Exercise training for autoimmune myasthenia gravis: A review of safety and effectiveness based on existing literature

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Introduction

Whilst autoimmune myasthenia gravis (MG) is a rare disease, it is the most common disease of the neuromuscular junction. Despite the significant advances in diagnosis and treatment, there is currently no cure for MG. Management consists of diverse pharmaceutic strategies to relieve symptoms and reduce the disease process with the ultimate aim of inducing disease remission.[1] Individuals not only suffer from the primary symptoms of MG but may also have secondary deconditioning as well as experience negative effects of medications such as corticotherapy. In recent times, the prevalence of MG has increased and whilst mortality has decreased over this century,[2] morbidity remains high, with symptoms and MG treatment creating huge burden for those living with this chronic disease. Health-related quality of life (HRQoL) is reduced, and MG has a negative impact on psychological, social, and economic well-being.[3,4]

Whilst a plethora of medications exist, with different therapeutic targets as well as varied management strategies,[5] the role of non-pharmacological management in MG is underdeveloped and underexploited.[6] Non-pharmacological treatments include allied health care such as physiotherapy, speech therapy, occupational therapy, psychological therapy but also music therapy, art therapy and exercise training.

Exercise is especially relevant to individuals with MG as exercise could have an effect on both the primary symptoms of the disease as well as the secondary consequences of MG. Exercise has demonstrated benefits in the general population as well as in various chronic neurological and non-neurological diseases.[7,8] Benefits include a reduction in pain,[9] fatigue,[10] anxiety,[11] depression[12] and morbimortality as well as improvements in strength and functional capacity. As MG is becoming more prevalent in older age, individuals have multiple comorbidities as well as age-related functional decline, which could be improved or managed with exercise. Exercise could also counter possible corticotherapy-induced myopathy and osteoporosis from long-term corticosteroid use. Further, exercise could play an immunomodulatory role in MG.[13] In addition, unlike many pharmacological agents, exercise has minimal, if any, side effects when adapted to the individual.

Observational studies evaluating daily physical activity (PA) demonstrate that individuals with MG may be less active and more sedentary than the general population.[14-16] Sedentary behaviour and reduced activity increase the risk for cardiovascular disease, type 2 diabetes, cancers and overall morbimortality.[17-19] Further, deconditioning creates a vicious cycle, increasing fatigue and weakness and consequently further limiting participation in activities of daily living (ADLs).[20] In addition to the health benefits that exercise can provide, individuals with MG express the desire to exercise. In a recent survey including 455 participants, 56% report exercising and of those that do not currently exercise, 77% express the desire to (NCT05408702, in writing).

In the past, exercise for individuals with MG was discouraged, even contraindicated as it was thought to worsen symptoms as well as the disease, causing exacerbations and even possible crises. This was presumably because individuals with MG typically experience *fatigability* with effort or repetitive movements. Similar to other neurological and neuromuscular diseases, this dogma was never supported by any scientific evidence of harmful effects and has been reconsidered recently in light of the emerging evidence demonstrating the safety of exercise in stable disease. Simultaneously, the dangers of disuse atrophy and sedentary behaviour have become omnipresent and it appears that fatigability in MG is likely exacerbated by weakness.[21]

There are currently no published guidelines to inform or guide patients nor healthcare practitioners working with individuals with MG. Several narrative reviews concerning exercise and MG have been published;[22-25] however, the most recent studies were not included.[26-28] Thus, the aim of this review is to present the current research evaluating the safety aspects as well as the effectiveness of exercise as an intervention for adults with autoimmune MG.

Method

To conduct this narrative review, Pubmed, Cochrane Central Register of controlled trials, the Physiotherapy Evidence Database and the clinical trials registry were searched using the terms autoimmune myasthenia and exercise with no limit on publication date. The last search was completed in December 2022. Reference lists of identified publications and previous reviews were also searched to identify additional studies. Due to the limited body of existing literature, all interventional trials (regardless of methodology) and without specific outcome measure requirement (i.e. all outcome measures were accepted) were included if published and available in English or French. Interventional studies involving exercise interventions regardless of duration, type, frequency, or delivery were included. Only studies of adults with MG were considered. Although exercise is a subcomponent of the broad term PA which is "any bodily movement produced by contraction of skeletal muscle that results in a substantial increase in energy expenditure,"[29] this review specifically focuses on exercise interventions. PA can include transport, leisure, occupational and household activities whereas exercise is defined as a "planned, structured, and repetitive form of PA with the intention or goal of maintaining or improving one's fitness and/or health."[29] Although important, studies involving exercise for electromyography-related evaluations and studies evaluating rehabilitation or self-management or specific respiratory training were not included nor were observational studies on PA in MG or case reports of exercise or sport in MG.

Exercise interventions are often classified into either strength/progressive resistance training (RT), aerobic (endurance) training (AT), or a combination of both. RT generally consists of repetitive lifting of weights or moving against high load resistance with the main aim of increasing strength by inducing muscular and neural adaptations. AT induces physiologic adaptations that differ from strength training. AT usually involves large muscle groups for longer durations, lower loads, with the aim of inducing adaptations in the heart, peripheral circulation, and skeletal muscle systems.[8,30]

Results

This review included nine interventional studies (one with abstract only) which evaluated the effects of exercise in adults with MG (details in supplementary data Table 1). An additional study evaluating a physical and psychological education programme to manage fatigue in MG was identified.[31] Whilst the programme incorporated some light physical exercises, the main focus was on education and empowerment so it was excluded from this review. The earliest study was published in 1993 and the remaining eight were published in the last decade. A total of 189 participants were enrolled and 174 were included in post-intervention analyses. Of those analysed and based on available data, the majority had generalised MG which was mild (MGFA II) for 49.7%, moderately severe (MGFA III) for 46.1%, severe (MGFA IV) for 0.6% and 3.6% had ocular MG (MGFA I). The mean age of participants ranged from 45-65 years and the average disease duration ranged from 8 to 19 years. Based on available data from eight studies, both sexes were represented however, there was a large female majority (91%[32] and 93%[26]) in two studies. Five studies did not report antibodies; of the other four studies, the majority included participants with acetylcholine receptor antibodies (73-100% of participants), two studies included participants with muscle-specific kinase antibodies and three studies included participants without known MG antibodies. Four studies explicitly stated that participants required stable disease to be eligible.

Exercise training interventions

Exercise interventions varied in terms of exercise type, session duration, session frequency, programme duration, exercise intensity, presence of supervision and setting (Table 1). Exercise type included aerobic training (AT),[26,33] resistance training (RT),[32,33] mixed AT/RT,[28,34-36] walking training[27] and balance training.[37] Where specified, session duration ranged from 30 to 90 minutes, frequency ranged from once per day to once per week and programme duration ranged from 8 to 24 weeks. The overall exercise intervention duration ranged from 8.5 hours to 36 hours depending on the study. AT intensity was defined by % maximum heart rate (HR) in three studies,[26,33,34] RT intensity was defined by repetition-maximum in three studies,[33-35] exercise intensity was otherwise undefined in five studies.[27,28,32,36,37] Exercise intensity was maintained or progressed by adjusting the resistance level, increasing weights, time, speed and/or number of repetitions or adjusting target HR for AT. The majority of studies included individually tailored training that was supervised in all but three studies.[26-28] Where specified, settings included hospital,[34] university,[33] physiotherapy gymnasiums[35,37] and home[26,28] or community-based.[27]

Study withdrawal and adherence to exercise training

Of a total of 9.5% reported dropouts, 10.9% were those participating in exercise and 7.5% were from control groups (only 2 studies with control groups). Of the 13 dropouts that were participating in exercise only one was possibly related to exercise due to worsening bulbar symptoms with RT[33] (Table 2). Other reasons for study withdrawal

were either not reported (1)[28] or due to lack of time (3),[33,34] work-related health problems (1),[34] spontaneous lumbar vertebral compression fracture (1),[35] spinal stenosis (1),[35] prescheduled thymectomy (1),[35] work-related injury (1),[33] work commitments (1),[37] or illness and cardiac arrhythmia (1).[37] One study did not provide information regarding dropouts.[36]

Adherence to the exercise programme was not reported in two studies.[36,37] One participant randomised to exercise refused exercise training.[26] Otherwise, whilst exact details are missing from most studies, based on available data, mean adherence to exercise was high ranging from 70-97%.[26,27,33-35] Reasons for missing sessions were only reported in one study: work commitments for most missed sessions and flu, weekend away, and menstrual pain/tiredness for missing occasional sessions.[26] One study reported difficulties in following the number of repetitions and training load.[32]

Exercise tolerance

Safety/tolerance of exercise training is summarised in Table 2. Of all nine studies, there was only one myasthenic crisis reported and this was in the control (rest) group.[27] No myasthenic crisis was reported in relation to exercise in any of the studies. Six MG exacerbations (3.2%) were reported with two necessitating hospitalisation. Five of these (2.7%) were in the control (usual care) group, thus unrelated to exercise[5] and one (0.5%) was a participant in the RT group.[33] However, it is possible that bulbar symptoms worsened prior to beginning RT as the Quantitative Myasthenia Score (QMGS) increased (speech and facial muscle strength items) during the run-in phase of the study prior to beginning exercise.[33] Five studies did not report adverse events (AEs).[28,32,34,36,37] One study reported bulbar symptoms in two participants (one temporary, the other withdrew as described previously).[33] The same study reported increased fatigue in three participants that was mild and temporary. For the 62 AEs reported over nine months in one study, there was no difference between the control and exercise arm.[26] Two other studies reported two AEs each which were unrelated to exercise.[27,35] Concerning changes in medication, six studies did not evaluate or did not report changes.[28,32,33,35,36] One single-arm study reported a decrease in acetylcholinesterase inhibitors (AchEi) following exercise in three (21%) participants.[34] Out of two controlled studies, one observed a decrease in both AchEi and corticosteroids (CS) in the exercise compared to the control (rest) arm[27] whilst the other study found no significant difference in dosage change of AchEi and CS between the two groups.[26]

Effectiveness of exercise

The benefits of exercise training are summarised in Table 3. HRQoL using the MG-specific patient-reported MGQOL-15 was evaluated in three studies but no improvement was found in favour of the exercise intervention.[26,27,33] Within-group analyses demonstrated worsening of HRQoL in the AT group in the Danish study.[33] Of the six studies evaluating knee extension strength, four studies demonstrated improvements with exercise (with RT but not AT in the study with 2 exercise arms),[26,32-34] whilst two studies did not show any change in knee extension strength with exercise.[27,35] Upper limb strength (elbow flexion,[26,32,35] elbow extension,[32] thumb abduction and finger extension[35]), was evaluated in three studies but no improvements were observed with exercise. Only one of five studies evaluating handgrip strength demonstrated an improvement with exercise.[28] With respect to function, walking capacity increased with exercise in three studies[26,35,36] whilst there was no change in five studies.[27,28,33,34,37] Timed-Up-and-Go performance improved in two[36,37] out of three studies,[34] 30-second sit-stand improved in all three studies that used this outcome.[33-35] Improvements were also observed in the stair climb test (RT not AT),[33] static standing balance[37] and box and blocks test (RT).[33]

Of three studies that used the MG-ADL as an outcome measure, only one showed an improvement following exercise.[26] Seven studies used various MG clinical scores including the Myasthenia Gravis Composite scale (MGC), the QMGS and the Myasthenia Muscle Score (MMS). Of these, three non-controlled studies showed improvements in post-exercise analyses on the QMGS[28,37] and MGC[34] and one controlled study showed improvements in the MMS in favour of exercise.[27] Two studies evaluated lower limb fatigability, one demonstrated a slight increase in resistance to fatigue with RT compared to AT[33] and the other study could not conclude due to the large inter-subject variability.[32] Two studies evaluated self-reported fatigue but did not demonstrate improvements with exercise.[33,34] One study demonstrated an improvement in exercise self-efficacy with exercise.[35] Finally, one uncontrolled study demonstrated improvements in immune markers with exercise[35] whilst another randomised controlled trial (RCT) found no between-group differences[26].

All studies evaluated the effects of exercise *immediately* post-intervention. Only two studies also included a no intervention follow-up period. Gains made immediately following the exercise intervention were unsustained at the 3-month follow-up in the MGEX study.[26] On the contrary, in the study by Wong et al., gains made in the QMGS and standing balance were sustained at the 4-week follow-

up whereas improvements in the TUG-cognitive were not maintained at follow-up.[37] Exercise dose-response, evaluated in two studies demonstrated that those that performed more exercise had greater benefits in leg strength and walking speed.[26,28]

Study design and methodological quality

The smallest sample size included 7 participants and the largest, 45 participants. Study designs varied between RCTs[26,27,33] and quasi-experimental single-group pre-post-test studies.[28,32,34-37] Only one study performed intention to treat analyses,[26] with the remaining studies performing per-protocol between group analyses, per-protocol within group analyses, or both. Only two studies included blinded assessors.[26,33] Concealed allocation was reported in only one of the three RCTs.[26] Only three studies calculated the sample size prospectively.[26-28] One study is only available as an abstract thus details are lacking.[36] Due to the nature of the intervention, no participants in any of the studies could be blinded. Participant retention was 80% or below in three studies[33-35] and unreported in one study.[36]

Discussion

The aim of this review was to summarise the current literature with respect to safety aspects and effectiveness of exercise interventions in adults with MG. Nine studies (one abstract only) were included. Evaluating exercise as an intervention presents certain challenges. Firstly, exercise is a complex intervention, consisting of multiple elements; exercise type, duration, frequency, intensity, individualised or generic, delivery (supervision and motivation) as well as setting. Secondly, exercise requires active participation which presents the challenge of adherence, particularly if the programme is ongoing, sessions are long and frequent. Not only can exercise be time consuming but it also has to fit into one's current lifestyle. Considering the age of the participants in this review, they are still likely to be working and may have children to care for. As with all therapies, the effects of exercise cannot be observed if adherence is not maintained.

Although few studies explicitly focused on safety and not all studies reported AEs, an important finding from this review, from precedent reviews and published case reports,[13,38-40] is that there is no data to support exercise as a harmful intervention in MG. Only four studies explicitly stated that participants had stable disease. There is no study to date demonstrating evidence of an exercise-related myasthenic crisis. One incidence of MG worsening was reported however as stated by the authors this may have occurred prior to exercise participation and, symptoms are known to fluctuate in MG so it is possible that this was the natural course of the disease, reinforcing the necessity for a non-exercise control group in future studies. The MGEX study demonstrates the possibility of MG exacerbation unrelated to exercise. The MGEX study actually supports the hypothesis of a protective effect of exercise as all five exacerbations were in the control group.[26] A similar finding has been reported in multiple sclerosis[41] and warrants further investigation in MG. Several studies from this review observed symptom improvement and medication reduction. There were several dropouts but adherence to exercise was otherwise reasonably high in most studies.

In terms of effectiveness, compared to a non-exercise control group, improvements were observed in walking capacity,[26] MG-ADL score,[26] knee extension strength[26] and MMS[27] in favour of exercise. In the single-group studies or within-group analyses, improvements were observed in knee extension,[32,34] handgrip strength,[28] walking capacity,[35,36] 30s sit-stand,[33-35] hand dexterity[33] and clinical scores (QMGS or MGC).[28,34,37] When comparing two exercise modes there was an improvement in the stair climb test and a reduction in knee extension fatigability in favour of RT compared to AT.[33] The minimal detectable change (MDC) and minimal clinically important difference (MCID) were rarely considered; the small observed gains were often below the MDCs or MCIDs (where known).[42] Improvements were not sustained in the 3-month follow-up in the MGEX trial, which reinforces the notion that the exercise programme was responsible for observed gains with benefits being lost with cessation of the programme.[26] In the study by Wong et al., two of the three improvements were sustained which may be explained by the fact that the four-week follow-up was shorter than the 3-month follow-up in the MGEX study.[37]

Two important outcomes directly reported by participants, HRQoL and self-perceived fatigue did not improve with exercise. Whilst it is preferable to use outcomes that are meaningful to participants, in a pragmatic trial, it can be challenging to identify sensible, reliable and meaningful outcomes. For example, in the MGEX study, the largest RCT to date and the only multicentre trial, HRQoL, did not demonstrate any change with exercise. In MG, HRQoL is most commonly evaluated using the MGQOL-15, an MG-specific standardised self-reported questionnaire. However, patient-reported outcomes can be impacted by expectations (positive or negative) and/or a response-shift phenomenon.[43] Response shift phenomenon has been defined as a change in the meaning of one's self-evaluation of a target construct i.e. HRQoL or fatigue which could be explained by various mechanisms such as a change in one's internal standard of measurement (recalibration), change in the importance (repriorisation) of component

domains, or a redefinition of the target construct (reconceptualization).[44] Response shift may attenuate treatment effects as individuals adapt to treatment side effects over time. Further, the fatigue scales used were not MG-specific and their responsiveness has not been evaluated in MG, which may be an explanation for their lack of change or improvement.

The scope of current evidence of exercise intervention in MG is small with only eight studies published and one abstract. The existing studies are of mixed quality with small sample sizes, keeping in mind that MG is a rare disease. Uncontrolled studies makes it difficult to interpret findings. Multiple different outcomes were used. There is an effort to improve standardization of existing outcome measures (MGNet, Benatar)[50]; however, more thought may be required as to which outcomes are most appropriate for exercise studies in MG, taking into account what is most important to the individual. Based on current evidence, it is impossible to compare safety and/or effectiveness of one type of exercise to another type (e.g AT vs RT), keeping in mind that intensity, duration, frequency and delivery varied amongst studies. We are also not able to conclude as to which type of exercise is best, how much should be done nor how often or at what intensity. Reporting of exercise interventions, adherence to exercise and AEs was lacking and/or insufficient in several studies. However, this is not unique to these specific studies.[45]

Other unanswered questions include when is best to begin or continue exercise in the MG disease course and whether a relationship exists between exercise and pharmacological therapies (e.g. exercise has an enhancing action on pharmacological therapies). With the plethora of new treatments being studied and becoming available in MG, it will be vital to understand the role and complementarity of exercise. Further studies are necessary to understand possible disease-modifying autoimmune response effects of exercise in MG. A future area of research could be whether exercise plays a role in preventing secondary generalisation in ocular MG.

Future studies should also consider wearables. These could be used as a monitoring tool, to stratify groups taking into consideration pre-intervention PA levels and to evaluate and encourage behaviour change[46] to further understand long-term and dosage-effects of exercise. A control group is important to truly understand the effects of exercise and whilst it is not possible to blind participants, assessors should systematically be blinded. Further, it is crucial to consider transferability. It is not a given that being enrolled in an exercise study and undergoing supervised or structured exercise over a period of time will transfer into incorporating exercise into daily life. One study demonstrated that the beneficial effects of exercise had worn off in the follow-up non-exercise period of the study.[26] Thus for sustained effects, it is necessary to continue exercise over a long-term period, making it important to find an activity that is feasible and enjoyable. Engaging in exercise without the structured environment of a trial, for those out of practice or having never undergone exercise is challenging. Multiple barriers exist including those related to and those unrelated to MG (NCT05408702, in writing).

Although no specific recommendations exist, we propose that general recommendations regarding moderate-intensity exercise can be applied safely to well-regulated individuals with mild-moderate MG.[47] Individuals may need to be reassured that mild-moderate intensity exercise will not worsen their disease. Healthcare providers should endorse and promote the safety and possible benefits of exercise and lifestyle PA.[48] Neurologists and treating physicians could play an essential role in promoting exercise by regularly enquiring about PA and exercise habits. Prescribing exercise and/or referral to a physiotherapist and/or exercise physiologist and/or coach is highly recommended to assist individuals in starting and progressing their exercises as well as educating and empowering individuals.[49] An individual exercise plan is useful not only from a physical/physiological perspective but also from a psychological and behavioural standpoint to assist individuals in finding an activity they enjoy which is fundamental for long-term adherence. This should incorporate the needs and priorities of the individual with the aim of achieving or maintaining the individual's highest or optimal function within their capacities. Smartphone and smartwatch applications are widely developing and can be useful for motivating as well as monitoring exercise levels with regular data being fed back to the individual and/or the prescriber.

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Table 1: Details of exercise interventions in the included studies

Study	Study design	Type exercise Aerobic (AT) Resistance (RT)	Intensity	Programme duration	Session duration	Frequency	Total planned training	Setting/Supervision
Birnbaum 9 months	Multicentre RCT, ITT analyses	Aerobic	Target HR = 70% maxHR	3 months	40 minutes	3/week	24 hours (1440 mins)	Home/unsupervised (1st 2-3 training sessions supervised)
Misra 3 months	RCT Per-protocol b/w grp & w/i grp analyses (proportions)	Walking		12 weeks	In 1-2 sessions 10min: week 1 20min: week 2 30min: week 3	Daily	8.5 hours (510mins)	Home/community Unsupervised
Chang 24 wks	Single-grp uncontrolled	Mixed AT/RT		24 weeks	30 minutes	At discretion of participant	Minimum 12 hours: 720 mins (1/week)	Home/unsupervised 1 supervised session per month
Westerberg 18 12 wks	Single-grp uncontrolled	Mixed AT/RT	AT: aim 80% maxHR RT: 10-RM	12 weeks	90 minutes	2/week	36 hours (2160 mins)	Hospital/supervised
Westerberg 17 12 wks	Single-grp uncontrolled	Mixed AT/RT	"moderate" AT: high load RT: 10-RM	12 weeks	70 minutes	2/week	28 hours (1680 mins)	PT setting/supervised
Rahbek 8 wks	RCT: 2 exercise arms Per-protocol b/w grp & w/i grp analyses	AT OR RT	AT: 70-85% maxHR RT: 15-RM to 8-RM	8 weeks 20 sessions	~ 40mins*	5/2 weeks	13.3 hours (800mins)	Sport Science University/ supervised
Hafer-Macko 3 months	Single-grp uncontrolled	Mixed AT/RT		3 months	60mins	3/week	36 hours (2160 mins)	Supervised
Wong 4wk pre, 16wks post + 4wk F/U: up to 24wks	Single-grp uncontrolled	Functional/ balance		16 sessions	~60mins* (based on Nitz & Choy)	1-2/week	16 hours (960mins)	PT setting/supervised
Lohi 10 wks	Single-grp, opposite untrained limb used as control	Resistance		10 weeks 27-30 sessions	~40mins*	2-3/week	20 hrs (1200mins) to 24.7 hrs (1480mins)	Supervised (< 20% unsupervised)

*specific data not provided, time is assumed. Grey cells: unspecified. AT: aerobic training, RT: resistance training, RM: repetition maximum

Table 2: Summary of safety/tolerance of included studies

Safety/tolerance								
Study	**Dropouts**	**Drop-outs possibly related to exercise**	**MG crisis**	**MG exacerbation**	**Other adverse events**	**Change in dose AChEI/CS or both**	**Electrophysiology**	**Worsening of MG possibly due to exercise**
Birnbaum EG vs CG (usual care) 9mo (3mo F/U)	2 (CG)^ 95% (41/43) completed + 2 prior to randomisation	0	0	CG: 5 (2 hospitalised)	62 31 EG & 31 CG	NS b/w grp difference in change AChEI or CS		0
Misra EG vs CG (rest) 3mo	2 (1 CG, 1 EG) **95%** (38/40) completed	0	1 CG (rest)	NR	EG: 1 FSGS	↓ dose AChEI & CS in EG compared to CG	ND	0
Chang Single-grp, 24 wks	1 **97%** (34/35) completed 24wks.	0	NR	NR	NR	NE/NR		0
Westerberg 18 Single-grp, 12 wks	3 **79%** (11/14) completed 12wks.	0	0	0	NR	↓ dose AChEI, n=3	↑ CMAP amp: RF ND CMAP: BB RNS: No deterioration~	0
Westerberg 17 Single-grp, 12 wks	3 **77%** (10/13) completed 12wks.	0	0	0	1: spontaneous lumbar compression fracture 1: spinal stenosis	NE/NR	↑ CMAP amp: BB & RF. ND CMAP: APB & EDB ND RNS post	0
Rahbek EG (RT) vs EG (AT) 8 wks	3 **80%** (12/15) completed 8wks	1 bulbar symptoms (RT)	0	1	2 : bulbar symptoms 3 : ↑ fatigue	NE/NR		1 (may have preceded exercise)
Hafer-Macko Single-grp, 3mo	NR	NR	NR	NR	NR	NR		NR
Wong Single-grp, 24wks	2 83% (6/7) post, 71% (5/7) F/U	0	NR	NR	NR	NE/NR		0
Lohi Single-grp, 10 wks	0	0	0	0	NR	NE/NR		0
TOTAL	**18 (9.5%)**	**1**	**1**	**6 (3.2%)**	**70**			**1**
EG (9 studies)	**13 (10.9%)**			**1 (0.5%)**	**39 (20.9%)**			**1**
CG (2 studies)	**3 (7.5%)**		**1**	**5 (2.7%)**	**31 (16.6%)**			
Before randomisation	**2**							

AChEi: Acetylcholinesterase inhibitors, APB: abductor pollicis brevis, AT: aerobic training, BB: biceps brachii, CG: control group, CS: corticosteroids, EDB: extensor digitorum brevis, EG: exercise group, F/U: follow-up, grp: group, ND: no difference, NE: not evaluated, NR: none reported, NS: not significant FSGS: focal segmental

glomerulosclerosis, mo: months, post: post-intervention, RF: rectus femoris, RNS: repetitive nerve stimulation, RT: resistance training, ~1 decrement post compared with 4 pre, ^ post-randomisation

Table 3: Summary of effectiveness of exercise on various outcomes used in the included studies

		Effectiveness of exercise on																	
			Strength			Function						Clinical MG score							
Study	Adherence to exercise	HRQoL (MGQOL)	KE	UL	Hand grip	Walking 6MWD	TUG	30STS	SCT	B&B dom	MG-ADL	QMGS	MGC	MMS	ESES	Fatigue	Fatigability	Depression/ Anxiety	Immune markers	Follow-up
Birnbaum	**96%** (22/23) participated in ET 70% adherence (of n=23). Mean 24 (range 0-38) 40min sessions.	ND b/w EG & CG	+ (CACE)	ND	ND	+					+			ND				ND	ND IL-6, TNF α	Not sustained
Misra	97% adherence of 19/20 (1 drop-out EG)	ND b/w grps	ND		ND	ND b/w grps					ND			+						
Chang	Median 56.3min/wk of 97%	ND			+	ND						+								
Westerberg 18	Mean 88±7% sessions of 79% (n=11/14, remaining participants)	ND	+		ND	ND*	ND	+				ND	+		ND	ND FSS				
Westerberg 17	2 = 71%, 8=95% of 79% of 10/13 remaining participants		ND	ND	ND	+		+					ND		+				+ miR-150-5p, miR-21-5p, IL-6	
Rahbek	Of 80% remaining participants, n=12/15: Mean 95%±8. AT: 91.7±9.8% RT: 98.3±4.1%	↓ AT (w/i grp) compared to RT (sig b/w grp)	+ RT w/i grp			ND		+ w/i grp both	+ RT b/w grp	+ RT w/i grp						ND MFIS	+ KE: RT			
Hafer-Macko	No information	ND				+	+				ND	ND								
Wong	NR					ND	+# & FoamEC					+								QMGS, FoamEC maintained
Lohi	Not all could complete repetitions or training load as planned.		+	ND													inconclusive			

Grey cells – outcome measure not used or no follow-up period, Electrophysiological measures not included. AT: aerobic training, CG: control group, EG: exercise group, ESES: Exercise self-efficacy, ET: exercise training, FoamEC: FoamEC: standing balance on foam with eyes closed, FSS: Fatigue Severity Score, KE: knee extension,

MFIS: Modified Fatigue Impact Scale, MGC: Myasthenia Gravis Composite Score, MMS: Myasthenia Muscle Score, ND: no difference, QMGS: quantitative myasthenia gravis score RT: resistance training, SCT: Stair Climb Test, TUG: Timed Up and Go test, UL: upper limb, 6MWD: Six-minute walking distance, 30STS: 30-Second Chair Stand Test, *12MWD, #TUGcognitive.

Supplementary data Table 1 presents all included interventional studies (most recent first)

Study, design, location	Design/method	Participants	Exercise Group (EG)/Control group (CG)	Adherence	Outcome measures (OM)	Adverse events	Dropouts	Results
Birnbaum, 2021 [3, 2] Multicentre RCT Study duration 9mo for each participant (3mo run-in, 3mo ex, 3mo F/U) Paris, France	**Single-blind parallel grp multicentre** **Randomised** 1:1 - computer generated, permuted blocks of randomly varying sizes, stratified by centre, **concealed allocation**	Eligibility Mild-mod gMG: MGFA II-III 18-70yrs, **Stable** for ≥ 6mo MGQOL score ≥ 15 No CI to exercise N= 45 included N=43 randomised Female: 40 (93%) Mean age: 45.5±10 yrs AChRab+ve: 35 (81%) MuSK+ve: 3 (7%) Seronegative: 5 (12%) MGFA II: 23 (53%) MGFA III: 20 (47%) Mean DD: 14.3±11 yrs Juvenile: 7 (16%) EOMG: 30 (70%) LOMG (> 50yrs): 6 (14%) Mean BMI: 28.4 (5.5) Obese (BMI ≥ 30): 13 (32%) Mean MGQOL: 22.1±9 Mean MMS: 86.6±11 Mean MG-ADL: 2.6±2.4 Mean 6MWD: 498±83m Mean FVC%: 84.6±13.1	**EG:** N = 23 **40min sessions, 3/week, 12 wks** 2 – 3 supervised sessions, then **unsupervised** at home with HR monitor **Individualized** target HR (70% of their HRmax, using 220-age as their HRmax) **AT:** Rowing machine Each 40 min moderate-intensity rowing session consisted of: 10min warm-up to reach individual target HR, followed by 20min plateau of constant aerobic activity at **70%HRmax**, followed by 5min power interval phase (5 sets of 10 consecutive pulls at maximum effort each minute, followed by regular intensity strokes for the remainder of each minute), 5min active cool-down. **CG:** N = 20 Usual care, nothing added	Training sessions (distance, time, Watts, date) recorded by the rowing machine N = 1 refused exercise. Adherence defined as having completed ≥ 20 (frequency) 30min (duration) sessions. Including n=23, mean 24 sessions & 70% adherence Non-adherence mainly due to work commitments. Reasons for missing occasional sessions: the flu, weekend away, menstrual pain/tiredness.	Primary: MGQOL-15 Secondary: MG-ADL score MMS score Strength (isometric MVC) KE + EF (Biodex) Handgrip (MyoGrip) 6MWD FVC/FEV1 MIP & MEP Dose AChEi Dose prednisone WHO-QoL BREF BDI (depression) STAI (anxiety) SEI (self-esteem) Serum IL-6 & TNF α	62 AEs reported, no difference b/w grps. CG: 5 MG exacerbations (2 hospitalised) EG: zero exacerbation, zero hospitalization.	2 dropouts CG 95.3% completed Lost to F/U < 5%	Analyses ITT, n=43 No b/w grp difference in MGQoL EG: ↓ MG-ADL & ↑ 6MWD, not maintained at 3mo F/U EG CACE analyses (based on compliance): ↑ KE strength, not maintained at 3mo F/U
Misra, 2021 [7] RCT Lucknow, India	**Randomisation** computer generated random numbers (no concealed allocation) No blinding	Eligibility Mild-mod gMG: MGFA II-III 15-70 years, MGQOL ≤ 45 No CI to exercise n = 40 included n = 38 analysed Median DD : 4.5 (1.2-24) yrs Median age: 45 (16-70) yrs	**12 weeks** **EG:** N= 20 Self-walking in 1 or 2 sessions: Week 1 10min **daily** Week 2: 20min daily Week 3 onwards: 30min daily Steps & distance recorded using "Step Tracker" (smartphone), verified fortnightly by telephone & at F/U	Monitored fortnightly by telephone. Subject & caregivers instructed to maintain a diary of Step Tracker including # steps & distance. Walking details	Primary: > 50% ↑ MGQOL-15 Secondary: > 50% improvement MG-ADL 6MWD (15m corridor) # steps (6MWT) MMS score Handgrip strength Dose AChEhI	EG: 1 – FSGC leading to renal failure at 2 months CG: 1 - MG crisis at 1 month	1 in each arm (cf AEs) 94.7% completed Lost to F/U 5.3%	N =38 analysed (per protocol) In favour of EG 1°: More subjects in EG had > 50% improvement in MGQOL & 6MWD than CG. However, comparing MGQOL score between the 2

	Analyses: Per-protocol baseline-3mo (compared proportions)	Female: 16 (42%) MGFA II: 8 (20%) MGFA III: 30 (80%) EG/CG Median MGQOL: 19/18 Median MMS: 68/60 Median 6MWD: 132/108 MG-ADL, Antibodies: no data	**Intensity** undefined **CG (Rest) :** N=20 Rest (sitting or lying) 30mins daily in 1 or 2 sessions (each ≥ 6-8h apart)	verified at F/U visits. Non-compliance of >30% on 2 consecutive sessions would lead to study exclusion. EG: 97% adherence 89% completed walking in 1 session. CG: 98%, all completed rest in 2 sessions.	Dose CS Decrement trapezius EMG (RNS 3Hz)			groups there was no difference b/w grps (supp data). Pre-post = improvement in both grps in MGQOL, MMS but no improvement in 6MWD ↓ dose AChEI + CS in EG compared to CG
Chang, 2021 [4] New Taipei City, Taiwan	Pre-post (baseline, 24-wks) No blinding	Eligibility Mild-mod gMG: MGFA II-III **No change meds** ≥ 6mo No IVIG/PLEX within 6mo prior to enrolment N = 35 included Female: 22 (63%) Mean age: 56.1± 8.6 yrs AChRab+ve: 100% MGFA II: 21 (60%) MGFA III: 14 (40%) Mean DD: 12.3±10.6 yrs Obese: 40% Sarcopenia: 8 (22.9%) MGQOL: 14.9±11.3 QMGS: 10.5±4.8 6MWD: 396±90m FVC%: 72.6±18.5 N=34 analysed (21 female)	**30-min sessions, 24-wks** **Individually** tailored **Aerobic resistance training** **Supervision by a researcher once per month** at hospital PT setting **Home, unsupervised**, sessions at the discretion of subject Session: 5min warm-up, 7 x 3min cycling intervals, 5min cool-down + squats, sit-stand, arms-out stretch, squat jumps, sprint on the spot, own body weight exercises. If easy, intensity ↑ gradually by ↑ reps + speed. Stretching. **Intensity** undefined Participants were free to decide how many exercise sessions per week they would perform and regularly reported their weekly exercise time. No CG	Median 56.3min/wk Median 2.9 sessions/wk	No 1° OM defined QMG score Handgrip strength FVC MG-QOL Gait speed - mean of 2 6MWT Body composition (DXA)	No negative effects reported – no info provided	1 dropout reported – no details provided Lost to F/U < 5% (2.9%)	Pre-post analyses Feasible, well-tolerated ↑ QMG 9 to 10.47±4.78 ↑ handgrip strength ↑Android/gynoid fat ratio High ex grp (>56.3min/wk) compared to low ex grp (<56.3min/wk): greater deterioration in arm muscle mass (high grp), greater ↑ FVC, ↑ gait speed, improvement QOL & QMGS low grp
Westerberg, 2018 [10]	Pre-post No blinding	Eligibility age ≥18 years, living nearby no concomitant condition no severe CVD, other disabling disease, pregnancy.	**90-min sessions, 2/week, 12-wk, Supervised –** Hospital setting Intensity & weights - **individually tailored** Each session: **AT, RT & balance**	11 completed the 12-wk program 75% to 96% (88±7%), max 24 sessions.	CMAP RF, BB. RNS 10 stimuli, decrement recorded b/w 1st & 4th (4 abnormal decrement)	None of them showed any signs of clinical deterioration	3 dropouts unrelated 2 – lack of time 1 work-related	↑ CMAP amplitude in RF (no correlation with change in RNS decrement). ND CMAP BB

Uppsala, Sweden Safety & efficacy, effects on functional muscle parameters		N= 14 included N= 11 analysed Mean age: 60±18 yrs Female: 6 (55%) Mean BMI: 26.3 Obese: 2/11 (18%) Mean DD: 16.4±11.6 yrs AChRab +ve: 8 (73%) MuSKab +ve: 1 (9%) Seronegative: 2 (18%) EOMG: 5 (45%) LOMG: 6 (55%) MGFA I: 2 MGFA IIa: 1, MGFA IIb: 2 MGFA IIIa: 3, MGFA IIIb: 2 MGFA IVa: 1 Mean MGC: 3.8 [0-9] Mean QMGS: 2.5 [0-6] 6MWD: 486±91m Accelerometer: median 8801 steps, SB 18.8h/24, 10h (waking hrs) Self-reported: strenuous exercise 0 to>120min/wk (median: <30min/wk). PA not regarded as exercise <30 min/wk to >300min/wk (median: 150–300min/wk).	**AT:** stationary bicycle interval training 5min warm-up, 7 intervals of 2min cycling against high load & 1min cycling against minimum load, 5min cool down. Level of resistance was set, continuously adjusted, according to HR **aiming for 80% of maxHR** during the 2min high load periods. **RT:** 7 resistance exercises (weightlifting, resistant band exercises, or exercises using own body weight) biceps curl, latissimus dorsi pulldown, triceps pushdown, leg curl, cable rowing, sit-ups, & leg press were carried out, each with 2 sets of **10 RM**. Increasing adjustments of RT weights were done individually. The active training program was followed by a set of 2 balance & 6 stretching exercises which were not changed over time. No CG	72–100% exceeded 70% of HRmax during the 2-minute high load periods. Ten (91%) increased weights ≥ 4 of the 7 strength exercises. All ↑'d resistance weights for leg press. Eight (73%) ↑'d bicycle resistance in the second half of the training.	Isometric muscle strength HHD (Lafayette): BB, KE Handgrip strength (Jamar) U/S muscle thickness: BB, RF, VI MGC score QMGS PEF% TUG 12MWT 30STS MGQOL FSS ESES Blood samples Body composition: DXA–BIA	(MGC/QMGS) or described other uneasiness regarding the training. No deterioration (RNS).	health problems 78.6% completed Lost to F/U 21.4%	↑ Isometric quadriceps force ↑ U/S muscle thickness (RF + VI) ↑ 30STS (median +2) ↑ median MGC (3 to 2)* DXA: ↓ fat (%),↑ muscle (%) RNS : only 1 subject had abnormal decrement compared with 4 prior to training Majority (72-100%) exceeded 70% of HRmax each session during the 2min high load. ↑ level of resistance in multiple exercises
Westerberg, 2017 [9] Uppsala, Sweden	Pre-post No blinding	Eligibility >18yrs, Well-regulated MG with ongoing treatment &/or mild fatigue: MGFA class I-II N=13 included N= 10 analysed MGFA I: 4 (40%) MGFA IIa: 3 (30%) MGFA IIb: 3 (30%) Female: 5 (50%) Mean age: 65±14 Mean DD: 19±13 [4-40] Mean BMI: 27.5±4.5	**70min sessions, 2/week, 12-wk** **AT (bicycle interval training)** & **RT** **Supervised by a PT,** PT setting **Individually tailored** Every session: **AT, RT & balance** **AT:** Stationary bicycle 30min: 5min warm-up, 7 intervals of 2min cycling against high load/resistance (**max tolerated**), 1min "recovery cycling" minimum load/resistance, ending with 5-min cool-down. **RT:** 40min, 8 resistance exercises - each with 2 sets of **10 repetition max.**	2 = 71% 8=95%	MGC score PEF CMAP, RNS 10 @ 3Hz decrement b/w 1st & 4th - APB, BB, RF, EDB Right-side isometric strength HHD (Lafayette): APB, BB, RF, EDB Handgrip strength (Jamar) Performance-based measures: TUG	Physical exercise was well tolerated & MGC score was unchanged. No change RNS	3 dropouts 1 – spontaneous lumbar vertebral compression fracture 1 – spinal stenosis 1 – prescheduled	↑ 6MWD ↑ 30STS ↑ CMAP amplitudes (mV): BB & RF ↑ ESES (↑ confidence) ↓ disease-specific micro-RNAs miR-150-5p & miR-21-5p. DXA-BIA - ↑% muscle ↓%fat Pulse (% of max; [220-age]) was

		AChRab +ve: 8 (80%) AChRab -ve: 2 (20%) Median MGC: 4.5(2.8) Mean 6MWD: 486±91 Mean 30SCS: 13.6±5.6 Mean TUG: 8.5±1.5 Baseline PA level (accelerometer): median 7872 steps/day N = 1 abnormal decrement (RNS)	Biceps curl, triceps pushdown, seated leg curl, cable pull-down, leg extension, cable rowing, sit-ups, leg press. **Balance**: 1-leg standing for 1min on each leg on variable surfaces. **Progression:** Increasing adjustments of bicycle resistance load & RT weights were done over the 12 wks as participants improved. **Intensity** "moderate intensity" No CG		6MWT 30STS Romberg test Toe-rise Endurance Test Serum levels IL-6, muscle enzymes, Disease-specific micro-RNAs (miR-150-5p & miR-21-5p) Body composition: DXA–BIA ESES		thymectomy 76.9% completed Lost to F/U 23.1%	consistent among subjects over the training period, whereas the resistance (Watt) gradually increased over the period, indicating a positive AT effect. Muscle resistance weights ↑ UL & LL
Rahbek, 2017 [8] 4wk run-in & 8wks exercise Arhus, Denmark	2 arms - type of exercise **randomised** - stratified by gender & QMG score 4 week run-in period Within grp (pre/post) & between grp analyses **Assessor-blinded**	Eligibility gMG: MGFA II-IV, 18-80 yrs Living nearby, No cardiorespiratory, orthopaedic or metabolic comorbidities, no dementia or pregnancy N=15 included MGFA IIa: 10 (66.7%) MGFA IIb: 4 (26.7%) MGFA IIIa: 1 (6.7%) Mean age: 55.6±17.2 Median QMGS: 5.5 (0-17) Mean BMI: 25.8±3.8 Female: 8 (53%) Mean DD: 7.6±6.6 PRT grp = 7 AT grp= 8 Antibodies: not reported N=12 analysed MGFA II: 11 (91.7%) MGFA III: 1 (8.3%)	**Both arms intervention:** **8 weeks, 20 training sessions** Schedule: 5 sessions per 2wks. **Moderate-high intensity PRT & AT** At the Sport Science training facilities, Aarhus University. All sessions were **supervised** by the same exercise physiologist. All sessions of both grps were preceded by a 5-min low-intensity aerobic warm-up. Most sessions were conducted on an individual basis, but some sessions overlapped, resulting in 2 or more subjects exercising concurrently. **AT protocol:** 3 sets of 10–12min cycling on a bicycle ergometer with 3min rest periods. Intensity progressed from **70 to 85% of maxHR** during the 8wk intervention. **PRT protocol:** Full-body including; weighted step-up, smith bench-press, leg-press, pull-down, hip flexion & lateral raises. All exercises progressed from 3 sets of 12 repetitions performed at **15-RM** in wk 1, to 3 sets of 8 repetitions	Adherence defined as % of sessions attended (of the 20 scheduled). **Only subjects who completed the intervention were included in adherence calculation.** AT: n = 6 completed PRT: n = 6 completed Mean adherence: 95%±8. AT: 91.7±9.8% PRT: 98.3±4.1%	Isokinetic dynamometer - isometric strength (MVC): KE, shoulder abd, EF, HE, HF Max neural drive iEMG – VL (during isometric test). Concentric isokinetic KE 100-0° at 90°/s Fatigability: 25-repetition isokinetic test of KE. Functional: 6MWT STS B&B SCT Aerobic Power: Incremental cycle test to exhaustion within 8–12 min (individual dependant). The highest recorded 30s average O_2 uptake rate attained during the test considered the peak rate of oxygen consumption (VO_2peak). MG-QoL15	Transient training-induced muscle soreness not regarded as an AE. Both grps reported AEs: bulbar symptoms (n = 1 PRT → withdrew, n = 1 AT temporary & did not affect participation) and mild, temporary ↑ fatigue both grps. No change in QMGS in either grp.	3 (20%) dropouts 1 PRT potentially related to PRT (bulbar symptoms requiring CS 4wks into the PRT) 2 AT grp unrelated to AT 1 = work related injury 1 = lack of time 80% completed Lost to F/U 20%	AT and PRT were feasible for most patients with mild MG. B/w grp analyses: MGQOL deteriorated in AT grp SCT improved PRT grp (AT worse) Within grp analyses: PRT ↑ KE strength (10%) PRT ↑ B&B^{dom} performance ↑ STS both grps ↓ fatigability end of test in PRT group.

			performed at **8-RM** in wk 8. Sets were interspaced by a 90- to 120-s rest period. No non-exercise CG		MDI MFIS			
Hafer-Macko, 2016 (abstract) [5] **3months**	Single grp	Eligibility: no data N = 9 Mean age: 63 **Stable** Mild-mod MG	**3 months** **1h 3/week** **AT(walking), RT (therabands) & breathing exercises** **Intensity** undefined	No information provided	MG-ADL MGQOL-15 QMGS TUG 1-RM leg press 6MWT Self-selected walking speed VC	None reported (abstract)	None reported	Improvement TUG, 1-RM leg press, peak walking speed, peak ventilator exchange
Wong 2014 [11] Brisbane, Australia 16wks & 4wk F/U Effects of a BST program on balance, strength & fitness	Single grp Repeated measures (pre/post & 4-week follow-up) No blinding	Eligibility Required confirmation from treating Dr that MG was controlled, symptoms were **stable**, & medication would not be changed during the study. Excluded: Cognitive deficits & any additional neurological or musculoskeletal condition that affected mobility. N = 7 included MGFA II: 5 (71%), MGFA III: 2 (29%) Female: 4 (57%) Mean age: 53.9 yrs [range 24–75] Mean DD: 7.9 yrs [range 5–20] N = 6 completed post-intervention assessment + analysed MGFA II: 5 (83%), MGFA III: 1 (17%) Female: 3 (50%) Mean age: 59±12 yrs [range 43–75] Mean DD: 10±5 yrs [range 5–20]	**1-2/week** depending on work commitments. **BST: 16-session workstation intervention within an exercise grp** **BST, strengthening, endurance training** **Exercises tailored individually** to physical ability as determined by initial assessment. **PT students** delivered the intervention **under PT supervision**. Examples: heel–toe walking, sit to stand, ball catching & throwing. Progressive increases in challenge were introduced if subject was able to cope. This was done by increasing the number of repetitions, altering the speed, introducing dual tasks, or changing the base of support or support surfaces. **Intensity** undefined No CG	1 dropout during the intervention period. 2 subjects participated once a week, 4 subjects twice a week. Compliance was otherwise not reported.	Improvement defined as ≥ 15% improvement b/w pre & post (& F/U 4wks post-intervention.) 6MWT TUG TUGmanual TUGcognitive Standing stability (foamEC) When subjects were taking AChEIs, assessments were undertaken approx. 3hrs after ingestion.	No subject reported or showed any AEs.	2 dropouts: 1 during intervention due to work commitments. 1 post-intervention due to illness and cardiac arrhythmia 71.4% completed Lost to F/U 28.6%	Improvement in QMGS (median 29%), TUGcognitive, FoamEC (change of 29% representing a ↓in COP sway velocity). Only improvement in QMGS (41%) & FoamEC (45%) indicating greater postural stability) maintained at F/U.

		Antibodies: not reported						
Lohi, 1993 [6] Gothenburg, Sweden	Within subject control – contralateral limb Randomised training to right or left UL & LL, comparator = contralateral UL & LL No blinding	<u>Eligibility</u> <50 years old Mild-mod MG Living nearby Excluded – other severe or disabling disease N=11 analysed Female: 10 (91%) 25-50yrs UL/LL Mild: 6 (55%) UL/LL Mod : 2 (18%) Oculo/bulbar: 3 (27%) → mod for calculations Antibodies: not reported	**2-3/per week, 10weeks** (unilateral UL & LL), **27-30 supervised sessions** + **≤ 5 unsupervised sessions** **Session time unspecified** **Weights based on individual MVC** EF, KE trained sitting, EE trained supine – upper arm vertical, forearm horizontal **Intensity** undefined	EE: Only 1 (9%) could perform as planned, 9 (82%) could not manage number of repetitions in each training set & 8 (73%) were unable to ↑ training load as planned. EF: 6 (55%) managed well whereas 4 (36%) had problems with number repetitions & 3 (27%) with ↑ing workload. KE: only 1 (9%) unable to use initially predicted training weight but managed later as did all others.	MVC EF, EE, KE - fixed dynamometer Fatigability test (EF, EE, KE): max contractions over 3mins – 3s on/2s off – peak value of each & mean decline calculated using linear regression analysis	AEs noted at each training session. None reported. No one complained of muscular pain or discomfort during the training period but not all completed	No dropouts Lost to F/U 0%	All reported that they gained better strength and resistance to fatigue during the training period. Two subjects improved their daily level of functioning, reporting that their walking distance had increased (not an outcome measure). Slight ↑ KE strength compared to untrained side Fatigability results inconclusive No change fatigue or max force EF/EE

AChEIs: Acetylcholinesterase inhibitors, AT: Aerobic training, BST: Balance strategy training, BDI: Beck Depression Inventory, BB: biceps brachii, B&B: Box and Block Test, CACE: compliers average causal effect, CG: Control group, CI: contraindication, CS: corticosteroids, CVD: cardiovascular disease, D: Duration, DD: disease duration, EE: elbow extension, EF: elbow flexion, EG: Exercise group, EMG RNS: electromyography repetitive nerve stimulation, ESES: Exercise Self-Efficacy Scale, FSS: Fatigue Severity Score, FoamEC: standing balance on foam with eyes closed, FSGC: focal segmental glomerulosclerosis F/U: Follw-up, F: frequency, HHD : hand-held dynamometer, HRQoL: Health-related quality of life, HR: heart rate, ITT: Intention-to-treat, I: Intensity, KE: knee extension, LL: lower limb, MD: missing data, MDI: Major Depression Inventory, MFIS: Modified Fatigue Impact Scale, MGC: Myasthenia Gravis Composite Score, MGQOL-15: Myasthenia Gravis health-related quality of life scale, MG-QoL15r: Myasthenia Gravis Quality of Life 15 revised, MG-ADL: impact of MG on activities of daily living scale, MMS: Myasthenia Muscle Score, PA: Physical activity, QMGS: quantitative myasthenia gravis score, SCT: Stair Climb Test, SEI: Self-esteem Inventory scale, STAI: State Trait Anxiety Inventory, STS: 30s Sit-to-stand test, 6MWT: Six-minute walking test, 6MWD: Six-minute walking distance, RCT: randomised control trial, RF: rectus femoris, RA: research assistant, RT: resistance training, 30STS: 30-Second Chair Stand Test, TUG: Timed Up and Go test, TUGmanual: TUG with dual task, TUGcognitive: TUG with dual task, 12MWT: Twelve-Minute Walk Test, UL: upper limb, VI: vastus intermedius, VAFS: visual analogue fatigue scale, WHOQoL BREF: World Health Organisation QoL scale, 1-RM: 1-repetition maximum, VC: vital capacity *Minimal important difference for improvement: QMGS 2 or 3 points, MGC 3 points [1]. NB: Where outcomes are listed, if there is no change they are not necessarily mentioned in the results column, Mean ± SD (range), median (range), [] min, max

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