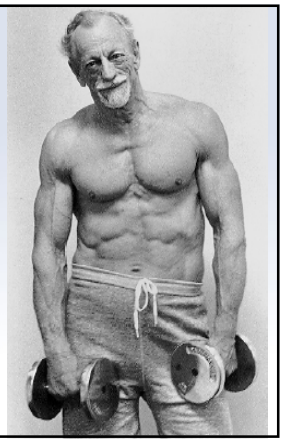
Disclosures

1. Speaker's bureau for EMD Serono
2. Consultant for Biogen Idec and Acorda Therapeutics
3. Funding from Biogen Idec, Acorda Therapeutics, Sun Health Technologies, NMSS, CMSC, and NIH
4. I secretly hope to look this good some day



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Overview

1. Framework
2. Exercise and Disease Modification
3. Exercise and Symptom Management
4. Participation Rates
5. Prescriptive Guidelines
6. Looking ahead: Next steps

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1. FRAMEWORK

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How Do We Evaluate the Questions?

Disease Modification*

- Progression of disability
- Relapse rate
- Neuroimaging metrics
  - Lesion volume
  - ROIs
- Animal models

Symptom Management

- Functioning
  - Fitness
  - Walking
  - Cognition
- Symptomology
  - Fatigue
  - Depression
- QOL

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*Based on a non-scientific survey of neurologists

Can We Evaluate the Questions? How Well?

Research Design

- Cross-sectional
- Prospective
- Quasi-experimental
- RCTs
- Duration of R_x
- 1° or 2° outcomes

Sample Characteristics

- Disability status
- Disease course
- Disease duration
- DMT or other medication
- Age/Sex

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2. EVIDENCE -- THE CASE FOR DISEASE MODIFICATION!

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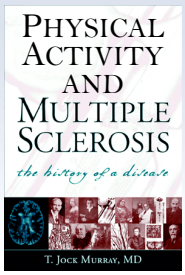
This is NOT a New Idea!



Exercise and disease progression in multiple sclerosis: can exercise slow down the progression of multiple sclerosis?

Ulrik Dalgas and Egon Stenager

Abstract: It has been suggested that exercise (or physical activity) might have the potential to have an impact on multiple sclerosis (MS) pathology and thereby slow down the disease process in MS patients. The objective of this literature review was to identify the literature linking physical exercise (or activity) and MS disease progression. A systematic literature search was conducted in the following databases: PubMed, SweMed+, Embase, Cochrane Library, PEDro, SPORTDiscus and ISI Web of Science. Different methodological approaches to the problem have been applied including (1) longitudinal exercise studies evaluating the effects on clinical outcome measures, (2) cross-sectional studies evaluating the relationship between fitness status and MRI findings, (3) cross-sectional and longitudinal studies evaluating the relationship between exercise/physical activity and disability/relapse rate and, finally, (4) longitudinal exercise studies applying the experimental autoimmune encephalomyelitis (EAE) animal model of MS. Data from intervention studies evaluating disease progression by clinical measures (1) do not support a disease-modifying effect of exercise; however, MRI data (2), patient-reported data (3) and data from the EAE model (4) indicate a possible disease-modifying effect of exercise, but the strength of the evidence limits definite conclusions. It was concluded that some evidence supports the possibility of a disease-modifying potential of exercise (or physical activity) in MS patients, but future studies using better methodologies are needed to confirm this.

Ther Adv Neurol Disord
(2012) 5(2) 81–95
DOI: 10.1177/1756285611420719

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Disability Progression

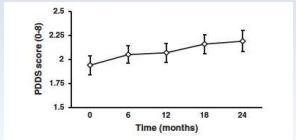

Fig. 1. Trajectory of linear change in Patient-Determined Disease Steps (PDDS) scale scores over 24-month period in 269 persons with relapsing–remitting multiple sclerosis. *Note.* Values are mean score with standard error of the mean.

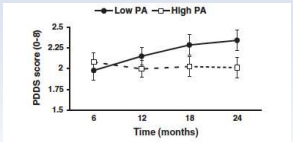

Fig. 2. Six-month change in Patient-Determined Disease Steps (PDDS) scale scores over a 24-month period in persons with relapsing–remitting multiple sclerosis who had low and high premorbid physical activities based on the lower and upper quartiles of scores for the Historical Leisure Activity Questionnaire, adjusting for baseline PDDS scores. *Note.* Values are mean score with standard error of the mean.

Independent of DMTs

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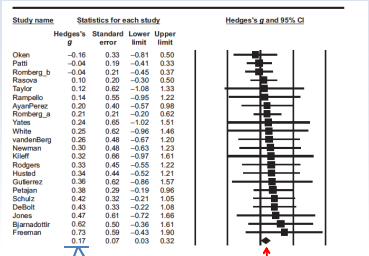
Motl et al, J Neurol Sci, 2012.

Walking Mobility (i.e., Disability)



2 times larger with supervision

MetaAnalysis

Snook & Motl, NNR, 2009.

Comparable with effect of DMTs

Relapse -- Systematic Review and Quantification

Number and rate of relapses, adverse events, and dropout reported per study.

Ref. no.	Relapses				Adverse events					Dropout			
	Total		Rate (%)		Total		Rate (%)		Type	Total		Rate (%)	
	CON	EX	CON	EX	CON	EX	CON	EX	EX	CON	EX	CON	EX
[4]	NR	NR	–	–	0	0	0.0	0.0		0	0	0.0	0.0
[5]	1	1	10.0	12.5	1	1	10.0	12.5	Illness	2	3	20.0	37.5
[6]	1	0	7.1	0.0	0	1	0.0	4.6	Stroke	2	0	14.3	0.0
[7]	3	3	20.0	10.0	0	0	0.0	0.0		6	6	40.0	20.0
[8]	1	0	7.7	0.0	0	0	0.0	0.0		1	2	7.7	13.3
[9]	NR	NR	–	–	0	1	0.0	5.3	low back pain	3	4	15.8	21.1
[10]	0	1	0.0	5.0	NR	NR	–	–		1	0	5.9	0.0
[11]	NR	NR	–	–	NR	NR	–	–		NR	NR	–	–
[12]	6	7	8.5	2.9	1	5	1.4	2.1	Ankle sprain	22	50	31.0	21.0
									Sacro-iliac joint pain; low back pain; hernia; RA flare-up; metatarsal fracture				
[13]	NR	NR	–	–	0	0	0.0	0.0		2	1	33.3	11.1
[14]	NR	NR	–	–	0	0	0.0	0.0		NR	NR	–	–
[15]	0	1	0.0	7.1	0	1	0.0	7.1	low back pain	0	2	0.0	14.3
[16]	0	0	0.0	0.0	1	0	7.7	0.0	Ankle sprain	1	0	7.7	0.0
[17]	0	0	0.0	0.0	0	0	0.0	0.0		5	6	31.3	37.5
[18]	NR	NR	–	–	0	2	0.0	10.0	Trigeminal neuralgia; illness	1	3	8.3	15.0
[19]	0	2	0.0	11.8	NR	NR	–	–		1	5	7.7	29.4
[20]	2	0	11.1	0.0	0	0	0.0	0.0		5	2	27.8	13.3
[21]	NR	NR	–	–	0	0	0.0	0.0		0	0	0.0	0.0
[22]	0	1	0.0	2.4	0	0	0.0	0.0		3	1	7.1	2.4
[23]	0	2	0.0	4.3	0	0	0.0	0.0		2	10	9.1	21.3
[24]	3	4	12.0	19.1	NR	NR	–	–		NR	NR	–	–
[25]	6	5	12.5	10.6	1	2	2.1	4.3	Knee pain	Traffic accident; upper respiratory tract infection	2	2	4.2	4.3
[26]	NR	NR	–	–	NR	NR	–	–			NR	NR	–	–
[27]	0	1	0.0	7.7	1	0	7.1	0.0	Pain		2	3	14.3	23.1
[28]	3	1	5.5	1.8	0	0	0.0	0.0			7	4	12.8	7.3
[29]	NR	NR	–	–	NR	NR	–	–			1	2	1.1	0.2

CON = control; EX = exercise; NR = not reported; RA = rheumatoid arthritis.

RR = .75
25% reduction in risk

Pilutti et al., J Neurol Sci, 2014.

Neuroimaging: T2 Lesion Volume

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Berengere Aubert-Broche, PhD
Damiano Fetco, MD
D. Louis Collins, PhD
Douglas L. Arnold, MD
Marcia Finlayson, PhD
Brenda L. Bassell, MD
Ruben W. Motl, PhD
E. Ann Yeh, MD

Objective: To evaluate the association between physical activity (PA) and multiple sclerosis (MS) disease activity, depression, and fatigue in a cohort of children with MS and monophasic acquired demyelinating syndrome (mono-ADS).

Methods: In this cross-sectional study of consecutive patients attending a specialized pediatric MS clinic, we administered the PedsQL Multidimensional Fatigue Scale, Center for Epidemiological Studies-Depression Scale, and Godin Leisure-Time Exercise Questionnaire. Quantitative MR analysis was performed to obtain whole brain and T2 lesion volume in a subset of participants (n = 60).

Results: A total of 110 patients (79 mono-ADS; 31 MS; 5–18 years; M:F 1:1.2) were included. Patients with MS reported less strenuous (33.21 ± 31.88 metabolic equivalents [METs] vs 15.97 ± 22.73 METs, $p = 0.002$) and total (44.48 ± 39.35 METs vs 67.28 ± 59.65 METs; $p = 0.0291$) PA than those with mono-ADS. Patients with MS who reported greater amounts of moderate PA METs had fewer sleep/rest fatigue symptoms ($r = -0.4$). Participation in strenuous PA was associated with smaller T2 lesion volumes ($r = -0.66$) and lower annualized relapse rate ($r = -0.66$). No associations were found between total brain volume and participation in PA.

Conclusions: Children with MS are less physically active than children with mono-ADS. Reasons for this are unclear, but may be related to ongoing disease activity, perceived limitations, or symptoms such as depression or fatigue. Children with MS reporting higher levels of strenuous PA had lower T2 lesion volumes and lower relapse rates, suggesting a potential protective effect of strenuous PA in this population. Further longitudinal studies are needed to establish the relationship of PA to MS symptoms and disease activity in this population. *Neurology® 2015;85:1–7*

Research Report

Aerobic fitness is associated with gray matter volume and white matter integrity in multiple sclerosis

Ruchika Shaurya Prakash*,†, Erin M. Snook[b], Robert W. Motl[c], Arthur F. Kramer[d]

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Neuroimaging: ROIs

Cardiorespiratory fitness and its association with thalamic, hippocampal, and basal ganglia volumes in multiple sclerosis

Robert W. Motl[a,*], Lara A. Pilutti[a], Elizabeth A. Hubbard[a], Nathan C. Wetter[b], Jacob J. Sosnoff[b], Bradley P. Sutton[b]

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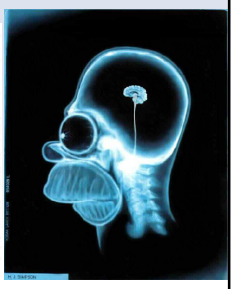
ABSTRACT

Background: There is little known about cardiorespiratory fitness and its association with volumes of the thalamus, hippocampus, and basal ganglia in multiple sclerosis (MS). Such inquiry is important for identifying a possible behavioral approach (e.g., aerobic exercise training) that might change volumes of deep gray matter (DGM) structures associated with cognitive and motor functions in MS.
Purpose: This study examined the association between cardiorespiratory fitness and volumes of the thalamus, hippocampus, and basal ganglia in MS.
Method: We enrolled 35 persons with MS who underwent a maximal exercise test for measuring cardiorespiratory fitness as peak oxygen consumption (VO_{2peak}) and brain MR. Volumes of the thalamus, hippocampus, caudate, putamen, and pallidum were calculated from 3D T1-weighted structural brain images. We examined associations using partial (pr) correlations controlling for demographic and clinical variables.
Results: VO_{2peak} was significantly associated with composite scaled volumes of the caudate ($pr = .47$, $p < .01$), putamen ($pr = .46$, $p < .05$), pallidum ($pr = .40$, $p < .05$), and hippocampus ($pr = .42$, $p < .05$), but not thalamus ($pr = .31$, $p = .09$), when controlling for sex, age, disability, and duration of MS.
Conclusion: Our results provide novel evidence that cardiorespiratory fitness is associated with volumes of DGM structures that are involved in motor and cognitive functions in MS.



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Neuroimaging: ROIs

Objectively Measured Physical Activity Is Associated with Brain Volumetric Measurements in Multiple Sclerosis

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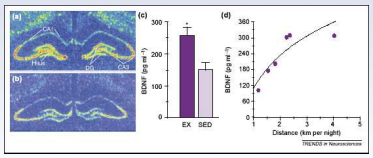
TABLE 2: Correlations between levels of physical activity and scaled composite volumes of normalized brain volume measures in 39 persons with MS.

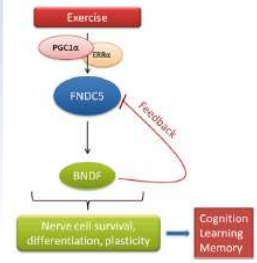
Variable	Model 1			Model 2			Model 3		
	MVPA (min/day)	Light physical activity (min/day)	Sedentary behavior (min/day)	MVPA (min/day)	Light physical activity (min/day)	Sedentary behavior (min/day)	MVPA (min/day)	Light physical activity (min/day)	Sedentary behavior (min/day)
NGMV (mm^3)	.304	.215	−.099	.297	.167	−.156	.370*	.219	.059
NWMV (mm^3)	.418**	.235	.124	.359*	.126	−.029	.433**	.171	.281
Hippocampus (mm^3)	.325*	.140	−.046	.284	.065	−.151	.499**	.018	.164
Thalamus (mm^3)	.404*	.163	.078	.352*	.065	−.058	.380*	.024	.228
Caudate (mm^3)	.418*	.267	−.065	.405**	.227	−.123	.539**	.198	.099
Putamen (mm^3)	.341*	.218	.015	.303	.144	−.072	.369*	.168	.125
Pallidum (mm^3)	.454**	.198	.162	.407**	.074	.027	.498**	.145	.253

Note: Model 1 = Pearson product-moment correlations (r); Model 2 = partial Pearson product-moment correlations (pr), controlling for days of valid accelerometer data and accelerometer wear time; Model 3 = partial Pearson product-moment correlations (pr), controlling for sex, age, clinical course of MS, and EDSS; **correlation is significant at the 0.01 level (2-tailed); *correlation is significant at the 0.05 level (2-tailed); MS = multiple sclerosis; MVPA = moderate-to-vigorous physical activity; NGMV = normalized gray matter volume; NWMV = normalized white matter volume.

How Could Exercise Influence the Brain in MS?



Cotman & Berchtold, Trends Neurosci, 2002.



Wrann et al., Cell Metab, 2013.

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Preclinical Research: Exercise and Animal Models

Review article

Effects of exercise in experimental autoimmune encephalomyelitis (an animal model of multiple sclerosis)

Rachel E. Klaren [a], Robert W. Motl [a,*], Jeffrey A. Woods [a], Stephen D. Miller [b]

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ABSTRACT

Exercise training has improved many outcomes in "clinical" research involving persons with multiple sclerosis (MS), but there is limited understanding of the underlying "basic" pathophysiological mechanisms. The animal model of MS, experimental autoimmune encephalomyelitis (EAE), seems ideal for examining the effects of exercise training on MS disease pathophysiology. EAE is an autoimmune T helper cell-mediated disease characterized by T-cell and macrophage infiltration and inflammation in the CNS. To that end, this paper briefly describes common models of EAE, reviews existing research on exercise and EAE, and then identifies future research directions for understanding the consequences of exercise training using EAE.

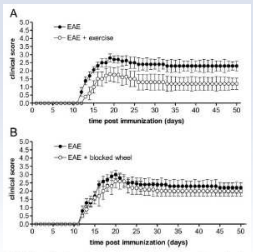

Fig. 1. Effects of exercise on EAE-induced motor deficits. A. The graph shows that the severity of EAE-induced clinical disturbances was attenuated in both acute and chronic phases of EAE in exercising mice ($n = 10$ mice for both groups, $p < 0.05$ at each time point starting from 12 dpi). The animals were randomly allocated to the two experimental groups the same day. B. EAE mice reared in cages equipped with a wheel with blocked movement developed motor deficits that were similar to those seen in mice in standard cages ($n = 10$ mice for both groups, $p > 0.05$ at each dpi). The animals were randomly allocated to the two experimental groups the same day.

Rossi et al, Neurobiol Dis, 2009.

3. EVIDENCE -- THE CASE FOR SYMPTOM MANAGEMENT!

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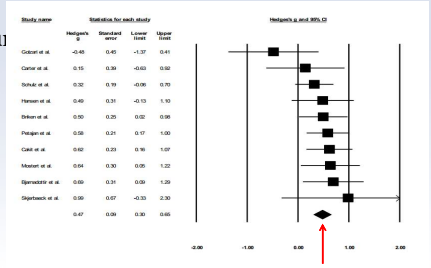
Aerobic Capacity

- Pictu



Favorable effect of exercise training

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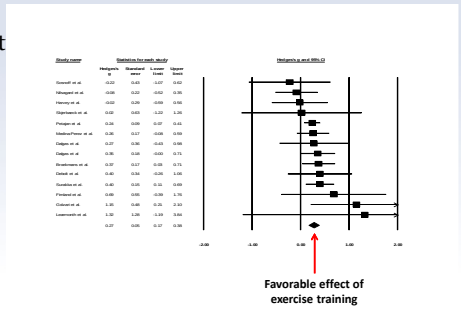
Platta et al., Med Sci Sports Exerc, 2015.

Muscle Strength

- Pict



Favorable effect of exercise training

Platta et al., Med Sci Sports Exerc, 2015.

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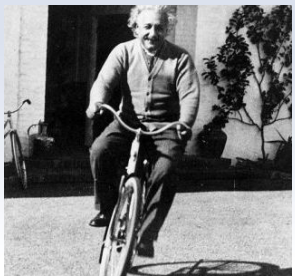
Other Outcomes: Cognition and Balance

Cognitive dysfunction and multiple sclerosis: developing a rationale for considering the efficacy of exercise training

Robert W Motl[1], Brian M Sandroff[1] and Ralph HB Benedict[2]

Abstract

Cognitive impairment is a prevalent, disabling, and poorly managed consequence of multiple sclerosis (MS). This underscores the importance of considering alternative approaches, such as exercise training, for managing cognitive impairment in persons with MS. The consideration of exercise training is warranted based on evidence summarized in literature reviews and meta-analyses that (1) aerobic fitness, physical activity, and exercise training are associated with better cognitive function in older adults; and (2) exercise training has comparable effects on mobility and quality of life outcomes in older adults and persons with MS. To date, research examining aerobic fitness, physical activity, and exercise training effects on cognition in MS is nascent and mostly includes cross-sectional designs that provide preliminary evidence for a well-designed randomized controlled trial (RCT). We believe that a future RCT should adopt research methodologies and practices from gerontology when examining exercise training and cognition in MS. This will maximize the potential for successfully generating a body of knowledge on exercise training and cognition with the potential for impacting the lives of persons with MS.



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Symptomatic Fatigue

Study name	Hedges's g	Standard error	Lower limit	Upper limit
Schulz et al. (2004)	-0.095	0.380	-0.840	0.650
Van den Berg et al. (2006)	-0.010	0.500	-0.990	0.970
Romberg et al. (2005)	0.040	0.210	-0.372	0.452
Petajan et al. (1996)	0.085	0.300	-0.503	0.673
Cakit et al. (2010)	0.099	0.316	-0.520	0.719
Geddes et al. (2009)	0.110	0.610	-1.086	1.306
Dettmers et al. (2009)	0.190	0.370	-0.535	0.915
Oken et al. (2004)	0.200	0.231	-0.253	0.652
Dalgas et al. (2010)	0.419	0.367	-0.301	1.138
Dodd et al. (2011)	0.480	0.240	0.010	0.950
Bjarnadottir et al. (2007)	0.490	0.520	-0.529	1.509
Learmonth et al. (2012)	0.656	0.419	-0.164	1.477
McCullagh et al. (2008)	0.753	0.218	0.326	1.180
Sutherland et al. (2001)	0.855	0.450	-0.028	1.738
Ahmadi et al. (2010)	1.270	0.480	0.329	2.211
Mostert & Kesselring (2002)	1.270	0.453	0.383	2.157
Kargarfard et al. (2012)	2.148	0.549	1.073	3.223
	0.452	0.116	0.224	0.680

Hedges's g and 95% CI

-4.00 -2.00 0.00 2.00 4.00

Favorable effect of exercise training

Figure 2. Average effect size, standard errors, an… from 17 studies included in the meta-analysis. CI = confidence interval.

Clinically Meaningful?

Pilutti et al., Psychosomatic Med, 2013.

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Exercise vs. Other Approaches

Meta-Analysis of Three Different Types of Fatigue Management Interventions for People with Multiple Sclerosis: Exercise, Education, and Medication

Mike Asano and Marcia L. Finlayson

TABLE 1: A summary of three types of intervention trials.

	Exercise intervention trials [25–34]	Educational intervention trials [35–42]	Pharmacological intervention trials (Amantadine or Modafinil) [43–49]
N trials included in the review	10	8	7
N samples included in the analyses	233	662	604*
ES (range)	−0.24 to 2.05	−0.16 to 1.31	−0.59 to 0.55
Pooled ES (random effects)	0.57	0.54	0.07
95% CI for the pooled ES	0.10 to 1.04	0.30 to 0.77	−0.22 to 0.37
P value	0.02	<0.001	0.63
Heterogeneity	Yes ($Q = 26.39$, $P = 0.003$; $I^2 = 65\%$)	Yes ($Q = 14.14$, $P = 0.04$; $I^2 = 50\%$)	Yes ($Q = 18.66$, $P = 0.004$; $I^2 = 67\%$)
Publication bias	No (Egger bias = 5.36, $P = 0.13$; Begg-Mazumdar = 0.29, $P = 0.29$)	No (Egger bias = 1.14, $P = 0.54$; Begg-Mazumdar = 0.21, $P = 0.55$)	No (Egger bias = −1.54, $P = 0.57$; Begg-Mazumdar = −0.24, $P = 0.38$)
N trials screened for the presence of fatigue as an eligibility criterion (%)	1 (10%)	6 (75%)	7 (100%)
Most common outcome used in the trials (*n*, %)	FSS (6, 60%)	MFIS (4, 50%)	FSS (5, 71%)
N of effective trials (%)	3 (30%)	6 (75%)	1 (14%)

*Include one trial reporting the outcome in a total cross-over sample combined together.

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Depressive Symptoms

Study name	Hedges's g	Standard error	Lower limit	Upper limit
Dettmers et al (2009)	-0.250	0.460	-1.152	0.652
Romberg et al (2005)	-0.072	0.205	-0.475	0.330
Cakit et al (2010)	0.056	0.314	-0.559	0.671
Hebert et al (2011)	0.092	0.392	-0.677	0.861
Oken et al (2004)	0.157	0.162	-0.161	0.476
Learmonth et al (2012)	0.335	0.260	-0.174	0.844
Sutherland et al (2001)	0.510	0.433	-0.339	1.360
Petajan et al (1996)	0.561	0.174	0.219	0.902
Ahmadi et al (2013)	0.561	0.319	-0.063	1.186
Skjerbaek et al (2013)	0.642	0.419	-0.179	1.462
Schulz et al (2004)	0.649	0.296	0.068	1.229
Dalgas et al (2010)	0.667	0.369	-0.056	1.390
Brikon et al (2013)	0.869	0.268	0.344	1.394
	0.360	0.092	0.180	0.540

Hedges's g and 95% CI

-1.50 -0.75 0.00 0.75 1.50

Favorable effect of exercise training

…nd overall effect sizes.

2 times larger with PAGs

Ensari et al., J Psychosomatic Res, 2014.

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Walking Ability

Exercise as a Therapy for Improvement of Walking Ability in Adults With Multiple Sclerosis: A Meta-Analysis

Melissa Pearson, BSc Hons, Gudrun Dieberg, PhD, Neil Smart, PhD

From the University of New England, School of Science and Technology, Armidale, New South Wales, Australia.

Abstract

Objective: To quantify improvements in walking performance commonly observed in patients with multiple sclerosis (pwMS), a systematic literature search and meta-analysis were conducted quantifying the expected benefits of exercise on walking ability in pwMS.

Data Sources: Potential studies were identified by systematic search using PubMed (1966 to March 31, 2014), EMBASE (1974 to March 31, 2014), CINAHL (1998 to March 31, 2014), SPORTDiscus (1991 to March 31, 2014), and the Cochrane Central Register of Controlled Trials (1966 to March 31, 2014). The search used key concepts of "multiple sclerosis" AND "exercise."

Study Selection: Randomized controlled trials of exercise training in adult pwMS.

Data Extraction: Data on patient and study characteristics, walking ability, 10-m walk test (10mWT), timed 25-foot walk test (T25FW), 2-minute walk test (2MWT), 6-minute walk test (6MWT), and timed Up and Go (TUG) were extracted and archived.

Data Synthesis: Data from 13 studies were included. In pwMS who exercised, significant improvements were found in walking speed, measured by the 10mWT (mean difference [MD] reduction in walking time of −1.76s; 95% confidence interval [CI], −2.47 to −1.06; $P<.001$), but no change in the T25FW (MD=−.59s; 95% CI, −2.55 to 1.36; $P=.55$). In pwMS who exercised, significant improvements were found in walking endurance as measured by the 6MWT and 2MWT, with an increased walking distance of MD=36.66m (95% CI, 15.14–57.79; $P<.001$) and MD=12.51m (95% CI, 4.79–20.23; $P=.001$), respectively. No improvement was found for TUG (MD=−1.05s; 95% CI, −2.19 to .09; $P=.07$).

Conclusions: Our meta-analysis suggests that exercise improves walking speed and endurance in pwMS.

Archives of Physical Medicine and Rehabilitation 2015;96:1339–60

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Exercise improves walking endurance and speed

- **2MWT: 12.5 meters father or 19% improvement**
- **10mWT: 1.76 seconds faster or 16.5% improvement***

***Approaches a meaningful change per stages in Goldman et al. (2013), Neurology.**

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Quality of Life

Effect of exercise training on quality of life in multiple sclerosis: a meta-analysis

RW Motl and JL Gosney

Using meta-analytic procedures, this study examined the overall effect of exercise training interventions on quality of life (QOL) among individuals with multiple sclerosis (MS). We searched MEDLINE, PSYCHINFO and CURRENT CONTENTS PLUS for the period of 1960 to November 2006 using the key words exercise, physical activity and physical fitness in conjunction with QOL and MS. We further conducted a manual search of bibliographies of the retrieved papers as well as literature reviews and contacted study authors about additional studies. Twenty-five journal articles were located and reviewed, and only 13 provided enough data to compute effect sizes expressed as Cohen's *d*. One hundred and nine effect sizes were retrieved from the 13 studies with 484 MS participants and yielded a weighted mean effect size of $g = 0.23$ (95% CI = 0.15, 0.31). There were larger effects associated with MS-specific measures of QOL and fatigue as an index of QOL. The nature of the exercise stimulus further influenced the magnitude of the mean effect size. The cumulative evidence supports that exercise training is associated with a sm[illegible] individuals with MS. *Multiple Sclerosis* 2008; **14**: 129–135. http://m[illegible]

The Real End-Point, but not a large change

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Motl & Gosney, Mult Scler, 2008.

Other Outcomes

Effects of Exercise Training on Fitness, Mobility, Fatigue, and Health-Related Quality of Life Among Adults With Multiple Sclerosis: A Systematic Review to Inform Guideline Development

Amy E. Latimer-Cheung, PhD,[a] Lara A. Pilutti, PhD,[b,c] Audrey L. Hicks, PhD,[b] Kathleen A. Martin Ginis, PhD,[b] Alyssa M. Fenuta, HBSc,[b] K. Ann MacKibbon, PhD,[b] Robert W. Motl, PhD[c]

From the [a]School of Kinesiology and Health Studies, Queen's University, Kingston, Ontario; [b]Department of Kinesiology, McMaster University, Hamilton, Ontario, Canada; and [c]Department of Kinesiology and Community Health, University of Illinois at Urbana-Champaign, Urbana, IL.

Abstract

Objective: To conduct a systematic review of evidence surrounding the effects of exercise training on physical fitness, mobility, fatigue, and health-related quality of life in adults with multiple sclerosis (MS).

Data Sources: The databases included EMBASE, 1980 to 2011 (wk 12); Ovid MEDLINE and Ovid OLDMEDLINE, 1947 to March (wk 3) 2011; PsycINFO, 1967 to March (wk 4) 2011; CINAHL all-inclusive; SPORTDiscus all-inclusive; Cochrane Library all-inclusive; and Physiotherapy Evidence Database all-inclusive.

Study Selection: The review was limited to English-language studies (published before December 2011) of people with MS that evaluated the effects of exercise training on outcomes of physical fitness, mobility, fatigue, and/or health-related quality of life.

Data Extraction: One research assistant extracted data and rated study quality. A second research assistant verified the extraction and quality assessment.

Data Synthesis: From the 4362 studies identified, 54 studies were included in the review. The extracted data were analyzed using a descriptive approach. There was strong evidence that exercise performed 2 times per week at a moderate intensity increases aerobic capacity and muscular strength. The evidence was not consistent regarding the effects of exercise training on other outcomes.

Conclusions: Among those with mild to moderate disability from MS, there is sufficient evidence that exercise training is effective for improving both aerobic capacity and muscular strength. Exercise may improve mobility, fatigue, and health-related quality of life.

Archives of Physical Medicine and Rehabilitation 2013;94:1800-28

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Summarizing and Linking the Pieces Together

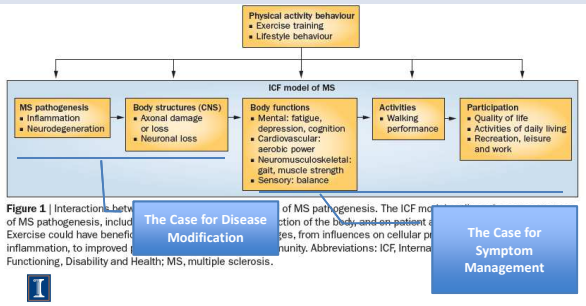

Figure 1 | Interactions betw[illegible] of MS pathogenesis. The ICF mo[illegible] of MS pathogenesis, includ[illegible]ction of the body, and on patient [illegible] Exercise could have benefi[illegible]tes, from influences on cellular p[illegible] inflammation, to improved [illegible]unity. Abbreviations: ICF, Interna[illegible] Functioning, Disability and Health; MS, multiple sclerosis.

The Case for Disease Modification

The Case for Symptom Management

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Motl & Pilutti, Nat Rev Neurol, 2013.

4. PARTICIPATION RATES

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Overall Physical Activity

Physical activity and multiple sclerosis: a meta-analysis

Robert W Motl, Edward McAuley and Erin M Snook*
Department of Kinesiology, University of Illinois at Urbana-Champaign, Urbana, IL, USA

Using meta-analytic procedures, this study involved a quantitative synthesis of the difference in physical activity among individuals with multiple sclerosis (MS) compared with nondiseased and diseased populations and then examined factors (i.e., moderators) that explain variation in the overall difference in physical activity. We searched MEDLINE, PsycINFO and Current Contents Plus using the key words physical activity, exercise and physical fitness in conjunction with multiple sclerosis; conducted a manual search of bibliographies of the retrieved papers; and contacted study authors about additional studies. Overall, 53 effects were retrieved from 13 studies with 2360 MS participants and yielded a weighted mean effect size (ES) of −0.60 (95% CI = −0.44, −0.77). The weighted mean ES was heterogenous, $Q = 1164.11$, $df = 52$, $P < 0.0001$. There were larger effects with objective versus self-report measures of physical activity, nondiseased versus diseased populations and primary progressive versus relapsing–remitting MS. The cumulative evidence suggests that individuals with MS are less physically active than nondiseased, but not diseased, populations.

Multiple Sclerosis *(2005)* **11**, 459–463

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The general population is physically inactive (60%)!

Moderate-to-Vigorous Physical Activity

Objectively Quantified Physical Activity in Persons With Multiple Sclerosis

Rachel E. Klaren, BS, Robert W. Motl, PhD, Deirdre Dlugonski, PhD, Brian M. Sandroff, MS, Lara A. Pilutti, PhD

From the Department of Kinesiology and Community Health, University of Illinois at Urbana-Champaign, Urbana, IL.

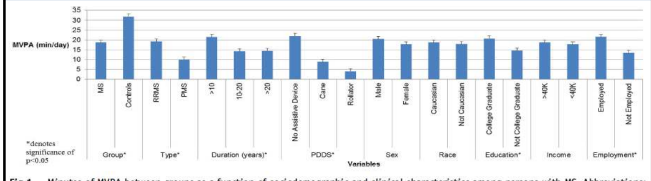

Fig 1 Minutes of MVPA between groups as a function of sociodemographic and clinical characteristics among persons with MS. Abbreviations: PMS, progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis. *Significance of $P < .05$.

5. PRESCRIPTIVE GUIDELINES

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Canadian Guidelines: Process

1. Systematic review as evidence base for guidelines
2. Consensus meeting of panel and unanimous agreement
3. Stakeholder involvement (exercise professionals, physicians, service providers) for rating consistency between evidence and guidelines
4. Additional feedback from adults with MS (N=112), health professionals (N=125), and others (N=28)
5. AGREE II evaluation

McMaster University

Development of Evidence-Informed Physical Activity Guidelines for Adults With Multiple Sclerosis

Amy E. Latimer-Cheung, PhD,[a] Kathleen A. Martin Ginis, PhD,[b] Audrey L. Hicks, PhD,[b] Robert W. Motl, PhD,[c] Lara A. Pilutti, PhD,[b,c] Mary Duggan,[d] Garry Wheeler, PhD,[e] Ravin Persad, BASc,[f] Karen M. Smith, MD[g,h]

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Canadian Guidelines: Product

	Aerobic Activity	Strength Training Activity
How often?	Two times per week • Aerobic and strength training activities can be done on the same day • Rest your muscles for at least one day between strength training sessions	Two times per week
How much?	Gradually increase your activity so that you are doing at least 30 minutes of aerobic activity during each workout session.	Repetitions are the number of times you lift and lower a weight. Try to do 10-15 repetitions of each exercise. This counts as 1 set. Gradually work up to doing 2 sets of 10-15 repetitions of each exercise.
How hard?	These activities should be performed at a moderate intensity. Moderate-intensity physical activity is usually a 5 or 6 on a scale of 10, and causes your heart rate to go up. As a general rule if you're doing moderate-intensity activity you can talk, but not sing a song, during the activity.	Pick a resistance (free weights, cable pulleys, bands, etc.) heavy enough that you can barely, but safely, finish 10-15 repetitions of the last set. Be sure to rest for 1-2 minutes between each set and exercise.
How to?	Some options for activity include: Aerobic activities • Upper Body Exercises: arm cycling • Lower Body Exercises: walking, leg cycling • Combined Upper and Lower body exercises: elliptical trainer	Strength training activities for the upper and lower body • Weight machines • Free weights • Cable pulleys
	Other types of exercise that may bring benefits • Elastic resistance bands • Aquatic exercise • Calisthenics	

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6. LOOKING AHEAD: NEXT STEPS

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Direct Comparison with Drug

Comparative effectiveness of exercise and drug interventions on mortality outcomes: metaepidemiological study

OPEN ACCESS

Huseyin Naci *researcher*[1] *fellow*[2], John P A Ioannidis *director*[3]

[1]LSE Health, London School of Economics and Political Science, London, UK; [2]Drug Policy Research Group, Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA, USA; [3]Stanford Prevention Research Center, Stanford University School of Medicine, Stanford, CA, USA

The findings of our review suggest that exercise and many drug interventions are often potentially similar in terms of their mortality benefits; exercise interventions should therefore be considered as a viable alternative to, or alongside, drug therapy.

Given the scarcity of financial resources to fund future trials of exercise interventions, one option would be to require such evidence from pharmaceutical companies that are under increasing pressure to perform active-comparator trials for market entry.[67 68] For example, regulators should consider requiring pharmaceutical sponsors of new drugs to include exercise interventions as an active comparator arm in drug trials. In cases where drug options provide only modest benefit, patients deserve to understand the relative impact that physical activity might have on their condition.

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Mechanistic Research

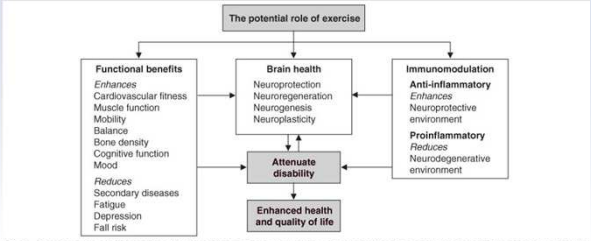

Fig. 1. A conceptual model highlighting the hypothetical effects of exercise in improving health, mobility and modulating disease activity in multiple sclerosis.

White & Castellano, Sports Med, 2008.

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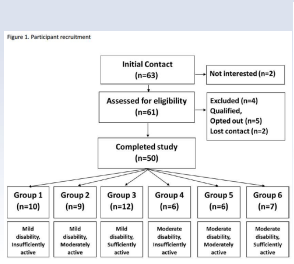
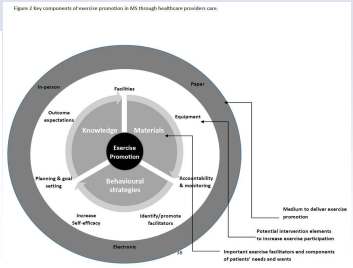
Project VIEWS: Views and Ideas on Exercise among people with MS





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NMSS, IL 0017

Project COMPLETe: Coordinate Multiple Sclerosis Exercise Toolkit

Objectives

1. Develop a conceptual model
2. Develop a tool kit
3. Evaluate the efficacy of the toolkit

Methods

- Qualitative research
  - Patients – VIEWS
  - Providers – Stage 2
  - Model – Stage 3
  - Tool kit – Stage 4
- RCT
  - Tool kit efficacy – Stage 5

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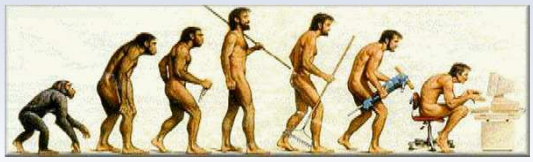
NMSS, Health Care Delivery and Policy Research mechanisms

Sit Less, Move More!



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The Health and Wellness Initiative

National Multiple Sclerosis Society

- 1st meeting, October, 2014
- 2nd meeting, October 2015
- Makeover from programs through research

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- Participants!
- Undergraduate students, graduate students, post-doctoral fellows, and colleagues.
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Thank you and questions

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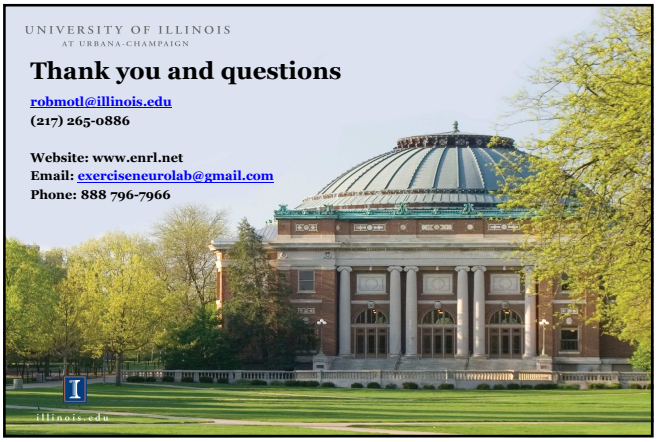

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