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ORIGINAL ARTICLE

# Recumbent stepping aerobic exercise in amyotrophic lateral sclerosis: a pilot study

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## Abstract

**Objectives** Aerobic exercise can promote neuroplastic responses in the healthy and injured brain. Although the role of exercise in amyotrophic lateral sclerosis (ALS) is debated, new evidence suggests that exercise may reduce disease progression. While common exercise modalities such as the treadmill and cycle ergometer have been explored in ALS, the safety and feasibility of a total body recumbent stepper have not been investigated. Additionally, the functional and neurophysiological effects of recumbent stepping in ALS are still unknown. Here, we investigated the safety and feasibility of a 4-week recumbent stepping program to slow disease progression in ALS and possibly facilitate neuroplasticity.

**Method** Nine individuals with ALS performed moderate intensity recumbent stepping for four weeks. Outcomes included participation satisfaction questionnaire, ALS Functional Rating Scale Revised (ALSFRS-R), clinical tests of walking and endurance, fatigue severity scale, Beck depression inventory, SF-12, and transcranial magnetic stimulation-induced motor evoked potentials (MEPs). All measurements were collected at baseline, post-intervention, and at the 1-month follow-up.

**Results** Eight participants completed the study without any adverse events. The ALSFRS-R scores were similar at the end of the study and at follow-up. No significant differences were noted for any of the clinical outcomes. MEPs were present only in two participants and changes in corticomotor excitability after exercise were minimal.

**Conclusions** Results from this preliminary study support the safety and feasibility of 12 sessions of total body recumbent stepping in individuals with ALS.

**Keywords** Aerobic exercise · Corticomotor excitability · Amyotrophic lateral sclerosis · ALSFRS-R · Recumbent stepping · Neuroplasticity

## Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that affects motor neurons in the brain, brainstem, and spinal cord. A key symptom of ALS is muscle weakness which typically follows an asymmetric onset in either the upper or lower extremity or facial muscles [1]. Progressive muscle weakness can cause dysfunction in mobility that can be worsened by reduced physical activity. This may lead to secondary complications such as orthostatic hypotension, respiratory compromise, and joint contractures that may further impair mobility and function [2]. This vicious cycle is further exacerbated by historical caution in recommending exercise programs for fear of inducing "overuse weakness" in the muscles and causing further damage [3]. Other reasons for restricting exercise include epidemiological studies that have linked intense physical activity, either occupational or related, to increased susceptibility to developing ALS [4–6].

Recently emerging evidence contrasts the current medical opinion that physical activity is a risk factor for ALS, and advocates exercise as a potential neuroprotective mechanism [7–10]. Indeed, exercise has been universally recommended for several neurological and neurodegenerative disorders to improve cardiovascular and motor function, and slow disease

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progression. Preliminary studies on transgenic mice models with ALS have shown that moderate intensity aerobic exercise can induce neuroprotection and prolong motoneuron survival [11–14]. Based on this available evidence, there is now an emerging focus on the recommendation of exercise prescription for ALS.

Very few randomized controlled trials have evaluated the effects of exercise training in individuals with ALS [15–20]. Findings from these studies suggest that exercise is safe and tolerable in ALS and may have the ability to slow disease progression. Most studies have incorporated resistance training and/or range of motion and stretching exercises primarily in home-based programs. More recently, aerobic exercise training (AET) is being explored as a therapeutic intervention for improving cognitive function and relearning of complex motor skills, due to its ability to facilitate neuronal excitability and neuroplasticity in healthy individuals and those with neurological disorders [21–26]. AET has also been explored by few studies in ALS [16, 19, 20, 27]. Sanjak et al. demonstrated that an 8-week supported treadmill ambulation protocol was safe and well tolerated in a small sample of individuals with ALS [27]. Findings from a recent randomized controlled trial that incorporated AET as one of the interventions, also demonstrated the safety and feasibility of a 24-week home exercise program on a mini-cycle for individuals with ALS [16].

Although the treadmill and cycle have shown to be feasible in ALS, they may not be suitable for all individuals with ALS, especially for those with greater motor impairments and poor trunk control. A combined upper and lower extremity exercise modality with safe, supported seating such as the total body recumbent stepper may be a more feasible alternative to cycle ergometry. Since individuals with ALS have decreased trunk control and impaired balance, recumbent stepping poses a lower risk of fall than treadmill training or cycling. In addition, recumbent stepping accommodates for exercise-induced fatigue and trunk weakness by providing trunk and leg support. The primary objective of this study was to investigate the safety, feasibility, and participant-reported feedback of 12 sessions of recumbent stepping in individuals with ALS. We also examined the efficacy of recumbent stepping on disease progression and other clinical outcomes immediately after exercise and at 1-month follow-up. Additionally, we explored neurophysiological markers of exercise-induced change by measuring corticomotor excitability of the motor cortex using transcranial magnetic stimulation (TMS).

## Methods

De-identified data that support the findings of this study are available from the corresponding author upon reasonable request. Please refer to Online Resource for detailed methods.

### Participants

This was a single group pretest-posttest study with a 1-month follow-up. We included individuals with a diagnosis of possible, probable, or definite ALS (as identified by the revised version of the El-Escorial criteria), and the ability to walk with or without an assistive aid for at least 10 m. We excluded individuals with (1) a history of severe cardiac, pulmonary, metabolic, orthopedic, or other medical conditions precluding participation; (2) significant cognitive or communication impairment; and (3) other neurological comorbidities and those with contraindications to transcranial magnetic stimulation (TMS). All participants demonstrated a complete understanding of the study protocol. A written informed consent was obtained from everyone and the study was approved by the Institutional Review Board.

### Outcomes

#### Safety and feasibility

Compliance was recorded based on the frequency of sessions (*n*, %) completed in total as well as adherence per session (exercise duration). Adverse events related to the training intervention were monitored throughout the study. We also measured participation satisfaction at the end of the study with the participation satisfaction questionnaire (PSQ), adapted from Courneya et al. [28]. The PSQ consists of items that evaluate five categories, i.e., overall trial satisfaction, burden of testing, perceived benefits, perceived barriers, and perceived support. Responses were assessed on a 5-point scale where a score of 1 represents "not at all," 2 represents "to a small extent," 3 represents "to some extent," 4 represents "to a moderate extent," and 5 represents "to a large extent."

The following outcome measures were measured before (pre), after (post), and at follow-up (1-month) post intervention.

#### Clinical outcomes

We used the ALS Functional Rating Scale-Revised (ALSFRS-R) to measure disease progression, the 10-m walk test (10MWT) to measure self-selected gait speed, the 6-min walk test (6MWT) to estimate cardiovascular endurance, the timed up and go test (TUG) to measure risk of fall, the fatigue severity scale (FSS) to assess global fatigue, the SF-12 to evaluate health-related quality of life (QoL), and the Beck depression inventory (BDI) to assess depression.

#### TMS

Corticomotor excitability of bilateral first dorsal interosseous (FDI) and tibialis anterior (TA) muscles was measured with

single pulse TMS. Recruitment curve (RC) slopes for motor evoked potential (MEP) amplitude ranging from 80% active motor threshold (AMT) to 140% AMT were considered as the primary outcome measure of corticomotor excitability [29]. Response to TMS was considered absent when no MEPs were elicited even after stimulating at 90–100% maximum stimulator output. Electromyographic activity was monitored for fasciculation responses during TMS. These responses were not considered as MEPs during the analysis.

### Intervention: Recumbent stepping training

The NuStep T5 Recumbent Cross Trainer (NuStep) (NuStep Inc., Ann Arbor, MI, USA) was used in this study. Participants were instructed to maintain 65–70 steps per minute for 40 min (5-min warm up, 30 min of exercise at target heart rate zone, and 5-min cool down). Participants were required to perform the exercise three times/week for 4 weeks, at moderate intensity (50–70% maximal heart rate) and rate of perceived exertion (RPE) 3–5 (i.e., moderate–somewhat heavy) using the modified Borg's scale (maximum 10) [30]. We monitored the RPE and heart rate (HR) after every 5 min. The bike resistance was gradually increased for achieving the target heart rate depending on the individual's tolerance. The resistance was not increased for participants with reduced leg strength. These participants were encouraged to step faster to reach their target heart rate. Although participants were encouraged to complete the training without taking pauses, they were provided with 1-min breaks as necessary to accommodate for exercise-induced fatigue. We compared weekly changes in peak watts, peak HR, average RPE, and total distance to evaluate the participants' progression over the course of the exercise program.

### Statistical analyses

A one-way repeated measures ANOVA was used to measure changes over time for clinical outcomes (gait speed, ALSFRS-R, 6MWD, FSS, SF-12 variables) and weekly differences for peak Watts, peak HR, total distance, and average RPE. The Friedman test was used for the TUG and BDI as they were not normally distributed. The level of significance was set to $p \leq 0.05$ and post-hoc tests were performed as necessary.

## Results

Initially, 14 individuals were screened and nine individuals (6 males/3 females, mean age 59.22 ± 12.32 years) were enrolled in the study. Two individuals qualified for the study but could not be contacted for the appointments. The remaining three individuals did not qualify as they were in later stages of the disease and were not ambulatory. One participant withdrew after 1 week of exercise training because of a fall at home. One participant did not attend the 1-month assessment and the data was imputed with the last observation carried forward method. Two participants could not perform the TUG as they were unable to get up from a chair independently. The demographic and clinical characteristics of our study participants ($n = 9$) are shown in Table 1. None of the participants presented with familial ALS. Please refer to Online Resource for detailed results.

### Safety and feasibility

Eight participants completed all 12 sessions (total 96 sessions, 100% compliance) without any adverse events. We did not observe major fluctuations in heart rate or blood pressure during the training sessions. All participants tolerated the stepping protocol for 40 min during each session (100% within session adherence). Three participants required 1-min recovery pauses two–three times during each session, but they still managed to complete the 40-min protocol. Average RPE was approximately 2/10 at the end of 4 weeks, i.e., "light" rating of exertion.

With respect to participant progression during the 4-week exercise, we did not find significant differences for peak Watts ($F(3, 21) = 2.76$, $p = 0.06$), peak HR ($F(3, 21) = 2.41$, $p = 0.09$), and average RPE ($F(1.36, 7.77) = 3.4$, $p = 0.08$). A significant main effect was noted for total distance ($F(3, 21) = 3.77$, $p = 0.02$) (Table 2). Post-hoc tests revealed that exercise training increased total distance by 0.11 miles from week 1 to week 4, which was not statistically significant. Figure 1 represents the average scores for each domain on the PSQ. Mean ± S.D. scores for each variable on the PSQ are as follows: overall trial satisfaction, 4.1 ± 0.07; burden of testing, 1.91 ± 1.08; perceived benefits, 2.38 ± 0.3; perceived barriers, 1.43 ± 0.44; and perceived support, 3.3 ± 1.21.

### Clinical parameters

No significant differences were noted between the pre, post, and 1-month assessments for any of the clinical variables (Fig. 2, Table 3).

### TMS outcomes

Out of nine participants, only two participants revealed MEPs only in their bilateral TA muscles during all evaluations. Exercise-induced changes in RC slopes were minimal, i.e., no change in one participant and a reduction of 14% (pre-post) and 24% (pre-1 month) in the second participant.

**Table 1** Participant characteristics

| Subject | Age (year)/ sex | Time since onset (year) | Time since diagnosis (year) | Initial ALSFRS-R | Respiratory subscale (ALSFRS-R) | % FVC | ALS Onset | Medication | Smoking history | MEP status (+/–) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 36/M | 1.58 | 1.16 | 39 | 12 | 98 | Spinal | None | N | – |
| 2 | 63/F | 7 | 7 | 26 | 6 | 13 | Bulbar | None | N | – |
| 3 | 57/M | 9 | 2 | 30 | 11 | 58 | Bulbar | None | Y | – |
| 4 | 67/M | 1 | 1 | 42 | 12 | 97 | Bulbar | Riluzole | Y | ++ |
| 5 | 58/F | 1.5 | 1 | 25 | 12 | n.d. | Spinal | Riluzole | Y | – |
| 6 | 67/M | 3 | 1.25 | 37 | 12 | 88 | Spinal | Riluzole | N | ++ |
| 7 | 80/M | 4 | 3 | 35 | 10 | 48 | Spinal | Riluzole | Y | + |
| 8 | 50/F | 10 | 2 | 38 | 11 | 72 | Spinal/atypical* | None | Y | + |
| 9 | 55/F | 7 | 3 | 25 | 5 | 77 | Spinal | Riluzole, edaravone | N | + |
| Mean | 59.22 | 4.89 | 2.37 | 33 | 10.11 | 68.8 | | | | |
| SD | 12.3 | 3.4 | 1.9 | 6.5 | 2.7 | 28.6 | | | | |
| Median | 58 | 4 | 2 | 35 | 11 | 74.5 | | | | |

*ALSFRS-R*, Amyotrophic Lateral Sclerosis Rating Scale–Revised; *% FVC*, % forced vital capacity predicted; *MEP*, motor evoked potential; *n.d.*, no data; *SD*, standard deviation. *This participant was diagnosed with atypical ALS with an 11-year history of progressive weakness in the upper extremities (strength 3 to 4/5) greater than lower extremities (strength 4/5). Deep tendon reflexes were normal except for the Achilles reflex which was absent. MEP status: ++ represents bilateral MEPs and + represents unilateral MEPs at baseline

## Discussion

Our results suggest that a supervised 4-week recumbent stepping aerobic exercise is safe and feasible for individuals with ALS. All participants completed the exercise protocol without any adverse events related to exercise. The ALSFRS-R scores were similar at the end of the study and at 1-month follow-up implying that disease progression was not adversely affected by the exercise program. However, there were no significant improvements in other clinical parameters. The effects of exercise on corticomotor excitability could not be completely evaluated as only two individuals had motor evoked potentials. Participants perceived that the study was rewarding and improved their quality of life and physical fitness.

Our protocol was well tolerated by all study participants. Even though the participants were in different stages of the disease (ALSFRS-R range 25–42), they could perform the stepping exercise comfortably. One individual dropped out of the study due to a balance-related fall at home that was unrelated to the study. Our findings suggest that the participants' adherence to the exercise intervention was excellent. Our feasibility- and safety-related findings concur with recent studies that investigated the effects of aerobic exercise [15, 16, 19]. Lunetta et al. compared standard care versus strictly monitored exercise in ALS and showed that the exercise group did not have any adverse effects [19]. Our findings are supported by another recent home-based exercise study which showed that resistance, endurance, and stretching/range of motion exercises are safe and do not worsen disease progression [16]. Our study participants are not representative of all individuals with ALS, but our exercise intervention can be tailored to any individual in the mild to moderate stages of the disease. We now show that moderate intensity AET with a recumbent stepper is feasible and can be incorporated in a rehabilitation program for ALS.

Although we found that 4 weeks of stepping AET did not adversely affect ALFRS-R scores or disease symptoms, we are unable to extrapolate our findings regarding slowing of disease progression due to the short study period. The ALSFRS-R is less sensitive to change in disease progression

**Table 2** Weekly changes in exercise performance

| | Week 1 | Week 2 | Week 3 | Week 4 |
|---|---|---|---|---|
| Peak Watts | 26.37 (16.34) | 26.95 (15.15) | 31.67 (21.24) | 29.54 (17.54) |
| Peak HR (bpm) | 101.91 (14.67) | 105.66 (14.65) | 109.29 (15) | 105.45 (15.16) |
| Average RPE | 2.96 (0.66) | 2.24 (0.72) | 2.2 (1.16) | 2.07 (1.1) |
| Total distance (miles) | 1.51 (0.33) | 1.54 (0.33) | 1.54 (0.33) | 1.62 (0.3) |

Values are mean ± S.D. *HR*, heart rate; *bpm*, beats per minute; *RPE*, rating of perceived exertion

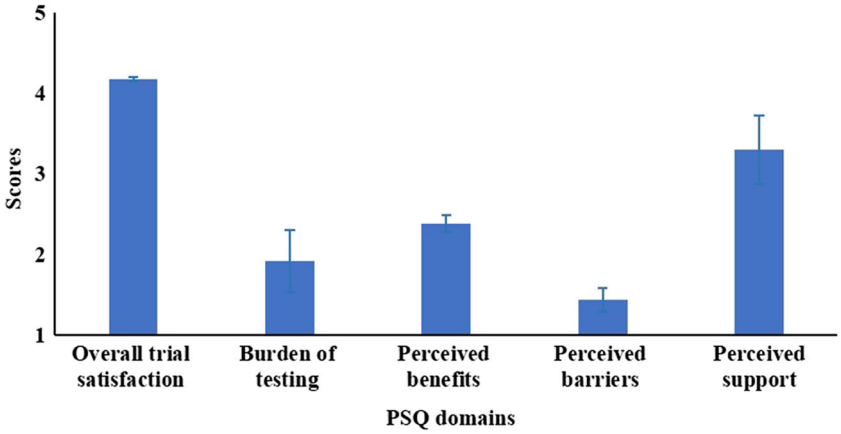


**Fig. 1** Participation satisfaction scores. Bars depict mean ± SEM. Scores on the participation satisfaction questionnaire range from 1 to 5, where 1 represents "not at all," 2 represents "to a small extent," 3 represents "to some extent," 4 represents "to a moderate extent," and 5 represents "to a large extent"

over shorter time periods such as 4 weeks which limits the findings of our study regarding safety of exercise [31]. Some exercise studies in ALS have shown small and significant beneficial effects of exercise on disease progression [15, 17, 19, 27], while others have reported no change in the ALSFRS-R following exercise [16]. Drory et al. evaluated the effects of a moderate intensity exercise (about 2–15 min twice a day) and reported a significant improvement in the ALSFRS-R and spasticity at the 3-month evaluation in the exercise group [18]. Dal Bello-Haas et al. assessed the effects of moderate intensity stretching and resistance exercises, and observed that the resistance group had higher ALSFRS-R and QoL scores at the end of the study [17]. Lunetta et al. showed that the strictly monitored exercise group [active limb exercise and exercise on the cycle ergometer (intensity, 60% maximal power) for 20 min performed for 6 months] had significantly better ALSFRS-R scores compared to control [19]. Recently, Clawson et al. showed that endurance (intensity, 40–70% of target HR for 30 min) and resistance exercises (40–70% 1 repetition maximum) performed over 6 months did not affect the decline in the ALSFSR-R and pulmonary forced vital capacity measures [16]. It is important to note that the exercise dosage in our study (i.e., frequency, duration, mode, and intensity) is different from these studies. Although our exercise intensity (i.e., moderate) is comparable with other studies as reported above, the exercise duration of 4 weeks is relatively shorter. Since most studies incorporated moderate intensity home-based exercise, the duration of intervention was longer, i.e., 6–12 months [16–18]. The duration of the intervention may explain the slowing in disease progression that was observed in these studies. The aim of this study was to establish safety and feasibility of the structured exercise program on a stepper. Future studies should address short- versus long-term exercise during the course of the disease to provide more insights into slowing of disease progression.

We did not observe any effects of recumbent stepping exercise on clinical parameters. There was a trend towards better quality of life (PCS domain of SF-12) and lower fatigue following the exercise intervention, but the changes were small and not statistically significant. Improvements in quality of life concurred with higher participants' self-reported perception of QoL (in the PSQ), suggesting that the stepping exercise may have induced positive psychological effects.

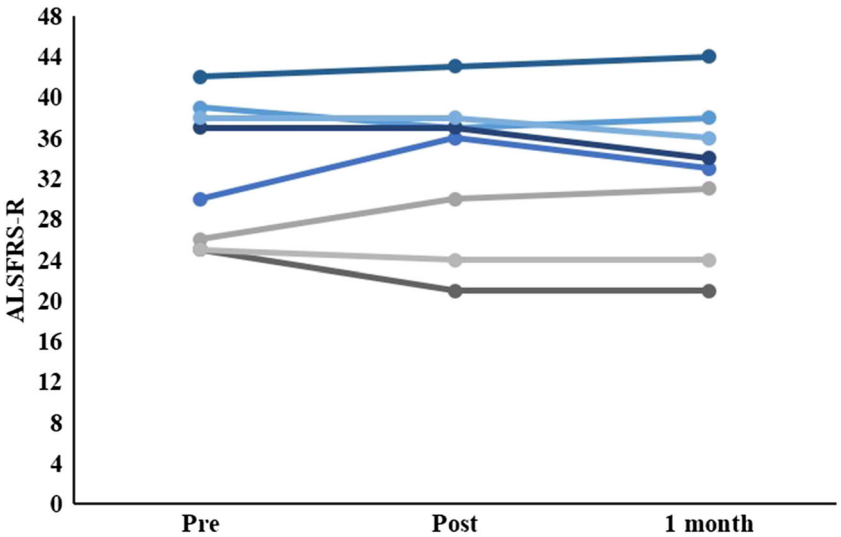


**Fig. 2** Change in ALSFRS-R. Individual ALS Functional Rating Scale–Revised (ALSFRS-R) at pre, post, and 1-month assessment

**Table 3** Comparison of clinical and gait parameters

| | Pre | Post | 1-month | *p* value |
|---|---|---|---|---|
| ALSFRS-R | 32.75 (7) | 33.25 (7.55) | 32.62 (7.4) | 0.8 |
| Gait speed (m/s) | 0.65 (0.44) | 0.68 (0.44) | 0.72 (0.42) | 0.27 |
| 6MWD (m) | 232.5 (192.32) | 234.88 (182.97) | 235.16 (195.49) | 0.91 |
| TUG (s) | 25.63 (34.07) | 26.24 (35.25) | 16.17 (8.82) | 0.5 |
| FSS | 32.87 (10.45) | 30.37 (10.86) | 28.62 (11.9) | 0.43 |
| SF–12 PCS | 33.03 (8.39) | 35.1 (10.49) | 35.1 (12.09) | 0.48 |
| SF–12 MCS | 58.05 (3.62) | 57.26 (7.81) | 56.3 (8.02) | 0.83 |
| BDI | 6.5 (2.56) | 7.12 (5.16) | 7.6 (3.7) | 0.63 |

Values are mean ± S.D. *ALSFRS-R*, ALS functional rating scale-revised; *6MWD*, 6-min walk distance (meters); *TUG*, timed up and go test (seconds); *FSS*, fatigue severity scale; *SF–12 PCS*, short form–12 physical composite summary; *SF–12 MCS*, short form–12 mental composite summary; *BDI*, Beck depression inventory

Only two participants had elicitable MEPs in the TA muscle that showed minimal to no change after exercise which limits our interpretation of aerobic exercise on CME. Most of our participants were about 4 years from disease onset, which may explain the absence of MEPs possibly due to a loss of functioning upper motor neurons during the course of the disease [32]. Other biomarkers of neuroplasticity, such as brain-derived neurotrophic factor or other growth factors, which are known to increase with aerobic exercise [26] may provide more information about exercise-mediated effects in ALS. A recent animal study that examined limb unloading of animals showed that prolonged disuse of muscles alters and affects the maturation of neural stem cells, suggesting that movement is crucial for maintaining the integrity of the nervous system [33]. Indeed, AET is being increasingly explored as a potential intervention to restore motor and cognitive function in neurodegenerative diseases such as Alzheimer's disease, [34] Parkinson's disease, [25, 35], and multiple sclerosis [36, 37]. Aerobic exercise on a stepper may not only be important for maintaining skeletal muscle and cardiovascular health, but also have critical benefits for health of the nervous system.

Implementing exercise programs for adults with ALS is challenging as barriers such as fatigue, muscle weakness, respiratory problems, limited transportation, and caregiver burden limit access to therapy. Short-term moderate-intensity recumbent stepping aerobic exercise appears to be safe for people with ALS and can be conveniently performed in a clinical, home, or gym setup under a caregiver's supervision. The caregiver can be trained by the rehabilitation team to monitor heart rate and RPE during exercise and stop exercising if necessary. The Nustep is ideal for exercising in such an environment as it can accommodate individuals in later stages of the disease who have some strength in their lower extremities but limited ambulatory capacity.

Although the preliminary findings of our study support safety and feasibility, there are some limitations that need to be accounted for. We did not perform exercise testing prior to training. We did not measure oxygen consumption during training, which may be relevant when exercising for longer periods. We did not measure respiratory capacity before and after training. It is possible that our aerobic exercise protocol may have influenced bulbar and respiratory muscle function, similar to the effects seen with respiratory muscle strengthening exercises [38]. It is important to interpret our findings with caution considering the small sample size and the lack of control in the study design. Our study protocol was short and did not incorporate a 6- or 12-month follow-up period which may be more suitable for observing changes in disease progression. This is especially relevant considering that the limited sensitivity of the ALSFRS-R to quantify disease progression over shorter periods of time. Some of our participants had a very long disease course which may have affected our findings, as they may not be as responsive to exercise compared to patients diagnosed more recently. Lastly, this exercise protocol may not be suitable for individuals in more advanced stages of ALS with limited movement and other chronic issues.

## Conclusions

Our study is the first to demonstrate that a 4-week exercise program on a recumbent stepper is safe and well tolerated by individuals with ALS. In situations where conventional exercise modalities such as the treadmill or cycle may be inappropriate, the recumbent stepper can be implemented as it causes lesser limb fatigue and provides greater trunk support. Since ALS is a disease that requires multidisciplinary management, regular physical activity in the form of recumbent stepping has the potential for inclusion in a rehabilitation program. Future studies are recommended to investigate the clinical and neurophysiological effects of a longer aerobic exercise recumbent stepping protocol on a larger cohort of individuals with ALS.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflicts of interest.

**Ethical approval** All research procedures were in accordance with the ethical standards of the institutional review board and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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