Exploring the Role of Physical Activity and Exercise for Managing Vascular Comorbidities in People with Multiple Sclerosis: A Scoping Review

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Background

- Vascular comorbidities are prevalent among people with multiple sclerosis (MS) and have adverse disease-related consequences:
  - These include diagnostic delays, increased relapse risk and disability progression, reduced health-related quality of life, and increased mortality risk (1).
- In the general population, physical activity (PA) and exercise training have proven highly beneficial at all levels of vascular disease risk management (2).
- People with MS participate in less PA and have lower physical fitness levels compared to non-diseased individuals, and both PA and fitness have been associated with disability status and disease progression (3). Consequently, PA and exercise represent behavioral targets for potentially managing vascular comorbidities and their consequences in people with MS.

Objective

To conduct a scoping review of existing evidence linking PA and exercise training to potential modification of vascular comorbidities and related risk factors in people with MS.

Methods

- Five electronic databases were searched from inception to Nov 2017.
- Search terms: "multiple sclerosis" AND "physical activity" OR "exercise" OR "fitness" OR "sedentary" OR "sitting" AND "vascular comorbidity" OR "obesity" OR "body mass index" OR "hyperlipidemia" OR "cholesterol" OR "heart disease" OR "atherosclerosis" OR "hypertension" OR "high blood pressure" OR "diabetes" OR "glucose resistance".
- Data were summarized by both vascular comorbidity subcategory and study design (observational vs. interventional).

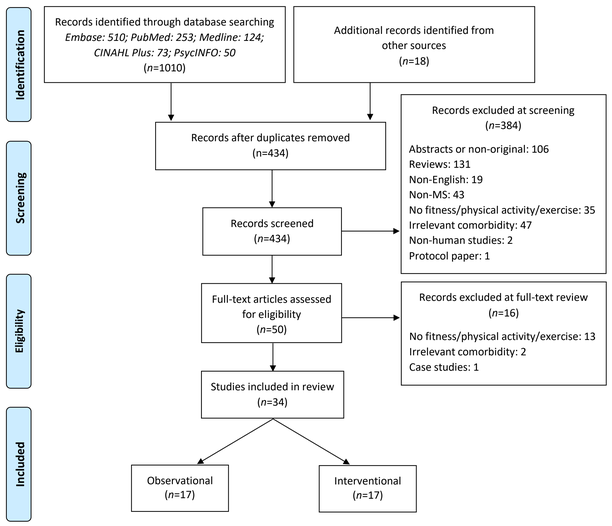


Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram depicting literature search and review process.

Results

- **Observational Studies (*n*=17)**
  - **Total Comorbidity (n=3) Obesity (*n*=12), Hyperlipidemia (*n*=2), Vascular Function/ Hypertension (*n*=1), Diabetes (*n*=1)**
  - **Data supporting a beneficial role for PA/fitness could be drawn from each comorbidity category.**
- **Interventional Studies (*n*=17)**
  - **Obesity (*n*=17), Hyperlipidemia (*n*=3), Vascular Function/Hypertension (*n*=4), Diabetes (*n*=4)**
  - **Modality highly variable (aerobic vs. resistance vs. combination vs. specialty [e.g. yoga, behavioral])**
  - **8-52 wks; 2-3 x/wk; <30-90 mins/session**

Ref.	*n*	Vascular Comorbidity: Type	Vascular Comorbidity: Measure	PA / Fitness Measure	Key Findings

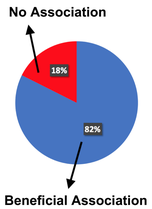
Balto et al. (2017)	69	Total Comorbidity (incl. Hyperlipidemia, Vascular Function/Hypertension, Diabetes)	Health history questionnaire, comorbidity questionnaire for MS	GLTEQ	↓ PA ↔ ↑ total # comorbidities (p<0.01)
					PA = # cardiovascular disease symptoms (p=0.10)

Marck et al. (2016)	2399	Total Comorbidity (incl. Vascular Function/Hypertension, Diabetes)	Self-Administered Comorbidity Questionnaire	IPAQ	↑ PA ↔ ↓ total # comorbidities (p=0.054)
Motl et al. (2011)	561	Total Comorbidity (incl. Vascular Disease/Hypertension)	Self-reported questionnaire	GLTEQ, Accelerometer	↓ PA (accelerometer) ↔ ↑ # cardiovascular comorbidities (r=–0.192/-0.225, p<0.01, OR1.4) ↓ PA (GLTEQ) ↔ ↑ # cardiovascular comorbidities (r=–0.161/-0.151, p<0.01, OR1.3)
Balto et al. (2016)	69	Obesity	BMI	GLTEQ	PA rates ↔ BMI (χ^2=4.9, p<0.05)
Hubbard et al. (2015)	1081	Obesity	BMI	Self-reported sitting time (IPAQ)	↑ sitting time ↔ ↑ BMI (p=0.009)
Kalron (2017)	436	Obesity	BMI	2MWT, 6MWT	↓ 2MWT/6MWT distance ↔ ↑ BMI (both p≤0.001)
Marck et al. (2014)	2232	Obesity	BMI	IPAQ	↓ PA ↔ ↑ BMI (p<0.001)
Pilutti et al. (2015)	64	Obesity	Body composition (%BF, fat mass, lean soft tissue, via DXA)	VO_{2peak}	VO_{2peak} ↔ %BF (r=–0.69/r=–0.65), fat mass (r=–0.50/r=–0.49), and lean soft tissue (r=0.41/r=0.37) (all p<0.05)
Schwartz et al. (2013)	563	Obesity	BMI	GLTEQ	↑ PA ↔ ↑ normal BMI (p<0.0001) ↓ PA ↔ ↑ obese BMI (p<0.001)
Snook et al. (2005)	34	Obesity	BMI, body composition (%BF, trunk fat, via DXA), waist circ.	GLTEQ, Pedometer, Accelerometer,	↑ PA (GLTEQ, pedometer, and accelerometer) ↔ ↓ BMI, %BF, trunk fat, and waist circ. (all p<0.05)
Ward et al. (2013)	25	Obesity	Body composition (%BF, lean mass-leg, via DXA)	Pedometer, 6MWT	PA (step-counts) = %BF, lean mass-leg/body mass ratio 6MWT = %BF 6MWT ↔ lean mass-leg (r=0.45, p<0.05)
Slawta et al. (2002)	123	Obesity, Hyperlipidemia, Diabetes	BMI, body composition (%BF, via ∑4-SKF), waist circ. Triglyceride, HDL, LDL, cholesterol Glucose levels	Leisure-time PA questionnaire	↑ PA ↔ ↓ BMI (p=0.002), %BF (p=0.0002), waist circ. (p=0.0001), triglyceride (p=0.0005), glucose (p=0.002) PA = HDL (p=0.09), LDL (p=0.27), cholesterol (p=0.06)
Tettey et al. (2014)	178	Hyperlipidemia	Triglyceride, HDL, LDL, cholesterol, ApoA-I, ApoB, ApoE	METs	↑ PA ↔ ↓ triglyceride (p=0.004), non-HDL (p=0.005), LDL/HDL ratio (p=0.038), cholesterol/HDL ratio (p=0.012), ApoB (p=0.004), ApoB/ApoA-I ratio (p=0.030)
Ranadive et al. (2012)	33	Vascular Function/Hypertension	FBF, CAC, cPWV	Accelerometer	PA = resting FBF and CAC PA ↔ peak FBF (r=0.38, p<0.05) PA ↔ cPWV (r=–0.33, p<0.05)

↑ Indicates higher measure; ↓ Indicates lower measure; ↔ Indicates significant association between measures; = Indicates no association between measures.

Table 1. Observational

14 of 17 (82.4%) identified observational studies, each reporting an association between higher levels of PA or cardiorespiratory fitness, or decreased sedentary behavior, and better function of at least one risk factor related to vascular comorbid conditions in people with MS.

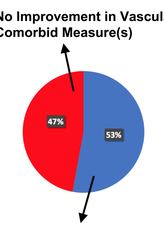


Ref.	*n*	Vascular Comorbidity: Type	Vascular Comorbidity: Measure	Intervention: Type	Intervention: Dur. (wks)	Key Findings
Pilutti et al. (2014)	82	Obesity	BMI, body composition (%BF, whole-body fat mass, lean mass, via DXA)	Behavioral intervention to increase lifestyle PA	24	↓ %BF (p=0.09) ↓ whole-body fat mass (p=0.05) = BMI (p=0.86) = lean mass (p=0.28)
Schmidt and Wonneberger (2014)	60	Obesity	Body composition (%BF, via ∑10-SKF)	Aerobic training (2x interval training, 1x continuous training /wk)	52	↓ %BF (p=0.01)
Wens et al. (2015a)	34	Obesity	Body composition (%BF, lean mass, via DXA)	HIIR (*n*=12): interval aerobic training (leg cycle ergometer) HCTR (*n*=11): continuous aerobic training (cycling/treadmill) Resistance training (leg press, leg curl, leg extension, arm curl, chest press) (all, *n*=23)	24	HIIR and HCTR: ↓ %BF (p=0.04 and p=0.02) HIIR: ↑ lean mass (p=0.01) HCTR: = lean mass (p>0.05)
Petajan et al. (1996)	46	Obesity, Hyperlipidemia	Body composition (%BF, via ∑4-SKF) Triglyceride, HDL, LDL, VLDL, cholesterol	Aerobic training (combined arm and leg cycle ergometer)	15	↓ SKF (p<0.05) = %BF (p=0.068) ↓ triglyceride, VLDL (both p<0.05) = HDL, LDL, cholesterol
Fragoso et al. (2008)	9	Obesity, Vascular Function/ Hypertension	BMI, body composition (%BF, %lean mass) Blood pressure (BP)	Aerobic training, resistance training, and stretching exercises	20	= BMI, %BF, %lean mass ↓ systolic BP before and after 3 min exercise (p=0.009, p=0.01) = diastolic BP before 3 min exercise (p=0.13) ↓ diastolic BP after 3 min exercise (p=0.03)
Wens et al. (2017)	34	Obesity, Diabetes	Body composition (%BF, lean mass, via DXA) Glucose and insulin levels (oral glucose tolerance test), muscle GLUT4 (biopsy)	HIIR (*n*=12): interval aerobic training (leg cycle ergometer) HCTR (*n*=11): continuous aerobic training (cycling/treadmill) Resistance training (leg press, leg curl, leg extension, arm curl, chest press) (all, *n*=23)	12	HIIR and HCTR: ↓ %BF, ↑ glucose tolerance (↓ fasting glucose levels [p<0.05], = fasting insulin) HIIR: ↑ lean mass ↑ muscle GLUT4 content (p<0.05) HCTR: = lean mass = muscle GLUT4 content (p=0.2)
Wens et al. (2015b)	45	Obesity, Diabetes	Body composition (%BF, fat mass, lean mass, via DXA) Glucose and insulin levels oral glucose tolerance test)	Aerobic training (cycling/treadmill and resistance training (leg press/curl/ extension, arm curl, chest press)	24	↑ lean mass (p<0.05) = %BF, fat mass = glucose tolerance, insulin levels
White et al. (2006)	12	Obesity, Hyperlipidemia Vascular Function/ Hypertension, Diabetes	BMI, body composition (%BF, via ∑3-SKF) Triglyceride, HDL, cholesterol Blood pressure (BP) Glucose levels	Resistance training (knee + spinal flexion/ extension, plantar flexion)	8	↓ triglyceride (p=0.02) ↓ # of elevated coronary artery disease risk factors (p<0.05) = BMI, %BF, HDL, cholesterol, systolic BP and diastolic BP, fasting glucose
Keytsman et al. (2017)	16	Obesity, Hyperlipidemia Vascular Function/ Hypertension, Diabetes	Body composition (%BF, fat mass, lean mass, via DXA) Triglyceride, HDL, LDL, cholesterol Blood pressure (BP) HbA1c, glucose and insulin levels, insulin sensitivity (HOMA)	HIIR: interval aerobic training (leg cycle ergometer) Resistance training (leg press, leg curl, leg extension, arm curl, chest press)	12	↓ 2h glucose, HOMA (p<0.05) = %BF, fat mass, lean mass, triglyceride, HDL, LDL, cholesterol, systolic BP and diastolic BP, HbA1c, fasting glucose, fasting insulin, 2h insulin

↑ Indicates increase in outcome measure in response to intervention; ↓ Indicates decrease in outcome measure in response to intervention; = Indicates no significant change in outcome measure in response to intervention.

Table 2. Interventional

9 of 17 (52.9%) identified interventional studies, each reporting improvement in at least one relevant measure of vascular comorbidity in response to training intervention in participants with MS.



Conclusions

- Cross-sectional data offers the most consistent, compelling evidence for the potential benefits of PA on vascular disease risk factors.
- The efficacy of exercise training in limiting vascular comorbidity risk and burden was dependent upon intervention type and duration.
- **Obesity**-related risk factor management
  - Role for PA/fitness/exercise – supported by 15/29 studies (51.7%)
  - Improvements in body composition seemed to require an intervention duration of ≥ 12 weeks. BMI was unaffected in each study
- **Diabetes**-related risk factor management
  - Role for PA/fitness/exercise – supported by 3/5 studies (60.0%)
  - High intensity aerobic training was more effective at limiting diabetes-related risk factors than mild-to-moderate training or resistance training alone.
- **Hyperlipidemia**- and **Hypertension/Vascular Function**-related risk factor management
  - Role for PA/fitness/exercise – supported by 4/5 studies (80.0%, hyperlipidemia) and 2/5 studies (40.0%, vascular function/hypertension)
  - Triglycerides, but not other lipids, were consistently ↓ with ↑ PA/exercise
  - Overall the extracted evidence for hyperlipidemia and hypertension was promising but limited/mixed, preventing conclusive conclusions

Future Directions

- Evidence points to a potential relationship between PA/exercise and risk factors related to vascular comorbidities in people with MS. PA and exercise training interventions may represent an effective therapeutic strategy for managing vascular comorbidities in people with MS, justifying further investigation
- Future studies aimed at supplementing interventional evidence should:
  - Be designed to measure vascular disease risk factors as a primary outcome
  - Include larger cohorts and heterogenous MS populations (man, woman, RRMS, SPMS, PPMS)
  - Use appropriate, validated measurements for vascular disease factors
  - Include long-term follow-up after completion of the intervention
  - Define which training regime is most effective in managing each comorbidity

References

1. Marrie R.A. *et al*. (2010). Vascular comorbidity is associated with more rapid disability progression in multiple sclerosis. *Neurology* 74(13): 1041-1047.
2. Thompson P.D. *et al*. (2003). Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease. *Circulation* 107(24): 3109-3116.
3. Sandroff B.M. *et al*. (2012). Physical activity and multiple sclerosis: new insights regarding inactivity. *Acta Neurol Scand* 126(4): 256-262.

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