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Review article

A meta-analysis of post-exercise outcomes in people with amyotrophic lateral sclerosis

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ABSTRACT

Objective: To systematically evaluate post-exercise outcomes related to function and quality of life in people with ALS.
Methods: PRISMA guidelines were used for identifying and extracting articles. Levels of evidence and quality of articles were judged based on *The Oxford Centre for Evidence-based Medicine Levels of Evidence* and the *QualSyst.* Outcomes were analyzed with Comprehensive Meta-Analysis V2 software, random effects models, and Hedge's G. Effects were examined at 0–4 months, up to 6 months, and > 6 months. Pre-specified sensitivity analyses were performed for 1) controlled trials vs. all studies and 2) ALSFRS-R bulbar, respiratory, and motor subscales. Heterogeneity of pooled outcomes was computed with the I^2 statistic.
Results: 16 studies and seven functional outcomes met inclusion for the meta-analysis. Of the outcomes explored, the ALSFRS-R demonstrated a favorable summary effect size and had acceptable heterogeneity and dispersion. While FIM scores demonstrated a favorable summary effect size, heterogeneity limited interpretations. Other outcomes did not demonstrate a favorable summary effect size and/or could not be reported due to few studies reporting outcomes.
Conclusions: This study provides inconclusive guidance regarding exercise regimens to maintain function and quality of life in people with ALS due to study limitations (e.g., small sample size, high attrition rate, heterogeneity in methods and participants, etc.). Future research is warranted to determine optimal treatment regimens and dosage parameters in this patient population.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a neuromuscular disease resulting in degeneration of upper and lower motor neurons leading to spastic and flaccid paralysis of the limb, trunk, respiratory, and bulbar musculature. Motor declines drastically impede patients' abilities to complete activities of daily living and impacts quality of life [1,2]. Disease progression in people with ALS is rapid, with an average life

Abbreviations: 6MWT, (6 Minute Walk Test); 25FWT, (25 Feet Walk Test); ALS, (amyotrophic lateral sclerosis); ALSFRS-R, (ALS Functional Rating Scale-Revised); DIGEST, (Dynamic Imaging Grade of Swallowing Toxicity); EAT-10, (Eating Assessment Tool); EMST, (Expiratory muscle strength training); FAC, (Functional Ambulation Categories); FIM, (Functional Independence Measurement); FOIS, (Functional Oral Intake Scale); FVC, (forced vital capacity); FSS, (Fatigue Severity Scale); IMST, (Inspiratory muscle strength training); ITT, (intention-to-treat); KEMS, (knee extension muscle strength); MEP, (maximum expiratory pressure); MIP, (maximum inspiratory pressure); MND, (motor neuron disease); MVIC, (maximum voluntary isometric contraction); PAS, (Penetration Aspiration Scale); PEF, (peak expiratory flow); PRISMA-2009, (Preferred Reporting Items for Systematic Reviews and Meta-Analyses); RCTs, (randomized controlled trials); RPE, (rating of perceived exertion); SNIP, (sniff nasal inspiratory pressure).

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expectancy of 2–5 years following diagnosis [3]. Life expectancy is frequently shorter for patients with bulbar onset (typically manifested by dysphagia [swallowing problem] and dysarthria [slurred speech]), comprising approximately one-third of cases [4–7]. The remaining two-thirds of cases will have initial symptom onset in the limbs. Although ALS is the most common motor neuron disease (MND), it is rare, with a prevalence of 5 cases per 100,000 people each year in the United States [8].

While there is no cure for ALS to date, recent studies have shown treatment may slow loss of function and improve quality of life, particularly when provided as part of an interdisciplinary approach to patient management [9]. There are currently four prescription drugs approved by the Food and Drug Administration for use with people with ALS, with two drugs (riluzole and edaravone) purposed to increase survival – albeit minimally [4]. Effective therapies for ALS are postulated to inhibit excessive motor neuron activity, decrease oxidative stress, and delay respiratory decline – the latter being the major cause of mortality [5,10–12]. Until a cure is found, clinical care continues to involve early interventions promoting improved symptom management [5].

In addition to pharmaceutical treatments, emerging studies have examined the impact of exercise in people with ALS. Exercise can result in a variety of neuromuscular benefits including cross-education (transference), increased motor unit activation and synchronization, as well as increased skeletal muscle fiber hypertrophy, protein synthesis, and capillary density, which may lead to more optimal functioning of the neuromuscular system [13,14]. While strenuous exercise has been avoided in people with ALS due to baseline fatigue, muscle atrophy and weakness from disuse and denervation, and concern for faster muscle degeneration [13,15–17], preliminary evidence demonstrates that moderate therapeutic exercise may be beneficial in symptom management and survival in people with ALS. While conducting exercise in people with ALS remains controversial in some settings, researchers have proposed a paradigm shift to a proactive management approach rather than a reactive one [18–20]. Therefore, we conducted a systematic review and meta-analysis that expanded upon previous reviews of the literature [20–24] to investigate the effects of all types of exercise (e.g., physical therapy, occupational therapy, speech therapy) on outcomes related to function and quality of life in people with ALS to determine whether exercise may be beneficial or detrimental.

2. Materials and methods

2.1. Protocol

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-2020) [25] guidelines were followed for reporting. Systematic review methods were established prior to conducting the review by determining the search strategy, article inclusion criteria, quality assessment methods, and data extraction methods. No protocol deviations were made.

2.2. Search strategy

Studies were identified and extracted according to PRISMA guidelines [25]. A single author conducted a search in four electronic databases (CINAHL, Scopus, PubMed, and Cochrane Library) from time of database inception until December 2021. Search terminology included: *ALS* OR *amyotrophic lateral sclerosis* OR *motor neuron disease* OR *Lou Gehrig's disease* AND *exercise* OR *remedial exercise* OR *exercise therapy* OR *strength* OR *resistance training* OR *range of motion*. Additionally, a manual search was conducted that included full-text original research articles.

2.3. Eligibility criteria

Articles were included based on the following inclusionary criteria: 1) original full-text article; 2) exercise-based intervention study; 3) published in English; and 4) intervention subjects were patients with a diagnosis of ALS/MND. Duplicate results were removed prior to screening.

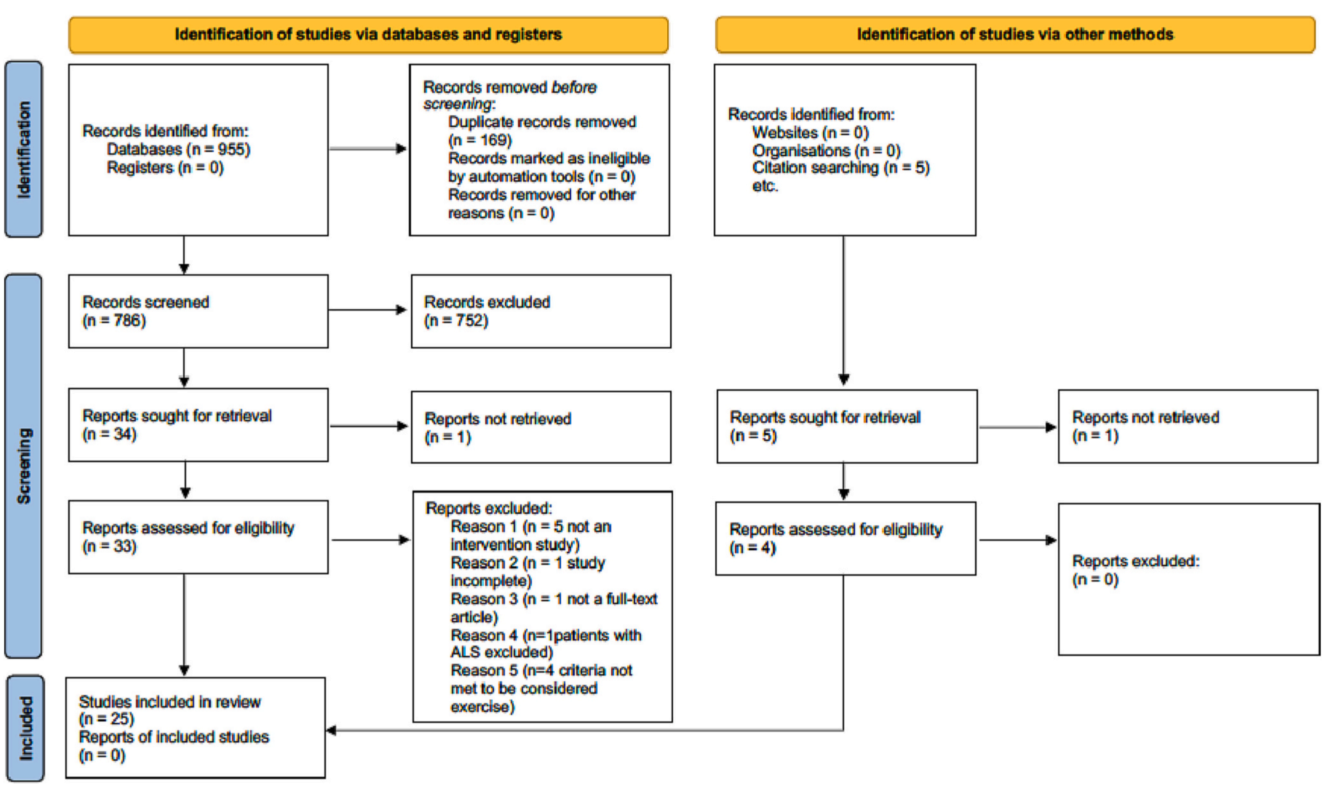

Fig. 1. Amyotrophic lateral sclerosis rating scale revised (PRISMA) flow diagram.

Table 1
Summary of the level of evidence and the appraisal of quality of studies for each outcome organized by how many studies report the outcome.

Outcomes	Study	Sample size	Level of evidence	Adjusted KMET score	Quality
ALSFRS-R	Plowman et al. (2019) [49]	48	1b	28/28 (100%)	Strong
	Zucchi et al. (2019) [35]	65	1b	26/28 (92.9%)	Strong
	van Groenestijn (2019) [45]	57	1b	26/28 (92.9%)	Strong
	Lunetta et al. (2016) [29]	60	1b	25/28 (89.3%)	Strong
	Clawson et al. (2018) [30]	59	1b	24/28 (85.7%)	Strong
	Bello-Haas et al. (2007) [37]	27	1b	24/28 (85.7%)	Strong
	Pinto et al. (2012) [51]	26	1b	24/28 (85.7%)	Strong
	Drory et al. (2001) [28]	25	1b	22/28 (78.6%)	Good
	Braga et al. (2018a) [34]	48	2b	25/28 (89.3%)	Strong
	Sanjak et al. (2010) [42]	9	2b	20/28 (71.4%)	Good
	Pinto & de Carvalho (2013) [52]	34	2b	19/28 (67.9%)	Good
	Sivaramakrishnan & Madhavan (2019) [43]	9	2b	19/28 (67.9%)	Good
FVC	Plowman et al. (2019) [49]	48	1b	28/28 (100%)	Strong
	Zucchi et al. (2019) [35]	65	1b	26/28 (92.9%)	Strong
	van Groenestijn (2019) [45]	57	1b	26/28 (92.9%)	Strong
	Lunetta et al. (2016) [29]	60	1b	25/28 (89.3%)	Strong
	Bello-Haas et al. (2007) [37]	27	1b	24/28 (85.7%)	Strong
	Pinto et al. (2012) [51]	26	1b	24/28 (85.7%)	Strong
	Pinto et al. (1999) [41]	20	2b	20/28 (71.4%)	Good
FSS	Merico et al. (2018) [33]	38	1b	25/28 (89.3%)	Strong
	Bello-Haas et al. (2007) [37]	27	1b	24/28 (85.7%)	Strong
	Pinto et al. (2012) [51]	26	1b	24/28 (85.7%)	Strong
	Clawson et al. (2018) [30]	59	1b	24/28 (85.7%)	Strong
	Drory et al. (2001) [28]	25	1b	22/28 (78.6%)	Good
	Sanjak et al. (2010) [42]	9	2b	20/28 (71.4%)	Good
	Sivaramakrishnan & Madhavan (2019) [43]	9	2b	19/28 (67.9%)	Good
MEP	Plowman et al. (2019) [49]	48	1b	28/28 (100%)	Strong
	Pinto et al. (2012) [51]	26	1b	24/28 (85.7%)	Strong
	Plowman et al. (2016) [48]	25	2b	20/28 (71.4%)	Good
FIM	Merico et al. (2018) [33]	38	1b	25/28 (89.3%)	Strong
	Pinto et al. (2012) [51]	26	1b	24/28 (85.7%)	Strong
	Pinto et al. (1999) [41]	20	2b	20/28 (71.4%)	Good
6MWT	Merico et al. (2018) [33]	38	1b	25/28 (89.3%)	Strong
	Sanjak et al. (2010) [42]	9	2b	20/28 (71.4%)	Good
	Sivaramakrishnan & Madhavan (2019) [43]	9	2b	19/28 (67.9%)	Good
SF-36	van Groenestijn (2019) [45]	57	1b	26/28 (92.9%)	Strong
	Bello-Haas et al. (2007) [37]	27	1b	24/28 (85.7%)	Strong
	Drory et al. (2001) [28]	25	1b	22/28 (78.6%)	Good
Survival time; time to death	Zucchi et al. (2019) [35]	65	1b	26/28 (92.9%)	Strong
	van Groenestijn (2019) [45]	57	1b	26/28 (92.9%)	Strong
	Lunetta et al. (2016) [29]	60	1b	25/28 (89.3%)	Strong
	Pinto & de Carvalho (2013) [52]	34	2b	19/28 (67.9%)	Good
Voluntary Cough Spirometry	Plowman et al. (2019) [49]	48	1b	28/28 (100%)	Strong
	Plowman et al. (2016) [48]	25	2b	20/28 (71.4%)	Good
McGill Quality of Life Questionnaire	Zucchi et al. (2019) [35]	65	1b	26/28 (92.9%)	Strong
	Lunetta et al. (2016) [29]	60	1b	25/28 (89.3%)	Strong
Visual analog scale for musculoskeletal pain	van Groenestijn (2019) [45]	57	1b	26/28 (92.9%)	Strong
	Clawson et al. (2018) [30]	59	1b	24/28 (85.7%)	Strong
	Drory et al. (2001) [28]	25	1b	22/28 (78.6%)	Good
ALS Quality of Life Score	Zucchi et al. (2019) [35]	65	1b	26/28 (92.9%)	Strong
	Clawson et al. (2018) [30]	59	1b	24/28 (85.7%)	Strong
Manual muscle strength test	Drory et al. (2001) [28]	25	1b	22/28 (78.6%)	Good
	Sanjak et al. (2010) [42]	9	2b	20/28 (71.4%)	Strong
Cardiopulmonary measures	van Groenestijn (2019) [45]	57	1b	26/28 (92.9%)	Strong
	Merico et al. (2018) [33]	38	1b	25/28 (89.3%)	Strong
	Braga et al. (2018a) [34]	48	2b	25/28 (89.3%)	Strong
Beck's Depression Inventory	Zucchi et al. (2019) [35]	65	1b	26/28 (92.9%)	Strong
	Sivaramakrishnan & Madhavan (2019) [43]	9	2b	19/28 (67.9%)	Good
MVIC	Bello-Haas et al. (2007) [37]	27	1b	24/28 (85.7%)	Strong
	Sanjak et al. (2010) [42]	9	2b	20/28 (71.4%)	Good
Physiologic measures of swallowing and PAS	Plowman et al. (2019) [49]	48	1b	28/28 (100%)	Strong
	Plowman et al. (2016) [48]	25	2b	20/28 (71.4%)	Good

2.4. Study selection

Articles were independently screened by a single author based on title, abstract, and full text. As needed, a second author was consulted for consensus on article eligibility.

2.5. Quality assessment and data extraction

Two authors independently judged level of evidence, study quality, and extracted relevant data for each eligible article. Level of evidence was assigned based on *The Oxford Centre for Evidence-based Medicine Levels of Evidence* [26]. Study quality was evaluated using the *QualSyst* [27], which consists of 14 items. For each *QualSyst* item, a score of 2 was assigned if the criteria were completely met, 1 if the criteria were partially met, and 0 if the criteria were not met. The *QualSyst* includes several items that may be scored as N/A, however, to make the scoring consistent across studies, we elected to score these items as 0 instead of N/A. Scores were totaled and a cumulative score was calculated in the form of a percentage. Overall study quality was determined based on the following criteria which were established by the authors' judgment:

Table 2
Summary of participant demographics.

Study	Sample	Sex (M/F)	Mean age ± SD (years)	Onset location (spinal/bulbar)	Mean disease duration ± SD (months)	Baseline ALSFRS-R
Bohannon (1983) [38]	ALS (*N* = 1)	0/1	56	1/0	22	Not reported
Pinto et al. (1999) [41]	ALS/MND (*N* = 20)	14/6	Treatment: 62 ± 14 Control: 64 ± 16	Not reported	0	Not reported
Drory et al. (2001) [28]	ALS (N = 25)	14/11	60	22/3	Treatment group: 20.7 Control group: 19.4	27.5
Bello-Haas et al. (2007) [37]	ALS (N = 27)	Not reported	Not reported	Not reported	Not reported	Not reported
Cheah et al. (2009) [50]	ALS/MND (N = 19)	12/7	Treatment: 54.2 ± 9.8 Control: 53.4 ± 9.5	16/3	Treatment group: 29.8 ± 15.7 Control group: 34.6 ± 33.8	Treatment group: 38.2 ± 6.5 Control group: 38.9 ± 2.7
Sanjak et al. (2010) [42]	ALS (N = 9)	4/5	62 ± 14.1 (39–77)	Not reported	Not reported	34 ± 5
Pinto et al. (2012) [51]	ALS (N = 26)	18/8	Group 1: 57.14 ± 9.3 Group 2: 56.8 ± 8.7	22/4	Group 1: 11.5 ± 5.3 Group 2: 12.6 ± 6.6	Group 1: 34.39 ± 3.64 Group 2: 33.5 ± 3.8
Pinto & de Carvalho (2013) [52]	ALS (N = 34)	20/14	Not reported	27/7	Treatment group: 36.99 ± 13.1 Control group: 24.06 ± 11	Treatment group: 34.3 ± 2.4 Control group: 33.8 ± 3.3
Tabor et al. (2016) [46]	ALS (N = 1)	1/0	71	1/0	21	32
Lunetta et al. (2016) [29]	ALS (*N* = 60)	38/22	Treatment: 61.1 ± 10.1 Control: 60.3 ± 9.9	42/18	Treatment group: 15.2 ± 7.2 Control group: 13.7 ± 6.1	Treatment group: 39.1 ± 4.7 Control group: 38.3 ± 5.1
Plowman et al. (2016) [48]	ALS (N = 25)	14/11	62.2 ± 10.5	15/10	14.5 ± 11.7	32 ± 8.5
Jensen et al. (2017) [40]	ALS (N = 6)	5/1	62.2 ± 8.2	4/2	5 patients: <12 1 patient: 180	39.7 ± 2.4
Clawson et al. (2018) [30]	ALS (*N* = 59)	39/20	Stretching group: 57.68 ± 9.72 Resistance group: 63.65 ± 10.55 Endurance group: 57.82 ± 11.88	45/14	Stretching group: 11.08 ± 13.21 Resistance group: 7.25 ± 7.21 Endurance group: 7.30 ± 6.80	Stretching group: 39.67 ± 3.71 Resistance group: 39.17 ± 4.91 Endurance group: 39.55 ± 4.97
Kato et al. (2018a) [31]	ALS (N = 2)	2/0	Case 1: 60 Case 2: 52	1/1	Case 1: 10, 20 Case 2: 15, 20	Case 1: 42, 33 Case 2: 44, 34
Kato et al. (2018b) [39]	ALS (N = 10)	9/1	61.9 ± 11.7	5/5	30.6 ± 31.3	41 ± 4.6
Robison et al. (2018) [47]	ALS (N = 1)	1/0	58	0/1	2	46
Kitano et al. (2018) [32]	ALS (*N* = 105)	72/33	Treatment: 62.8 ± 10.2 Control: 62.7 ± 12.1	70/35	Treatment group: 26.4 ± 18.8 Control group: 18 ± 20.4	Treatment group: 41.1 ± 4.5 Control group: 40.3 ± 4.4
Merico et al. (2018) [33]	ALS (*N* = 38)	23/14	Treatment: 61.6 ± 10.6 Control: 59.8 ± 14.7	37/1	Treatment group: 30.2 ± 11.8 Control group: 30.3 ± 6.7	Treatment group: 36.1 ± 4.71 Control group: 34.5 ± 3.6
Braga et al. (2018a) [34]	ALS (N = 48)	32/16	Not reported	38/10	Treatment group: 10.8 ± 6.5 Control group: 10.79 ± 7.7	Treatment group: 42.92 ± 3.51 Control group: 41.13 ± 4.83
Braga et al. (2018b) [44]	ALS (N = 10)	7/3	57 ± 9.1	9/1	7.6 ± 4.12	43 ± 2.1
Zucchi et al. (2019) [35]	ALS (*N* = 65)	49/16	Not reported	54/11	Treatment group: 15.67 ± 9.74 Control group: 16.64 ± 8.98	Treatment group: 39.84 ± 5.70 Control group: 40.15 ± 5.17
van Groenestijn (2019) [45]	ALS (N = 57)	40/17	Treatment group: 60.9 ± 10.0 Control group: 59.9 ± 10.7	45/12	Treatment group: 15.5 ± 10.9Control group: 18.0 ± 14.0	Treatment group: 42.3 ± 3.5 Control group: 42.3 ± 4.2
Plowman et al. (2019) [49]	ALS (*N* = 48)	29/19	Treatment group: 63.1 ± 10.0 Control group: 60.1 ± 10.3	35/11 2 mixed	Treatment group: 20.9 ± 14.5 Control group: 16.9 ± 6.8	Treatment group: 36.6 ± 6.3 Control group: 37.5 ± 6.1
Pegoraro et al. (2019) [36]	ALS (*N* = 18)	11/7	61.1 ± 12.8	Not reported	51.6 ± 12	34.6 ± 4.9
Sivaramakrishnan & Madhavan (2019) [43]	ALS (N = 9)	5/4	59.22 ± 12.3	6/3	28.44	33

≥80% indicated strong quality, 60% to 79% indicated good quality, 50% to 59% indicated average quality, and < 50% indicated poor quality.

Findings were imported into Microsoft Excel for independent review. Following data extraction, studies were initially categorized into four exercise regimens (combined treatment [28–37], resistance exercise [38–40], aerobic endurance [41–45], and respiratory muscle strength training approaches) [46–52]. However, due to the limited data for studies that explored respiratory muscle strength training (expiratory muscle strength training [EMST], inspiratory muscle strength training [IMST]) [46–52] and aerobic endurance exercise regimens [41–45], as well as the heterogeneity observed in outcomes and treatment protocols for studies that explored combined exercise regimens [28–37], a meta-analysis based on exercise regimen was not feasible.

Therefore, studies were recategorized based on similar post-exercise outcomes to determine treatment response. Combining studies based on outcomes is a meta-analytic technique that has been used in similar research studies [53]. Studies were included in the meta-analysis if they were a level 1b or 2b study, were rated as having good to strong quality (≥60%) and reported effect data for extraction. Outcomes were analyzed with Comprehensive Meta-Analysis (CMA) V2 software and random effects models and were reported as Hedge's G. Based on the studies that were included, effects were examined at 0–4 months, up to 6 months, and > 6 months. Outcomes evaluated included the ALS functional rating scale revised (ALSFRS-R) [54,55], forced vital capacity (FVC), the fatigue severity scale (FSS) [56], the McGill quality of life questionnaire (McGill QOL) [57], functional independent measure (FIM) scores [58], maximum expiratory pressure (MEP), and penetration-aspiration scale (PAS) scores [59,60]. Pre-specified sensitivity analyses were performed for 1) controlled trials vs. all studies and 2) ALSFRS-R bulbar, respiratory, and motor subscales. Heterogeneity of the pooled outcome measures was computed with the I^2 statistic and was

Table 3
Summary of study results following exercise regimens for functional outcomes reported.

Study	Exercise arms	Dosage	Results
ALSFRS-R			
Plowman et al. (2019) [49]	Active EMST (N = 24): devices set to 50% of MEP Sham EMST(N = 24): devices set to 0% resistance	Sets: 5 Reps: 5 Days per week: 5 Length of exercise regimen: 8 weeks	No significant difference in ALSFRS-R scores between groups.
Cheah et al. (2009) [50]	IMST (N = 9): first week: device 15% of SNIP, second week: device 30% of SNIP, third week: 45% of SNIP, fourth week: 60% of SNIP, and then maintained at 60%; Sham (N = 10)	Length of exercise: 10 min Times per day: 3 Days per week: 7 Length of regimen: 12 weeks	No significant difference in ALSFRS-R scores between groups.
Zucchi et al. (2019) [35]	Intensive exercise regimen (N = 32): aerobic and endurance resistance exercise training Control exercise regimen (N = 33): aerobic and endurance resistance exercise training	Length of exercise: 45 min Days per week: 2–5 Length of exercise regimen: 10 weeks	No significant difference in ALSFRS-R scores between groups.
van Groenestijn (2019) [45]	Aerobic endurance training (N = 27): aerobic exercises (cyclergometer, treadmill, stepboard, and muscle strengthening exercises) Usual care (N = 30): neuropalliative care by multidisciplinary care team	Length of exercise: 20–60 min Days per week: 3 Length of exercise regimen: 16 weeks	No significant difference in ALSFRS-R scores between groups.
Lunetta et al. (2016) [29]	Active exercise (N = 30): three subgroups: active exercises associated with cycloergometer activity (n = 10), active exercises (n = 10), passive exercises (n = 10) Control exercise programs (N = 30): passive and stretching exercises	Length of exercise: 20 min Days per week: 2 Length of exercise regimen: 6 months	ALSFRS-R total scores and motor sub scores were higher for the exercise group (p = 0.0298, p = 0.0293).
Clawson et al. (2018) [30]	Resistance (N = 18): cuff weights for the upper limbs and hip flexion Endurance (N = 20): upper and lower limb cycling Stretching/range of motion (N = 21): passive upper and lower limb stretching with a partner	Length of exercise regimen: 6 months	No significant changes in ALSFRS-R scores or differences between groups.
Bello-Haas et al. (2007) [37]	Home exercise program (N = 13): individualized upper and lower extremity resistance exercise + usual care stretching exercises; Control exercise (N = 14): upper and lower extremity stretching 1×/day	Times per day: 1 Length of regimen: 6 months	Differences in ALSFRS-R scores between groups at 3 and 6 months (p = 0.05, p = 0.02, p = 0.01).
Pinto et al. (2012) [51]	Active IMST (N = 13): Device set to 30–40% resistance Delayed intervention (N = 13): First 4 months device set to lowest resistance, last 4 months followed IMST protocol	Length of exercise: 10 min Times per day: 2 Length of regimen; 4–8 months	No significant difference in ALSFRS-R scores between groups.
Drory et al. (2001) [28]	Individualized daily exercise program designed by physical therapist (N = 14); Control (N = 11)	Length of exercise: 15 min Times per day: 2 Length of regimen: 3–12 months	Slower decline in ALSFRS-R scores in exercise group at 3 months (p < 0.001).
Braga et al. (2018a) [34]	Cardiopulmonary exercise training (N = 24): standard of care exercises+ aerobic exercise protocol on a treadmill Control exercise: range of motion exercises, limbs relaxation, trunk balance, gait training.	Days per week: 2 Length of exercise regimen: 6 months	• Higher ALSFRS-R scores at time point two for CPET group (p = 0.035). • Spinal ALSFRS-R scores (p < 0.001) and the CPET group (p = 0.021) were significant predictors of overall ALSFRS-R scores at time point two (R^2 = 0.51).
Sanjak et al. (2010) [42]	Supported treadmill ambulation (N = 9)	Length of exercise: 30 min (5 min exercise/5 min rest) Days per week: 3 Length of regimen: 8 weeks	Improvement in ALSFRS-R scores, RPE, and 6MWT at 4 and 8 weeks ($p \leq 0.05$).
Pinto & de Carvalho (2013) [52]	Early intervention exercise group (N = 11); Late intervention exercise group (N = 7): IMST with device set to 30–40% of maximum inspiratory pressure; Historical control group (N = 16)	Length of exercise: 10 min Times per day: 2 Length of exercise regimen: 8–32 months	No significant difference in ALSFRS-R scores between groups.
Sivaramakrishnan & Madhavan (2019) [43]	Recumbent stepping (N = 9):	Length of exercise: 40 min Days per week: 3 Length of exercise regimen: 4 weeks	No significant differences in ALSFRS-R scores 1-month post-treatment.
Pegoraro et al. (2019) [36]	Progressive muscular strength training, aerobic	Length of exercise: 60 min	Improvement in ALSFRS-R scores ($p \leq 0.05$).

(continued on next page)

Table 3 (*continued*)

Study	Exercise arms	Dosage	Results
	endurance exercises ($N = 18$): cycle ergometer, arm-leg ergometry or treadmill, standard rehab (stretching, active mobilization, general reinforcement)	Days per week: 7 Length of exercise regimen: 6 weeks	
Kitano et al. (2018) [32]	Home based exercise ($N = 21$): muscle stretching and strength training for upper and lower limbs Historical cohort ($N = 84$): exercise under the direction of a physical therapist	Frequency/ reps: determined by a physical therapist Length of exercise regimen: 6 months	Total ALSFRS score and respiratory sub score was higher for the exercise group ($p = 0.44$, $p < 0.001$).
Jensen et al. (2017) [40]	Resistance training ($N = 6$): upper and lower body resistance exercises	Days per week: 2–3 Sets: 2–3 Reps: 5–12 Length of exercise regimen: 24 weeks (12 weeks lead-in, 12 weeks resistance training)	Decline in ALSFRS-R scores at the same rate or more after training.
Braga et al. (2018b) [44]	Home-based aerobic exercise program ($N = 10$): treadmill protocol, training zone above ventilator threshold 1, below 75% of predicted maximum heart rate, $SpO2 \geq 93\%$	Length of exercise: 25 min Days per week: 1 Length of exercise regimen: 6 months	Decline in ALSFRS-R scores ($p = 0.008$).
Robison et al. (2018) [47]	IMST and EMST ($N = 1$): device set to 30% of MIP/MEP	Reps: 25 each Days per week: 5 Length of exercise regimen: 24 months	Two-point decrease in ALSFRS-R score.
Tabor et al. (2016) [46]	Sham/EMST (N = 1): for sham, spring-loaded valve removed from device; for EMST, device set to 50% of MEP	Number of reps: 25 Days per week: 5 Length of exercise regimen: 16 weeks (8 weeks sham, 8 weeks active EMST)	ALSFRS-R scores remained relatively stable from baseline (32), post-sham (29), and post EMST (30).
FIM			
Merico et al. (2018) [33]	Specific exercise program (N = 23): aerobic workout and isometric contractions Control exercise (N = 15): stretching, active mobilization, general muscle reinforcement	Length of exercise regimen: 5 weeks	• Difference in FIM scores after 5 weeks for both groups ($p < 0.05$); no difference between groups ($p > 0.05$). • FIM scores were associated with ventilation during exercise ($r = 0.25$, $p < 0.01$), resting heart rate ($r = -0.20$, $p = 0.01$), R biceps strength ($r = 0.24$, $p < 0.01$), and the 6MWT ($r = 0.23$, $p < 0.01$).
Pinto et al. (2012) [51]	Active IMST ($N = 13$): Device set to 30–40% resistance Delayed intervention (N = 13): First 4 months device set to lowest resistance, last 4 months followed IMST protocol	Length of exercise: 10 min Times per day: 2 Length of regimen; 4–8 months	No significant differences in FIM scores between groups.
Pinto et al. (1999) [41]	Treatment ($N = 8$): Endurance-based exercise: Bruce or Naughton ramp treadmill protocol with Bipap STD until anaerobic threshold was reached; Control ($N = 12$)	Length of regimen: 1 year	Higher FIM scores for exercise group ($p < 0.03$).
Pegoraro et al. (2019) [36]	Progressive muscular strength training, aerobic endurance exercises ($N = 18$): cycle ergometer, arm-leg ergometry or treadmill, standard rehab (stretching, active mobilization, general reinforcement)	Length of exercise: 60 min Days per week: 7 Length of exercise regimen: 6 weeks	Improvement in FIM scores ($p \leq 0.05$).
Survival time; time to gastrostomy, noninvasive ventilation/invasive ventilation, deaths			
Zucchi et al. (2019) [35]	Intensive exercise regimen (N = 32): aerobic and endurance resistance exercise training Control exercise regimen (N = 33): aerobic and endurance resistance exercise training	Length of exercise: 45 min Days per week: 2–5 Length of exercise regimen: 10 weeks	No significant differences between groups in survival, time to gastrostomy, noninvasive ventilation/ invasive ventilation.
van Groenestijn (2019) [45]	Aerobic endurance training ($N = 27$): aerobic exercises (cyclergometer, treadmill, stepboard, and muscle strengthening exercises) Usual care ($N = 30$): neuropalliative care by multidisciplinary care team	Length of exercise: 20–60 min Days per week: 3 Length of exercise regimen: 16 weeks	Patients who completed the exercise training protocol ($n = 10$) had longer survival times than those who did not ($n = 17$).
Lunetta et al. (2016) [29]	Active exercise ($N = 30$): three subgroups: active exercises associated with cycloergometer	Length of exercise: 20 min Days per week: 2	No significant differences between groups in survival.

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Table 3 (*continued*)

Study	Exercise arms	Dosage	Results
	activity (n = 10), active exercises (n = 10), passive exercises (n = 10) Control exercise programs (N = 30): passive and stretching exercises	Length of exercise regimen: 6 months	
Pinto & de Carvalho (2013) [52]	Early intervention exercise group (*N* = 11); Late intervention exercise group (*N* = 7): IMST with device set to 30–40% of maximum inspiratory pressure; Historical control group (*N* = 16)	Length of exercise: 10 min Times per day: 2 Length of exercise regimen: 8–32 months	• Patients in the early and late intervention groups survived longer ($p < 0.001$). • FVC was a prognostic factor for the exercise group ($p < 0.05$) and diagnostic delay was a prognostic factor for the control ($p < 0.05$). • IMST, gender, and phrenic nerve response amplitude were predictive of mortality ($p < 0.05$).
Barthel Index			
Pinto et al. (1999) [41]	Treatment (N = 8): Endurance-based exercise: Bruce or Naughton ramp treadmill protocol with Bipap STD until anaerobic threshold was reached; Control (N = 12)	Length of regimen: 1 year	No significant differences in Barthel Index scores between groups.
Pegoraro et al. (2019) [36]	Progressive muscular strength training, aerobic endurance exercises (*N* = 18): cycle ergometer, arm-leg ergometry or treadmill, standard rehab (stretching, active mobilization, general reinforcement)	Length of exercise: 60 min Days per week: 7 Length of exercise regimen: 6 weeks	Improvement in Barthel Index scores ($p \leq 0.05$).

said to be present when Q > df or Q > 30, which corresponds to $p < 0.5$. To evaluate publication bias, Begg-Mazumdar's Kendall's tau, Egger's bias, and visual inspection of the funnel plot were employed.

3. Results

The search yielded 959 total results, with 25 research articles initially meeting inclusionary criteria for the systematic review (Fig. 1).

3.1. Study design and methodological quality

Of the 25 eligible studies, the majority (40%; $n = 10$) were randomized controlled trials (RCTs) (Level 1b) [28–30,33,35,37,49–51], followed by cohort (Level 2b) (28%; $n = 7$) [34,36,41–43,48,52] and case series (Level 4) (28%; n = 7) [31,38–40,44,46,47], and case control (Level 3b) (4%; $n = 1$) [32] investigations. Most studies (80%) were

Table 4
Summary of study results following exercise regimens for muscular outcomes reported.

Study	Exercise arms	Dosage	Results
ASH			
Clawson et al. (2018) [30]	Resistance (*N* = 18): cuff weights for the upper limbs and hip flexion Endurance (*N* = 20): upper and lower limb cycling Stretching/range of motion (*N* = 21): passive upper and lower limb stretching with a partner	Length of exercise regimen: 6 months	No significant changes in ASH scores or differences between groups.
Drory et al. (2001) [28]	Individualized daily exercise program designed by physical therapist (N = 14); Control (*N* = 11)	Length of exercise: 15 min Times per day: 2 Length of regimen: 3–12 months	Decreased spasticity as measured by ASH scores in exercise group at 3 months ($p < 0.05$).
Kato et al. (2018b) [39]	Individualized physical therapy exercises (*N* = 10): lower limb muscle strengthening exercises and respiratory, gait, and stair-climbing exercises	Length of exercise regimen: 2–3 weeks	No significant changes in ASH scores.
Grip Strength			
Cheah et al. (2009) [50]	IMST (*N* = 9): first week: device 15% of SNIP, second week: device 30% of SNIP, third week: 45% of SNIP, fourth week: 60% of SNIP, and then maintained at 60%; Sham (N = 10)	Length of exercise: 10 min Times per day: 3 Days per week: 7 Length of regimen: 12 weeks	After training withdrawal, both groups had declines in grip strength ($p < 0.01$).
Clawson et al. (2018) [30]	Resistance (N = 18): cuff weights for the upper limbs and hip flexion Endurance (*N* = 20): upper and lower limb cycling Stretching/range of motion (*N* = 21): passive upper and lower limb stretching with a partner	Length of exercise regimen: 6 months	No significant changes in grip strength or differences between groups.
van Groenestijn (2019) [45]	Aerobic endurance training (*N* = 27): aerobic exercises (cyclergometer, treadmill, stepboard, and muscle strengthening exercises) Usual care (N = 30): neuropalliative care by multidisciplinary care team	Length of exercise: 20–60 min Days per week: 3 Length of exercise regimen: 16 weeks	No significant changes in grip strength or differences between groups.

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Table 4 (*continued*)

Study	Exercise arms	Dosage	Results
Manual muscle strength test			
Drory et al. (2001) [28]	Individualized daily exercise program designed by physical therapist ($N = 14$); Control ($N = 11$)	Length of exercise: 15 min Times per day: 2 Length of regimen: 3–12 months	No significant differences in manual muscle strength between groups.
Sanjak et al. (2010) [42]	Supported treadmill ambulation ($N = 9$)	Length of exercise: 30 min (5 min exercise/5 min rest) Days per week: 3 Length of regimen: 8 weeks	No significant differences in manual muscle strength between groups.
30 s chair rise, timed up and go			
Sivaramakrishnan & Madhavan (2019) [43]	Recumbent stepping (N = 9):	Length of exercise: 40 min Days per week: 3 Length of exercise regimen: 4 weeks	No significant differences in the timed up and go test post-treatment.
Jensen et al. (2017) [40]	Resistance training ($N = 6$): upper and lower body resistance exercises	Days per week: 2–3 Sets: 2–3 Reps: 5–12 Length of exercise regimen: 24 weeks (12 weeks lead-in, 12 weeks resistance training)	Improvement in 30 s chair rise/timed up and go test.
Neurophysiological Index			
Cheah et al. (2009) [50]	IMST ($N = 9$): first week: device 15% of SNIP, second week: device 30% of SNIP, third week: 45% of SNIP, fourth week: 60% of SNIP, and then maintained at 60%; Sham ($N = 10$)	Length of exercise: 10 min Times per day: 3 Days per week: 7 Length of regimen: 12 weeks	No significant difference in neurophysiological index between groups.
Pinto et al. (2012) [51]	Active IMST ($N = 13$): Device set to 30–40% resistance Delayed intervention ($N = 13$): First 4 months device set to lowest resistance, last 4 months followed IMST protocol	Length of exercise: 10 min Times per day: 2 Length of regimen; 4–8 months	No significant differences in neurophysiological index between groups.
KEMS			
Kato et al. (2018a) [31]	Resistance exercise ($N = 2$): lower limb muscle strengthening exercises	Length of exercise: 30 min Days per week: 5 Length of exercise regimen: 2 weeks	• KEMS improved by 20% or more during the first hospitalization for both patients; KEMS was maintained for 10 months for case 1.
Kato et al. (2018b) [39]	Individualized physical therapy exercises ($N = 10$): lower limb muscle strengthening exercises and respiratory, gait, and stair-climbing exercises	Length of exercise regimen: 2–3 weeks	KEMS improved for stronger and weaker limbs ($p < 0.01$).
MVIC			
Bello-Haas et al. (2007) [37]	Home exercise program ($N = 13$): individualized upper and lower extremity resistance exercise + usual care stretching exercises; Control exercise ($N = 14$): upper and lower extremity stretching 1×/day	Times per day: 1 Length of regimen: 6 months	Slower decline in lower extremity MVIC in the exercise group at 6 months ($p = 0.03$).
Sanjak et al. (2010) [42]	Supported treadmill ambulation ($N = 9$)	Length of exercise: 30 min (5 min exercise/5 min rest) Days per week: 3 Length of regimen: 8 weeks	No significant differences in MVIC post-treatment.

rated as having “strong” or “good” quality, with an average *QualSyst* score of 73.3% (±18.03). The most common biases observed on the *QualSyst* were regarding the items insufficient description of method of subject selection or source of input variable, inadequate sample size, and inadequate control of confounding variables. Table 1 shows a summary of the level of evidence and the appraisal of the study quality for each outcome.

3.2. Participant characteristics

A total of 723 participants (459 males) diagnosed with definite or probable ALS/MND were included across all studies. When symptom onset location was reported, most patients (76.3%; $N = 495$) presented with spinal onset. Baseline ALS Functional Rating Scale Revised (ALSFRS-R) scores were reported in 22 studies and ranged from 32 to 46, suggesting minimal-mild to mild-moderate disease severity [54,55]. Complete demographic information can be viewed in Table 2.

3.3. Exercise regimen and treatment outcomes

A summary of the interventions organized by outcomes are included in Tables 3–6.

A total of 10 studies utilized a combination of aerobic endurance, resistance, and stretching/range of motion [28–37]; 3 employed resistance exercise only [38–40]; 5 consisted of solely aerobic endurance [41–45]; and 7 studies employed RMST (IMST and/or EMST) [46–52]. Length of exercise regimens ranged from 2 weeks to 2 years in duration. No adverse outcomes attributed to participation in the exercise intervention were reported in any study. The most reported outcome was the ALSFRS-R total score ($n = 20$), following by forced vital capacity (FVC)

Table 5
Summary of study results following exercise regimens for respiratory and swallow outcomes reported.

Study	Exercise arms	Dosage	Results
FVC			
Plowman et al. (2019) [49]	Active EMST (N = 24): devices set to 50% of MEP Sham EMST(N = 24): devices set to 0% resistance	Sets: 5 Reps: 5 Days per week: 5 Length of exercise regimen: 8 weeks	No significant difference in FVC between groups.
van Groenestijn (2019) [45]	Aerobic endurance training (N = 27): aerobic exercises (cyclergometer, treadmill, stepboard, and muscle strengthening exercises) Usual care (N = 30): neuropalliative care by multidisciplinary care team	Length of exercise: 20–60 min Days per week: 3 Length of exercise regimen: 16 weeks	Slower FVC decline rate for treatment group (p = 0.48).
Cheah et al. (2009) [50]	IMST (N = 9): first week: device 15% of SNIP, second week: device 30% of SNIP, third week: 45% of SNIP, fourth week: 60% of SNIP, and then maintained at 60%; Sham (N = 10)	Length of exercise: 10 min Times per day: 3 Days per week: 7 Length of regimen: 12 weeks	No significant difference in FVC between groups.
Zucchi et al. (2019) [35]	Intensive exercise regimen (N = 32): aerobic and endurance resistance exercise training Control exercise regimen (N = 33): aerobic and endurance resistance exercise training	Length of exercise: 45 min Days per week: 2–5 Length of exercise regimen: 10 weeks	No significant difference in FVC between groups.
Lunetta et al. (2016) [29]	Active exercise (N = 30): three subgroups: active exercises associated with cycloergometer activity (n = 10), active exercises (n = 10), passive exercises (n = 10) Control exercise programs (N = 30): passive and stretching exercises	Length of exercise: 20 min Days per week: 2 Length of exercise regimen: 6 months	No significant difference in FVC between groups.
Clawson et al. (2018) [30]	Resistance (N = 18): cuff weights for the upper limbs and hip flexion Endurance (N = 20): upper and lower limb cycling Stretching/range of motion (N = 21): passive upper and lower limb stretching with a partner	Length of exercise regimen: 6 months	No significant changes in FVC or differences between groups.
Bello-Haas et al. (2007) [37]	Home exercise program (N = 13): individualized upper and lower extremity resistance exercise + usual care stretching exercises; Control exercise (N = 14): upper and lower extremity stretching 1×/day	Times per day: 1 Length of regimen: 6 months	No significant difference in FVC over time or between groups.
Pinto et al. (2012) [51]	Active IMST (N = 13): Device set to 30–40% resistance Delayed intervention (N = 13): First 4 months device set to lowest resistance, last 4 months followed IMST protocol	Length of exercise: 10 min Times per day: 2 Length of regimen; 4–8 months	No significant difference in FVC between groups.
Braga et al. (2018a) [34]	Cardiopulmonary exercise training (N = 24): standard of care exercises+ aerobic exercise protocol on a treadmill Control exercise: range of motion exercises, limbs relaxation, trunk balance, gait training.	Days per week: 2 Length of exercise regimen: 6 months	Higher FVC predicted at time point one for CPET group (p = 0.002).
Pinto et al. (1999) [41]	Treatment (N = 8): Endurance-based exercise: Bruce or Naughton ramp treadmill protocol with Bipap STD until anaerobic threshold was reached; Control (N = 12)	Length of regimen: 1 year	Attenuated FVC decline rate for exercise group (p < 0.02).
Pinto & de Carvalho (2013) [52]	Early intervention exercise group (N = 11); Late intervention exercise group (N = 7): IMST with device set to 30–40% of maximum inspiratory pressure; Historical control group (N = 16)	Length of exercise: 10 min Times per day: 2 Length of exercise regimen: 8–32 months	FVC was a prognostic factor for the exercise group (p < 0.05) and diagnostic delay was a prognostic factor for the control (p < 0.05).
Braga et al. (2018b) [44]	Home-based aerobic exercise program (N = 10): treadmill protocol, training zone above ventilator threshold 1, below 75% of predicted maximum heart rate, SpO2 ≥ 93%	Length of exercise: 25 min Days per week: 1 Length of exercise regimen: 6 months	No significant changes in FVC following exercise protocol.
Robison et al. (2018) [47]	IMST and EMST (N = 1): device set to 30% of MIP/MEP	Reps: 25 each Days per week: 5 Length of exercise regimen: 24 months	Stable FVC (104% predicted).
MEP			
Plowman et al. (2019) [49]	Active EMST (N = 24): devices set to 50% of MEP Sham EMST(N = 24): devices set to 0% resistance	Sets: 5 Reps: 5 Days per week: 5 Length of exercise regimen: 8 weeks	Increase in MEP for active EMST group pre to post treatment (p = 0.009).
Cheah et al. (2009) [50]	IMST (N = 9): first week: device 15% of SNIP, second week: device 30% of SNIP,	Length of exercise: 10 min Times per	MEP declined for both groups following training

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Table 5 (*continued*)

Study	Exercise arms	Dosage	Results
	third week: 45% of SNIP, fourth week: 60% of SNIP, and then maintained at 60%; Sham (N = 10)	day: 3 Days per week: 7 Length of regimen: 12 weeks	withdrawal ($p <$ 0.05).
Pinto et al. (2012) [51]	Active IMST (*N* = 13): Device set to 30–40% resistance Delayed intervention (N = 13): First 4 months device set to lowest resistance, last 4 months followed IMST protocol	Length of exercise: 10 min Times per day: 2 Length of regimen; 4–8 months	No significant difference in MEP between groups.
Plowman et al. (2016) [48]	EMST (*N* = 25): devices set to 50% of MEP	Sets: 5 Reps: 5 Days per week: 5 Length of exercise regimen: 5 weeks	Increase in MEP over time ($p <$ 0.03).
Robison et al. (2018) [47]	IMST and EMST (*N* = 1): device set to 30% of MIP/MEP	Reps: 25 each Days per week: 5 Length of exercise regimen: 24 months	MEP: 89 cm H_20 increase.
Tabor et al. (2016) [46]	Sham/EMST (N = 1): for sham, spring-loaded valve removed from device; for EMST, device set to 50% of MEP	Number of reps: 25 Days per week: 5 Length of exercise regimen: 16 weeks (8 weeks sham, 8 weeks active EMST)	MEP: 5 cm H_20 decline after sham training; 52 cm H_20 increase after active EMST.
6MWT			
Cheah et al. (2009) [50]	IMST (*N* = 9): first week: device 15% of SNIP, second week: device 30% of SNIP, third week: 45% of SNIP, fourth week: 60% of SNIP, and then maintained at 60%; Sham (*N* = 10)	Length of exercise: 10 min Times per day: 3 Days per week: 7 Length of regimen: 12 weeks	After training withdrawal, both groups had declines in 6MWT ($p = 0.01$).
Merico et al. (2018) [33]	Specific exercise program (*N* = 23): aerobic workout and isometric contractions Control exercise (*N* = 15): stretching, active mobilization, general muscle reinforcement	Length of exercise regimen: 5 weeks	No significant differences in 6MWT over time or between groups.
Sanjak et al. (2010) [42]	Supported treadmill ambulation (*N* = 9)	Length of exercise: 30 min (5 min exercise/5 min rest) Days per week: 3 Length of regimen: 8 weeks	Improvement in 6MWT at 4 and 8 weeks ($p \leq 0.05$).
Sivaramakrishnan & Madhavan (2019) [43]	Recumbent stepping (N = 9):	Length of exercise: 40 min Days per week: 3 Length of exercise regimen: 4 weeks	No significant differences in 6MWT 1-month post-treatment.
Voluntary Cough Spirometry			
Plowman et al. (2019) [49]	Active EMST (*N* = 24): devices set to 50% of MEP Sham EMST(N = 24): devices set to 0% resistance	Sets: 5 Reps: 5 Days per week: 5 Length of exercise regimen: 8 weeks	No significant differences in voluntary cough spirometry measures between groups.
Plowman et al. (2016) [48]	EMST (*N* = 25): devices set to 50% of MEP	Sets: 5 Reps: 5 Days per week: 5 Length of exercise regimen: 5 weeks	No significant differences in voluntary cough spirometry measures following EMST.
Tabor et al. (2016) [46]	Sham/EMST (N = 1): for sham, spring-loaded valve removed from device; for EMST, device set to 50% of MEP	Number of reps: 25 Days per week: 5 Length of exercise regimen: 16 weeks (8 weeks sham, 8 weeks active EMST)	Cough inspired volume and median cough total within an epoch increased following sham and active EMST training.
MIP			
Cheah et al. (2009) [50]	IMST (N = 9): first week: device 15% of SNIP, second week: device 30% of SNIP, third week: 45% of SNIP, fourth week: 60% of SNIP, and then maintained at 60%; Sham (*N* = 10)	Length of exercise: 10 min Times per day: 3 Days per week: 7 Length of regimen: 12 weeks	MIP declined for both groups following training withdrawal ($p =$ 0.05).
Pinto et al. (2012) [51]	Active IMST (*N* = 13): Device set to 30–40% resistance Delayed intervention (*N* = 13): First 4 months device set to lowest resistance, last 4 months followed IMST protocol	Length of exercise: 10 min Times per day: 2 Length of regimen; 4–8 months	No significant difference in MIP between groups.
Robison et al. (2018) [47]	IMST and EMST (N = 1): device set to 30% of MIP/MEP	Reps: 25 each Days per week: 5 Length of exercise regimen: 24 months	MIP: 63 cm H_20 increase.
Cardiopulmonary measures			
Merico et al. (2018) [33]	Specific exercise program (*N* = 23): aerobic workout and isometric	Length of exercise regimen: 5 weeks	Difference in oxygen consumption after 5 weeks for

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Table 5 (*continued*)

Study	Exercise arms	Dosage	Results
	contractions Control exercise (N = 15): stretching, active mobilization, general muscle reinforcement		specific exercise group (p < 0.05).
van Groenestijn (2019) [45]	Aerobic endurance training (N = 27): aerobic exercises (cyclergometer, treadmill, stepboard, and muscle strengthening exercises) Usual care (N = 30): neuropalliative care by multidisciplinary care team	Length of exercise: 20–60 min Days per week: 3 Length of exercise regimen: 16 weeks	No significant differences in aerobic capacity/ oxygen uptake.
Braga et al. (2018a) [34]	Cardiopulmonary exercise training (N = 24): standard of care exercises+ aerobic exercise protocol on a treadmill Control exercise: range of motion exercises, limbs relaxation, trunk balance, gait training.	Days per week: 2 Length of exercise regimen: 6 months	Difference in oxygen uptake between groups at time point two (p < 0.05).
VC			
Cheah et al. (2009) [50]	IMST (N = 9): first week: device 15% of SNIP, second week: device 30% of SNIP, third week: 45% of SNIP, fourth week: 60% of SNIP, and then maintained at 60%; Sham (N = 10)	Length of exercise: 10 min Times per day: 3 Days per week: 7 Length of regimen: 12 weeks	VC declined for both groups following training withdrawal (p < 0.05).
Sanjak et al. (2010) [42]	Supported treadmill ambulation (N = 9)	Length of exercise: 30 min (5 min exercise/5 min rest) Days per week: 3 Length of regimen: 8 weeks	No significant changes in VC over treatment period.
PEF			
Pinto et al. (2012) [51]	Active IMST (N = 13): Device set to 30–40% resistance Delayed intervention (N = 13): First 4 months device set to lowest resistance, last 4 months followed IMST protocol	Length of exercise: 10 min Times per day: 2 Length of regimen; 4–8 months	No significant differences in PEF between groups.
Robison et al. (2018) [47]	IMST and EMST (N = 1): device set to 30% of MIP/MEP	Reps: 25 each Days per week: 5 Length of exercise regimen: 24 months	PEF: 324 L/min increase.
Physiologic measures of swallowing and PAS			
Plowman et al. (2019) [49]	Active EMST (N = 24): devices set to 50% of MEP Sham EMST(N = 24): devices set to 0% resistance	Sets: 5 Reps: 5 Days per week: 5 Length of exercise regimen: 8 weeks	Global swallow function and swallowing efficiency decreased for the sham group (p = 0.02).
Plowman et al. (2016) [48]	EMST (N = 25): devices set to 50% of MEP	Sets: 5 Reps: 5 Days per week: 5 Length of exercise regimen: 5 weeks	Increase in hyoid displacement (p < 0.02).
SNIP			
Cheah et al. (2009) [50]	IMST (N = 9): first week: device 15% of SNIP, second week: device 30% of SNIP, third week: 45% of SNIP, fourth week: 60% of SNIP, and then maintained at 60%; Sham (N = 10)	Length of exercise: 10 min Times per day: 3 Days per week: 7 Length of regimen: 12 weeks	SNIP declined for both groups following training withdrawal (p < 0.05).
Pinto et al. (2012) [51]	Active IMST (N = 13): Device set to 30–40% resistance Delayed intervention (N = 13): First 4 months device set to lowest resistance, last 4 months followed IMST protocol	Length of exercise: 10 min Times per day: 2 Length of regimen; 4–8 months	No significant differences in SNIP between groups.

(n = 13), measures of fatigue (n = 10), quality of life scales (n = 9), and maximum expiratory pressure (MEP)/maximum inspiratory pressure (MIP) (n = 7). Although five studies (20%) did not demonstrate significant improvements after completion of the exercise intervention [30,35,43–45], most studies (N = 20, 80%) reported significant positive changes in their primary outcome of interest [28,29,31–34,36–42,46–52].

3.4. Combination of aerobic endurance, resistance, and stretching/range of motion

For the 10 studies which employed a combination of aerobic, endurance and stretching/range of motion exercise regimen, the majority of studies (N = 6; 60%) employed an RCT design, with sample sizes ranging from 10 to 105 participants [28–37]. While each study reported tolerability of the exercise regimens, attrition over time ranged from 0% to 80% [28–37]. A total of 31 post-exercise outcomes were examined across combination exercise regimen studies. Eight studies found statistically significant improvements and/or attenuated decline in measures of ALS functioning, overall disease progression, and patient reported outcomes [28,29,31–34,36,37]. In contrast, two studies did not find any significant differences in outcomes after exercise completion [30,35]. Furthermore, one study found that an intensive exercise regimen (defined as 5 sessions/week) led to an increase in FSS scores, suggesting an increase in overall fatigue severity that may impact patients' function [35].

3.5. Resistance exercise

Three studies examined resistance exercise employing a case study or case series design, with participants ranging from one to six participants. No study reported adverse outcomes and one patient withdrew for

Table 6
Summary of study results following exercise regimens for patient reported outcomes reported.

Study	Exercise arms	Dosage	Results
FSS			
Merico et al. (2018) [33]	Specific exercise program ($N = 23$): aerobic workout and isometric contractions Control exercise ($N = 15$): stretching, active mobilization, general muscle reinforcement	Length of exercise regimen: 5 weeks	• Difference in FSS after 5 weeks for specific exercise group ($p < 0.05$). • FSS scores were associated with oxygen consumption ($r = 0.26, p < 0.01$), resting heart rate ($r = 0.29, p < 0.01$), R biceps strength ($r = -0.21, p = 0.01$), R tibial strength ($r = -0.19, p = 0.02$), the MRC sum score ($r = -0.28$, p < 0.01), and the 6MWT ($r = -0.27$, p $<$ 0.01).
Bello-Haas et al. (2007) [37]	Home exercise program ($N = 13$): individualized upper and lower extremity resistance exercise + usual care stretching exercises; Control exercise ($N = 14$): upper and lower extremity stretching 1×/day	Times per day: 1 Length of regimen: 6 months	No significant difference in FSS scores between groups at 3 or 6 months.
Pinto et al. (2012) [51]	Active IMST (N = 13): Device set to 30–40% resistance Delayed intervention (N = 13): First 4 months device set to lowest resistance, last 4 months followed IMST protocol	Length of exercise: 10 min Times per day: 2 Length of regimen; 4–8 months	No significant difference in FSS between groups.
Clawson et al. (2018) [30]	Resistance ($N = 18$): cuff weights for the upper limbs and hip flexion Endurance ($N = 20$): upper and lower limb cycling Stretching/range of motion ($N = 21$): passive upper and lower limb stretching with a partner	Length of exercise regimen: 6 months	No significant changes in FSS or differences between groups.
Drory et al. (2001) [28]	Individualized daily exercise program designed by physical therapist ($N = 14$); Control ($N = 11$)	Length of exercise: 15 min Times per day: 2 Length of regimen: 3–12 months	No significant difference in FSS between groups.
Sanjak et al. (2010) [42]	Supported treadmill ambulation ($N = 9$)	Length of exercise: 30 min (5 min exercise/5 min rest) Days per week: 3 Length of regimen: 8 weeks	Non-significant decrease in FSS score over treatment period.
Sivaramakrishnan & Madhavan (2019) [43]	Recumbent stepping ($N = 9$):	Length of exercise: 40 min Days per week: 3 Length of exercise regimen: 4 weeks	No significant differences in FSS 1-month post-treatment.
Pegoraro et al. (2019) [36]	Progressive muscular strength training, aerobic endurance exercises ($N = 18$): cycle ergometer, arm-leg ergometry or treadmill, standard rehab (stretching, active mobilization, general reinforcement)	Length of exercise: 60 min Days per week: 7 Length of exercise regimen: 6 weeks	Improvement in FSS scores ($p \leq 0.05$).
SF-36			
Cheah et al. (2009) [50]	IMST (N = 9): first week: device 15% of SNIP, second week: device 30% of SNIP, third week: 45% of SNIP, fourth week: 60% of SNIP, and then maintained at 60%; Sham ($N = 10$)	Length of exercise: 10 min Times per day: 3 Days per week: 7 Length of regimen: 12 weeks	No significant differences in SF-36 scores between groups.
van Groenestijn (2019) [45]	Aerobic endurance training ($N = 27$): aerobic exercises (cyclergometer, treadmill, stepboard, and muscle strengthening exercises) Usual care ($N = 30$): neuropalliative care by multidisciplinary care team	Length of exercise: 20–60 min Days per week: 3 Length of exercise regimen: 16 weeks	No significant differences in SF-36 scores between groups.
Bello-Haas et al. (2007) [37]	Home exercise program ($N = 13$): individualized upper and lower extremity resistance exercise + usual care stretching exercises; Control exercise ($N = 14$): upper and lower extremity stretching 1×/day	Times per day: 1 Length of regimen: 6 months	Difference in physical functioning sub score of SF-36 at 6 months ($p = 0.02$).
Drory et al. (2001) [28]	Individualized daily exercise program designed by physical therapist (N = 14); Control ($N = 11$)	Length of exercise: 15 min Times per day: 2 Length of regimen: 3–12 months	No significant changes in SF-36 over time or differences between groups.
McGill Quality of Life Questionnaire			
Zucchi et al. (2019) [35]	Intensive exercise regimen ($N = 32$): aerobic and endurance resistance exercise training	Length of exercise: 45 min Days per week: 2–5	No differences in McGill Quality of Life scores between groups.

(continued on next page)

Table 6 (*continued*)

Study	Exercise arms	Dosage	Results
	Control exercise regimen ($N = 33$): aerobic and endurance resistance exercise training	Length of exercise regimen: 10 weeks	
Lunetta et al. (2016) [29]	Active exercise ($N =$ 30): three subgroups: active exercises associated with cycloergometer activity ($n = 10$), active exercises (n = 10), passive exercises (n = 10) Control exercise programs (N = 30): passive and stretching exercises	Length of exercise: 20 min Days per week: 2 Length of exercise regimen: 6 months	McGill Quality of Life scores improved from baseline to 180 days for the exercise group ($p = 0.0031$).
Visual analog scale for musculoskeletal pain			
Drory et al. (2001) [28]	Individualized daily exercise program designed by physical therapist ($N = 14$); Control ($N = 11$)	Length of exercise: 15 min Times per day: 2 Length of regimen: 3–12 months	Increase in subjective pain over time in both groups.
van Groenestijn (2019) [45]	Aerobic endurance training ($N = 27$): aerobic exercises (cyclergometer, treadmill, stepboard, and muscle strengthening exercises) Usual care ($N = 30$): neuropalliative care by multidisciplinary care team	Length of exercise: 20–60 min Days per week: 3 Length of exercise regimen: 16 weeks	No significant changes in visual analog scale ratings of musculoskeletal pain or differences between groups.
Clawson et al. (2018) [30]	Resistance ($N = 18$): cuff weights for the upper limbs and hip flexion Endurance ($N = 20$): upper and lower limb cycling Stretching/range of motion ($N = 21$): passive upper and lower limb stretching with a partner	Length of exercise regimen: 6 months	No significant changes in visual analog scale ratings of musculoskeletal pain or differences between groups.
ALS Quality of Life Score			
Zucchi et al. (2019) [35]	Intensive exercise regimen ($N = 32$): aerobic and endurance resistance exercise training Control exercise regimen (N = 33): aerobic and endurance resistance exercise training	Length of exercise: 45 min Days per week: 2–5 Length of exercise regimen: 10 weeks	No significant difference in ALS Quality of Life scores between groups.
Clawson et al. (2018) [30]	Resistance (N = 18): cuff weights for the upper limbs and hip flexion Endurance (N = 20): upper and lower limb cycling Stretching/range of motion ($N = 21$): passive upper and lower limb stretching with a partner	Length of exercise regimen: 6 months	No significant changes in ALS Quality of Life scores or differences between groups.
Beck's Depression Inventory			
Zucchi et al. (2019) [35]	Intensive exercise regimen ($N = 32$): aerobic and endurance resistance exercise training Control exercise regimen ($N = 33$): aerobic and endurance resistance exercise training	Length of exercise: 45 min Days per week: 2–5 Length of exercise regimen: 10 weeks	No significant differences in Beck's Depression Inventory scores between groups.
Sivaramakrishnan & Madhavan (2019) [43]	Recumbent stepping ($N = 9$):	Length of exercise: 40 min Days per week: 3 Length of exercise regimen: 4 weeks	No significant differences in Beck's Depression Inventory scores 1-month post-treatment.

reasons unrelated to the exercise program [40]. A total of 9 post-exercise outcomes were examined across resistance exercise regimen studies. Resistance exercise led to variable outcomes with one study reporting no consistent trends [38], one study reporting improvements in muscle strength, and one study reporting mixed results in measures of function and muscle strength [40].

3.6. Aerobic endurance

One aerobic endurance exercise study was a randomized controlled trial ($N = 57$), three were cohort studies ($N = 20$, $N = 9$, N = 9) and one was a case series ($N = 10$) [41–45]. Aerobic exercise regimens were well-tolerated and the attrition rate ranged from 0% to 44% across studies [41–44]. A total of 32 post-exercise outcomes were examined across aerobic endurance exercise regimen studies. Two studies found statistically significant improvements in several measures of ALS functioning and patient perception [41,42], while two studies found no statistically significant differences in any outcome [43,45], and another found a statistically significant decline in several functional measures following the exercise regimen [44]. No adverse events were reported.

3.7. Respiratory muscle strength training

EMST: Four studies employed EMST, including two case studies, one study with a delayed intervention clinical trial ($N = 25$), and one study was a double-blind, randomized, controlled trial ($N = 48$). No study reported adverse events related to the intervention [46–49]. The attrition rate in the delayed intervention clinical trial was 40% and in the double-blind, randomized, controlled trial was 4.2% [48,49]. EMST led to improvements in MEP in all four studies [46–49]. A total of 9 post-exercise outcomes were examined across EMST exercise regimen studies. The impact of EMST on voluntary cough measurements, FVC, and ALSFRS-R scores was mixed across studies. In addition to this, one study that examined the impact of EMST and IMST found an increase in MIP [47]. Two studies found that EMST led to positive improvements in swallow function as well [48,49].

IMST: Of the four studies examining IMST, one was a case study, one was a cohort study ($N = 34$), and two were randomized, controlled trials ($N = 19$, $N = 26$) [47,50–52]. Across studies, IMST was well-tolerated and attrition rates ranged from 0 to 23.1% [50,51]. A total of 21 post-exercise outcomes were examined across IMST exercise regimen studies. All four studies found that IMST led to improvements or

Table 7
Summary of statistical analyses reported related to study outcomes.

Study	Power analysis performed	Attrition	ITT analysis	Effect sizes	Adherence to treatment
Bohannon (1983) [38]	N/A (case study)	0%	N/A (case study)	Not reported	Not reported
Pinto et al. (1999) [41]	No	0%	N/A (cohort study)	Not reported	Not reported
Drory et al. (2001) [28]	No	3 months: 28% 6 months: 44% 9 months: 68% 12 months: 80% (unable to perform statistical analyses at 9 and 12 months)	Not reported	Not reported	Not reported
Bello-Haas et al. (2007) [37]	Yes	33%	Yes	Yes ($d = 0.53$)	"Moderate-High"
Cheah et al. (2009) [50]	No	5%	Yes	Not reported	Experimental: 81.7 ± 28.0% Control: 85.2 ± 24.9%
Sanjak et al. (2010) [42]	No	33%	N/A (cohort study)	Not reported	"Excellent"
Pinto et al. (2012) [51]	No	Study entry: 7.7% 4 months: 15.4% 8 months: 23.1%	Yes	Not reported	"Excellent"
Pinto & de Carvalho (2013) [52]	Not reported	Not reported	N/A (cohort study)	Not reported	Not reported
Tabor et al. (2016) [46]	N/A (case study)	0%	N/A (case study)	Not reported	100%
Lunetta et al. (2016) [29]	Yes	End of treatment period: 6.7% End of follow-up period: 21.7% (dropout rates and reasons for dropouts did not differ significantly between groups, $p = 0.141$)	Not reported	Not reported	"Good, most patients completed the prescribed exercise sessions"
Plowman et al. (2016) [48]	No	40%	N/A (cohort study)	Not reported	79%
Jensen et al. (2017) [40]	No	16.7%	N/A (case series)	Not reported	3 participants: 85–95% 2 participants: 50–60%
Clawson et al. (2018) [30]	Yes	Before 3 months: 18.6% Between 3 and 6 months: 25.4%	Not reported	Not reported	Stretching/range of motion group: 85% had ≥50% adherence Resistance group: 78% had ≥50% adherence Endurance group: 50% had ≥50% adherence
Kato et al. (2018a) [31]	No	0%	N/A (case study)	Not reported	Not reported
Kato et al. (2018b) [39]	No	0%	N/A (case series)	Not reported	Not reported
Robison et al. (2018) [47]	No	0%	N/A (case study)	Not reported	100%
Kitano et al. (2018) [32]	Yes	28.6%	N/A (case control studies)	Yes ($d = 0.35$–0.71)	Exercise completion: 5.9 ± 1.6 times per week
Merico et al. (2018) [33]	No	17.4%	Not reported	Not reported	Not reported
Braga et al. (2018a) [34]	No	0%	N/A (cohort study)	Yes ($d = -0.26$, 1.99, $f^2 = 1.04$)	Not reported
Braga et al. (2018b) [44]	No	0%	N/A (case series)	Not reported	"Excellent," average number of sessions: 29
van Groenestijn (2019) [45]	Yes	43.9%	Yes	Not reported	10/27 participants completed ≥75% of sessions
Zucchi et al. (2019) [35]	Yes	End of treatment: 10.8% One year: 43.1% End of follow-up: 69.2%	Not reported	Not reported	Not reported
Plowman et al. (2019) [49]	No	4.2%	Not reported	Not reported	95–100%
Pegoraro et al. (2019) [36]	No	0%	N/A (cohort study)	Not reported	Not reported
Sivaramakrishnan & Madhavan (2019) [43]	No	22.2%	N/A (cohort study)	Not reported	100%

attenuated declines in various measures of pulmonary function, although not all study results reached significance [47,50–52]. In addition to this, one study found that patients that completed IMST lived significantly longer [52]. No adverse events were reported.

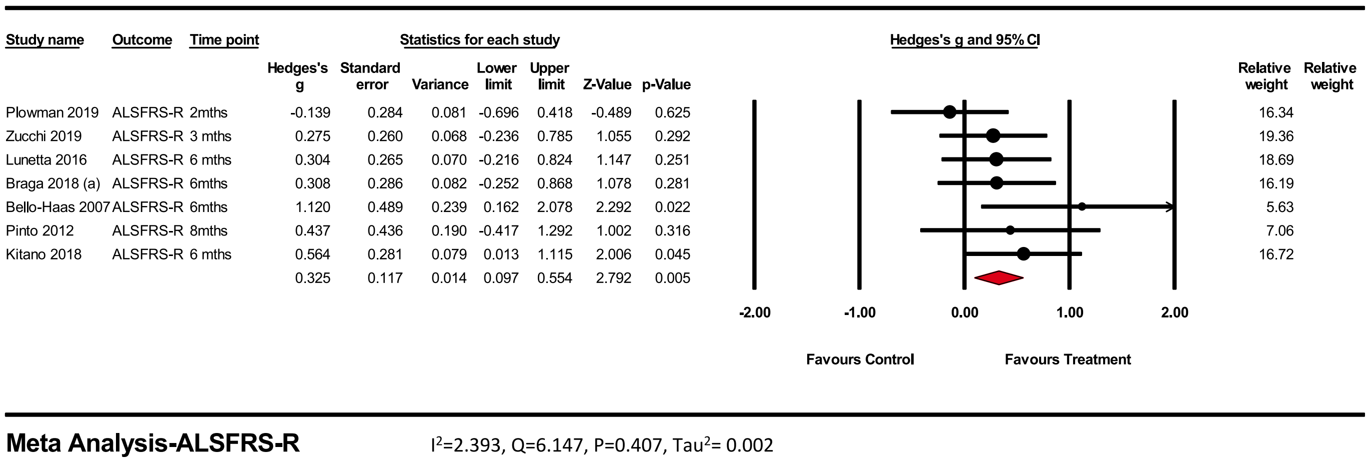
3.7.1. Statistical analyses metrics of study outcomes

Table 7 summarizes statistical analyses measures that were reported from each of the studies.

Across studies, the attrition rate ranged from 0% to 80%. While most studies reported whether exercise regimens resulted in statistically significant differences in outcomes, few studies reported effect sizes ($N = 5$, 20%). Similarly, intention-to-treat (ITT) analyses was reported for four out of ten studies that likely could have reported it (40%).

3.7.2. Meta-analysis of study outcomes

While 25 research articles initially met inclusion criteria, only 16 studies (64%) were judged to be level 1b or 2b, were graded as having good-strong quality, and were included in the meta-analysis. Results from the meta-analysis revealed that only the ALSFRS-R total score demonstrated a favorable summary effect size (Hedge's $G = 0.325$, $p <$



Study name	Outcome	Time point	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Plowman 2019	ALSFRS-R	2mths	-0.139	0.284	0.081	-0.696	0.418	-0.489	0.625	16.34
Zucchi 2019	ALSFRS-R	3 mths	0.275	0.260	0.068	-0.236	0.785	1.055	0.292	19.36
Lunetta 2016	ALSFRS-R	6 mths	0.304	0.265	0.070	-0.216	0.824	1.147	0.251	18.69
Braga 2018 (a)	ALSFRS-R	6mths	0.308	0.286	0.082	-0.252	0.868	1.078	0.281	16.19
Bello-Haas 2007	ALSFRS-R	6mths	1.120	0.489	0.239	0.162	2.078	2.292	0.022	5.63
Pinto 2012	ALSFRS-R	8mths	0.437	0.436	0.190	-0.417	1.292	1.002	0.316	7.06
Kitano 2018	ALSFRS-R	6 mths	0.564	0.281	0.079	0.013	1.115	2.006	0.045	16.72
			0.325	0.117	0.014	0.097	0.554	2.792	0.005	

Fig. 2. Effect of exercise on amyotrophic lateral sclerosis rating scale revised (ALSFRS-R) scores across 7 studies (treatment $n = 139$, control $n = 208$).

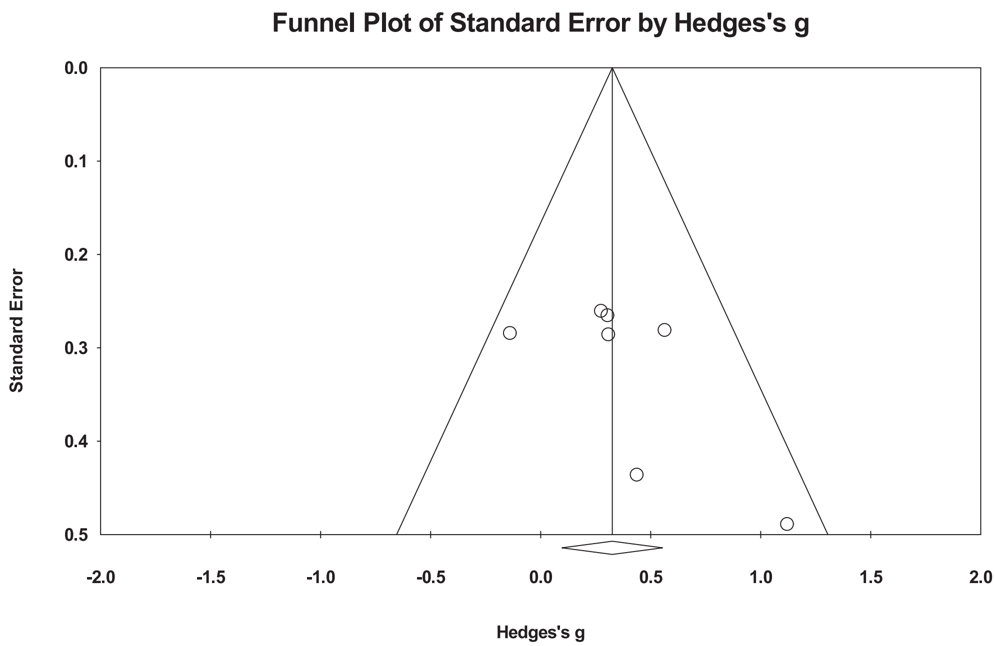
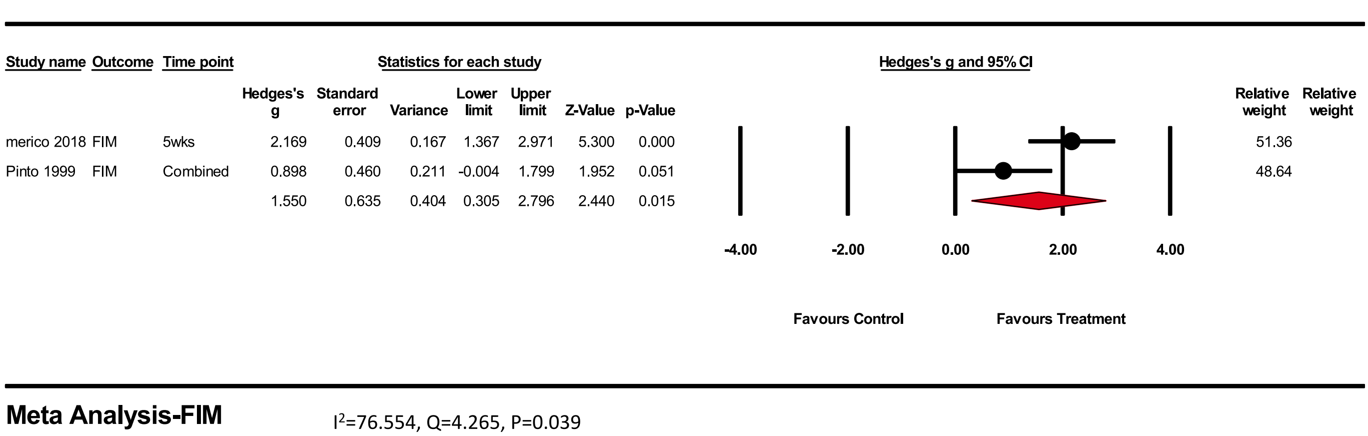


Fig. 3. Funnel plot demonstrating potential publication bias (fail safe $N = 11$ studies).



Study name	Outcome	Time point	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
merico 2018	FIM	5wks	2.169	0.409	0.167	1.367	2.971	5.300	0.000	51.36
Pinto 1999	FIM	Combined	0.898	0.460	0.211	-0.004	1.799	1.952	0.051	48.64
			1.550	0.635	0.404	0.305	2.796	2.440	0.015	

Fig. 4. Effect of exercise on functional independence measure (FIM) scores across 2 studies (treatment $n = 31$, control $n = 27$).

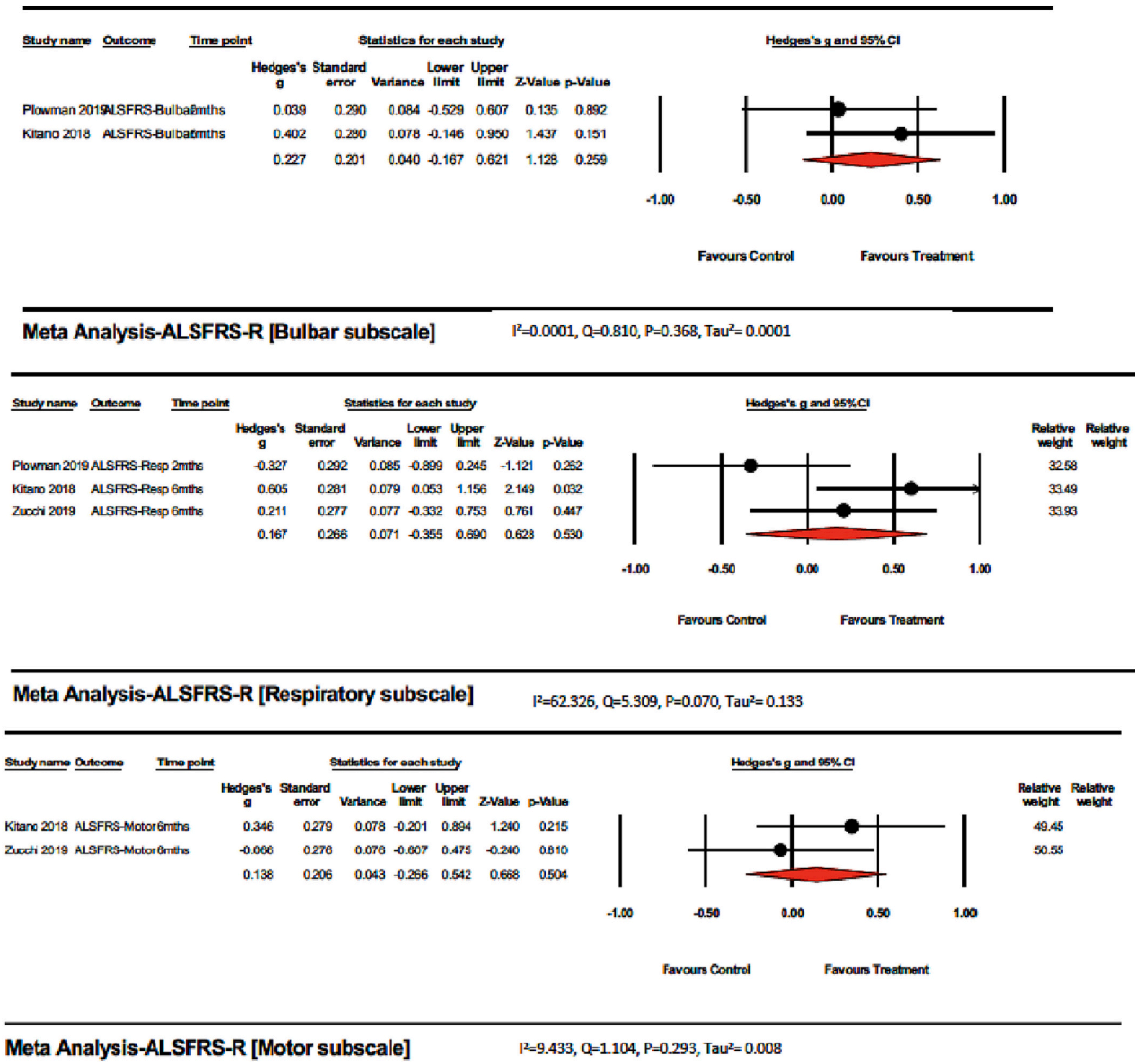


Fig. 5. Effect of exercise on amyotrophic lateral sclerosis rating scale revised ALSFRS-R subscale scores.

0.05), and had acceptable heterogeneity ($I^2 = 2.393$) and dispersion (Cochran's Q = 6.147, $P = 0.407$, $Tau^2=0.002$) (Fig. 2).

A funnel plot for ALSFRS-R scores can be viewed in Fig. 3, which shows plot asymmetry suggestive of publication bias (Begg-Mazumdar's Kendall's tau = 0.476, $p < 0.067$; Egger's bias = 2.64, (95% CI = -1.62–6.9), $t = 1.59$, df = 5, $p < 0.086$).

While FIM scores also demonstrated a favorable summary effect size, the heterogeneity limited interpretations ($I^2 = 76.554$, sensitivity analysis failed) (Fig. 4).

There were no other significant findings due to the limited number of studies that reported outcomes. Forest plots for the other outcomes examined can be viewed in Figs. 5–9.

4. Discussion

This systematic review and meta-analysis evaluated the effects of exercise on outcomes related to function and quality of life in people with ALS to determine the potential risks and benefits of people with ALS engaging in various exercise regimens. A broad range of exercise regimens were implemented (aerobic endurance, resistance, stretching/range of motion, and respiratory muscle strength training [EMST and/or IMST]), with various dosage parameters employed (frequency, repetitions, intensity, and duration). The studies included also examined a wide range of outcomes to determine the impact of exercise on function and quality of life. Despite heterogeneity across methodologies, most studies demonstrated that exercise-based interventions were safe, well-tolerated, and may lead to maintenance and/or improvements in function and quality of life for people with ALS with mild-moderate functional impairment. However, importantly, only a limited number of outcomes could be included in the meta-analysis, and furthermore, only one outcome (the ALSFRS-R) exhibited a favorable summary effect size due to the heterogeneity of outcomes and methodologies deployed across studies.

Several other systematic reviews and meta-analyses have recently

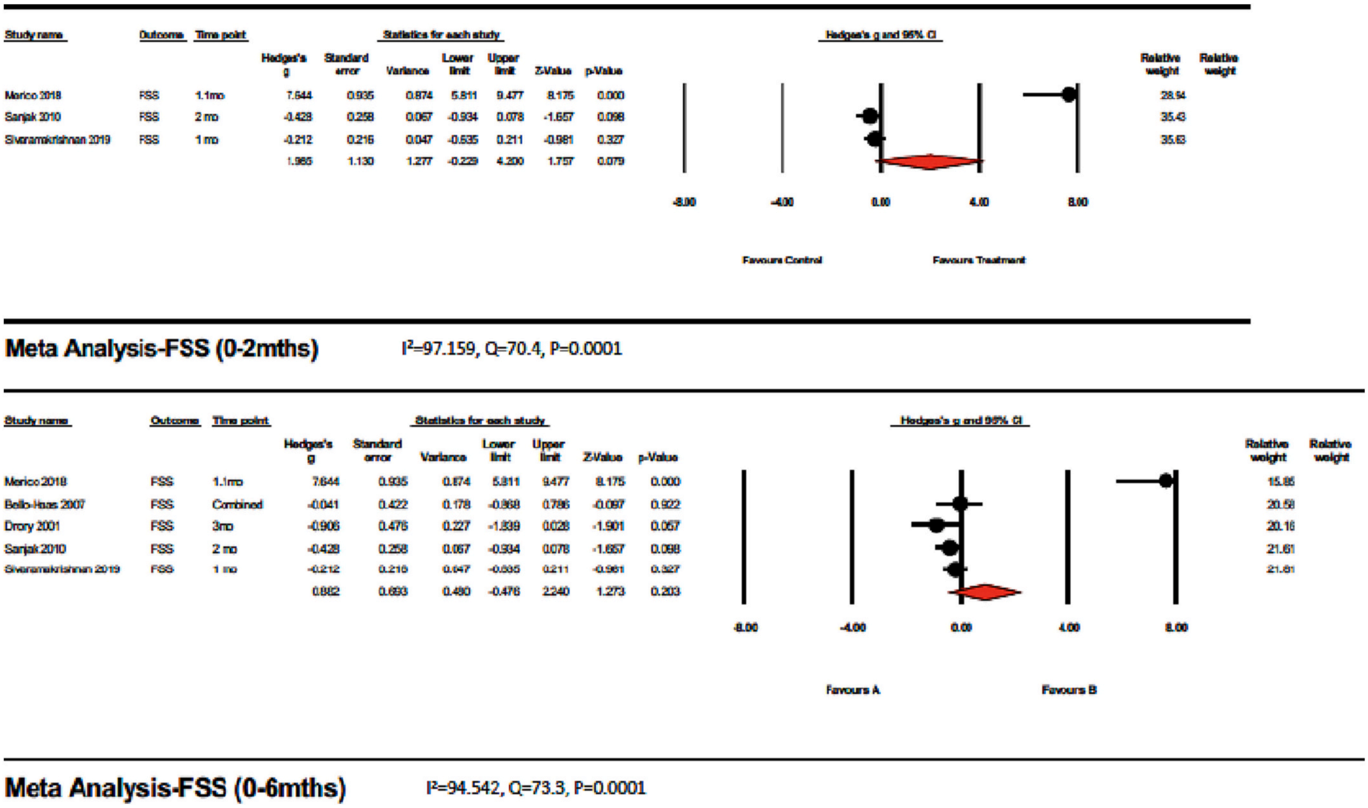


Fig. 6. Effect of exercise on fatigue severity scale (FSS) scores.

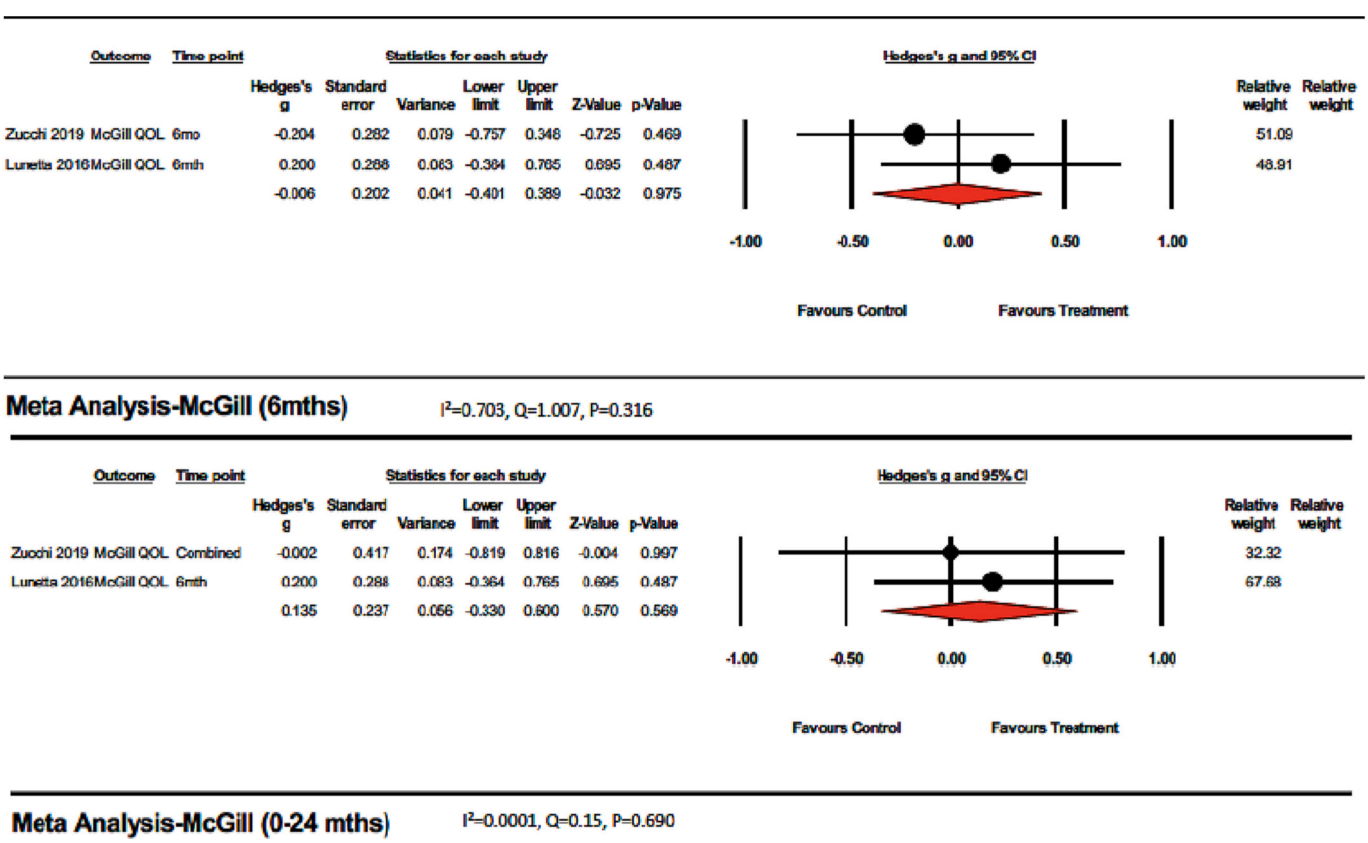


Fig. 7. Effect of exercise on McGill Quality of Life Questionnaire scores.

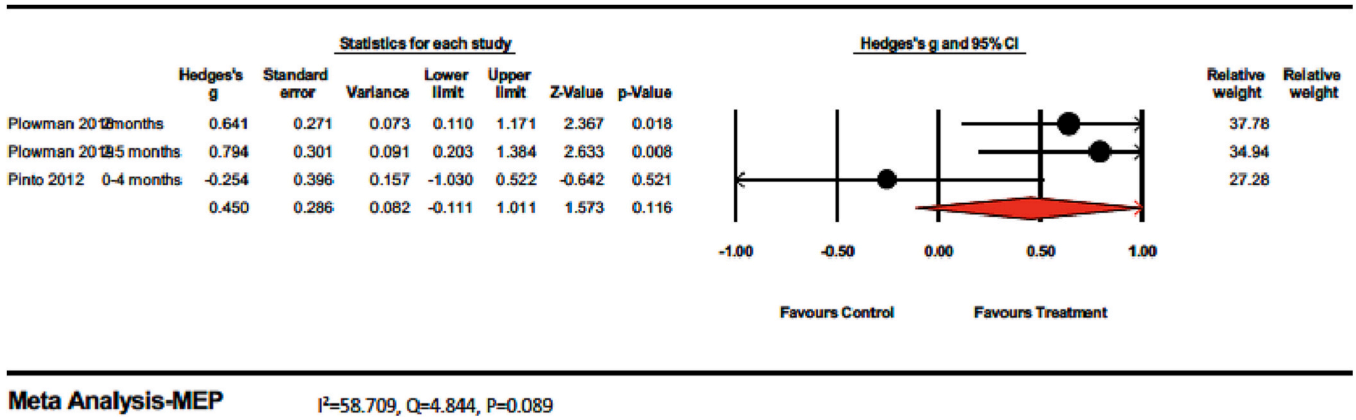


Fig. 8. Effect of exercise on maximum expiratory pressure (MEP).

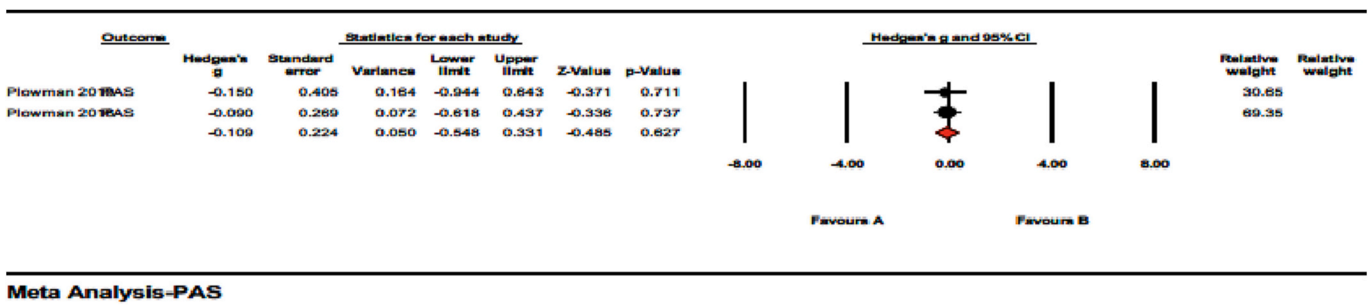


Fig. 9. Effect of exercise on swallowing safety (penetration-aspiration scale scores).

examined the effects of exercise regimens on function and quality of life in people with ALS [20–24]. In contrast to the present study, a recent systematic review examined the impact of specific exercise modalities including resistance, aerobic endurance exercise, and concurrent training in both animal and human models [20]. Unlike the present study, Tsitkanou et al. did not focus solely on clinical trials in humans and also did not include stretching/range of motion exercise regimens or respiratory muscle strength training [20]. However, similar to the present study, the authors of this previous systematic review concluded that the results of their review should be interpreted cautiously given some of the limitations of the studies included in the review such as small sample sizes, the heterogeneity of people with ALS, and poor study designs that resulted in potential confounding variables [20]. Another recent systematic review and meta-analysis evaluated the safety and efficacy of exercise regimens vs. standard of care exercise or no exercise in people with ALS [21]. Unlike the present study, Lijiao et al. included only randomized controlled trials in their meta-analysis, which may have limited their study findings given that high-quality observational studies may demonstrate more favorable effects than poorly designed randomized controlled trials [61]. Furthermore, excluding non-RCTs from systematic reviews/meta-analysis, particularly in rare patient populations such as individuals with ALS, may inadvertently exclude research studies that provide clinically relevant data [61]. Similar to the present study and the study by Tsitkanou et al., [20] Lijiao et al. [21] acknowledged study limitations (small sample size, high attrition rates, heterogeneity of exercise regimens and outcomes examined, etc.). However, unlike the present study, the results of this prior meta-analysis should be interpreted with caution because the authors did not appropriately account for and report on statistical measures of heterogeneity [62]. Additionally, Lijiao et al. [21] drew over-reaching conclusions about the efficacy of exercise regimens in people with ALS given the current level of research evidence. For example, the authors stated that aerobic endurance exercise is the most effective exercise in people with ALS despite including data from only two studies with 55 individuals with ALS and results revealing small-moderate effect sizes.

4.1. Study limitations

A primary limitation of the current study was including only full-text articles available in English. As such, this may have led to the exclusion of other relevant research studies that have been reported in the grey literature. Additionally, only a single author performed study selection for this review, however, it's important to note that another author was consulted for consensus as needed. People with ALS are challenging to study due to the rapidly progressing nature of the disease. This is exemplified by the high attrition rates and small sample sizes in many research studies examining exercise in people with ALS. Thus, many research studies included in this review were likely under-powered (majority did not calculate a power analysis), limiting the validity of study findings. In addition to this, exercise may impact people with ALS differently due to individual patient factors such as age, body mass index, FVC, spinal vs. bulbar onset, idiopathic vs. genetic ALS, time since diagnosis, psychosocial factors, cognitive function, premorbid health, socioeconomic status, and whether or not they are on medications [10–12,63,64]. While most studies had clear inclusion/exclusion criteria for patients enrolled and reported common patient demographic/clinical information (age, onset type, etc.), few studies reported whether patients had idiopathic vs. genetic ALS and what medications (if any) patients were on. According to the baseline characteristics of people with ALS included in these research studies, exercise regimens have only been explored in patients with minimal-mild disease severity (>40 ALSFRS-R scores) and mild-moderate disease severity (39–30 ALSFRS-R scores) [54,55]. Therefore, the findings from these studies support the implementation of exercise-based interventions in the early stages of ALS disease progression. While most studies reported disease duration and functional measures of ALS, they did not stratify patients to treatment arms based on disease duration or rate of progression, which could lead to bias and profoundly influence findings due to imbalanced groups. The types of exercise as well as the frequency, repetitions, intensity, and duration of exercise regimens varied greatly across studies. Exercise frequency ranged from 2×/week to 3×/day, up to 7 days/week, with repetitions of sets ranging from 20 to 25, intensity ranging from 30 to 60% of a patient's maximum value, and treatment duration ranging from 2 weeks to 2 years. Importantly, the small sample sizes, limited data due to lack of study replication, and heterogeneity of treatments and outcomes explored across studies resulted in few statistically significant findings from the meta-analysis and limits the strength of findings to date. Replication of research findings along with further research to determine the optimal types of exercise and the appropriate dosage for exercise training and maintenance for people with ALS is vital.

5. Conclusions

The current systematic review and meta-analysis provides support that deliberate, well-designed exercise regimens are safe, well-tolerated, and may prolong function, life, and quality of life in people with ALS with mild-moderate functional impairment. Unfortunately, methodological heterogeneity (study design and conduct), participant heterogeneity (time since disease onset, baseline disease severity), and clinical heterogeneity (variable interventions and outcomes) limited the aggregation of study findings to determine a more precise treatment effect for each outcome. Therefore, while results are promising, variability prohibits firm conclusions. Future studies should expand upon these promising preliminary results by conducting large, multi-site, randomized controlled trials that examine the impact of various exercise regimens over a longer period to assist in elucidating superior exercise regimens and optimal dosage parameters for exercise training in this vulnerable patient population. Replication studies are strongly encouraged which would allow for aggregation of study data in this rare population.

CRediT authorship contribution statement

Cara Donohue: Data curation, Formal analysis, Investigation, Writing – original draft. **Giselle Carnaby:** Formal analysis. **Mary Catherine Reilly:** Data curation, Investigation. **Ryan J. Colquhoun:** Methodology. **Kendrea L. (Focht) Garand:** Conceptualization, Methodology, Supervision.

Declaration of Competing Interest

The authors report no conflict of interest.

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