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# Effects of therapeutic exercise on disease severity, balance, and functional Independence among individuals with cerebellar ataxia: A systematic review with meta-analysis

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## ABSTRACT

**Background:** Balance impairments are common in cerebellar ataxia. Exercises are beneficial in this population.

**Objective:** Explore the benefits of therapeutic exercises on disease severity, balance and functional independence in cerebellar ataxia.

**Methods:** Databases were searched from inception until July 2021. Methodological quality was assessed using the Physiotherapy Evidence Database (PEDro) scale and the Newcastle-Ottawa Scale (NOS); and quality of evidence was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) tool.

**Results:** Twenty-six studies were included and eight studies of low to high PEDro methodological quality were meta-analyzed. 'Low' to 'moderate' GRADE quality evidence supports the use of therapeutic exercises to reduce disease severity, assessed using the Scale for the Assessment and Rating of Ataxia [weighted mean difference (WMD):  $-3.3$ ; 95% confidence interval (95%CI):  $-3.7$ ,  $-2.8$ ;  $p < .01$ ]; and improve balance, assessed using the Berg Balance Scale (WMD:  $2.6$ ; 95%CI:  $1.1$ ,  $4.2$ ;  $p < .01$ ). The effect of therapeutic exercises on functional independence was insignificant (WMD:  $1.6$ ; 95%CI:  $-1.5$ ,  $4.6$ ;  $p = .31$ ).

**Conclusion:** Low to moderate evidence from studies of low to high methodological quality provides some support for therapeutic exercises for reducing disease severity among non-hereditary degenerative cerebellar ataxia and improving balance among acquired cerebellar ataxia. Exercises did not benefit functional independence. Additional studies of large sample size and high methodological quality are necessary to substantiate these findings.

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## KEYWORDS



Spinocerebellar ataxia; hereditary ataxia; balance exercises; ataxia severity; functional independence

## Introduction

Cerebellar ataxia is a heterogeneous group of movement disorders caused by damage to the cerebellum or its connections (Marsden and Harris, 2011). Health conditions that result in ataxia are categorized as non-hereditary or hereditary degenerative, or due to an acquired underlying cause (Manto and Marmolino, 2009). The global prevalence of the dominant form of hereditary ataxia is 2.7 per 100,000 (Ruano, Melo, Silva, and Coutinho, 2014). Individuals with cerebellar ataxia report a significant decline in quality of life (Pérez-Flores, Hernández-Torres, Montón, and Nieto, 2020) and a greater reduction in the performance of activities of daily living (Miyai, 2012; Winser et al., 2020). Impaired balance is associated with all types of ataxias. Falls due to impaired balance is common among individuals with cerebellar ataxia and more than 70% of individuals with cerebellar ataxia

experience at least one fall within 12 months (Fonteyn et al., 2010). Improving balance among the population is crucial for improving community participation and reducing healthcare costs associated with accidental falls (Winser et al., 2020). Besides poor balance, individuals with cerebellar ataxia present with incoordination of limb and eyeball movement, speech impairment and altered muscle tone (Manto and Marmolino, 2009).

Pharmacological and surgical management techniques have limited scope for improving the symptoms of cerebellar ataxia (Matsugi, 2017); in contrast, rehabilitative intervention plays a key role in the management of patients with cerebellar ataxia (Cassidy, Naylor, and Reynolds, 2018). Exercises can prevent the development of secondary complications and minimize the dependency level of patients for the performance of activities

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of daily life (Fonteyn et al., 2014). Evidence supports the use of conventional rehabilitation programs that combine physiotherapy and occupational therapy to obtain greater functional gains in patients with cerebellar ataxia, including improvements in activities of daily living and gait parameters (Miyai et al., 2012). Biofeedback therapy during gait (Marquer, Barbieri, and Pérennou, 2014) and treadmill training (Fonteyn et al., 2014) improves gait and balance. Aerobic exercises including static cycling for four weeks is found to reduce the disease severity (Barbuto et al., 2020) and individualized home exercises including static and dynamic balance exercises can improve locomotion in this population (Keller and Bastian, 2014). In sum, the benefits of therapeutic exercises are suggestive of an improvement in: static and dynamic balance (Keller and Bastian, 2014); limb coordination (Miyai et al., 2012); and gait (Ilg et al., 2009) that results in the functional gain. Although the efficacy of the spectrum of therapeutic interventions have been investigated, evidence-based guidelines for exercises are not currently available for the treatment of balance impairments and associated problems in individuals with cerebellar ataxia (Fonteyn, Keus, Verstappen, and van de Warrenburg, 2013).

Previous systematic reviews examining the assessment and treatment of balance and postural control among individuals with cerebellar ataxia have provided a moderate level of evidence to support the use of rehabilitation exercises to improve postural control (Marquer, Barbieri, and Pérennou, 2014; Martin, Tan, Bragge, and Bialocerkowski, 2009; Milne et al., 2017). Past reviews exploring the effects of exercise on cerebellar ataxia have not included a meta-analysis. In recent years, additional research has been conducted to explore various interventions intended to improve balance among this population. Said the benefits of therapeutic exercises among individuals with cerebellar ataxia, an updated systematic review with a quantitative meta-analysis is necessary to contribute to the growing body of literature examining the effects of therapeutic exercises for the management of cerebellar ataxia. Therefore, this systematic review aims to examine the available evidence exploring the efficacy of therapeutic exercises on the disease severity, as assessed using the Scale for the Assessment and Rating of Ataxia (SARA) or the International Cooperative Ataxia Rating Scale (ICARS); balance, as assessed using the Berg Balance Scale (BBS) or the balance subscales of the SARA and ICARS; and functional independence, as assessed using the Functional Independence Measure (FIM) among adults with cerebellar ataxia secondary to a non-hereditary or hereditary degenerative, or due to an acquired underlying cause.

## Methods

This systematic review was designed and presented according to the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021). This review was registered with the PROSPERO (ref: CRD42020181588) before the onset of the data search. The following databases were searched, from database inception to July 2021: AMED, EBSCO, Embase, MEDLINE, CINAHL, and Web of Science. Search terms were constructed into three themes, including ataxia, assessments, and exercise intervention. The search terms under each theme were combined using “OR,” and the three themes were combined using “AND.” The search strategy for the MEDLINE database is presented in Appendix 1. Studies generated through the electronic search were exported to a citation manager (ENDNOTE X9, Clarivate Analytics, Philadelphia, Pennsylvania, USA). Studies were included in this systematic review if they: 1) included participants with ataxia due to a non-hereditary or hereditary degenerative, or due to an acquired underlying cause or any combination of possible causes; 2) included adults older than 18 years; 3) delivered an exercise-based intervention; and 4) assessed the treatment effects using the SARA, ICARS, BBS, or FIM or any combination of these outcome measures. Studies were excluded if they: 1) were published in languages other than English; or 2) were conference abstracts. Due to the heterogeneity of the health conditions resulting in ataxia (Fonteyn et al., 2014) and the limited number of high-quality studies (Winsler et al., 2018); in this review, studies were not restricted based on study design. We considered all study designs including randomized controlled trials, non-randomized controlled trials, single-group designs, case reports, and case series for inclusion. In this review, we restricted therapeutic exercises to those interventions within the scope of physiotherapy practice (Pagliarulo, 2011).

The search process and duplicate removal were conducted by one reviewer (CYH). The title, abstract, and full text were screened by two reviewers (WKC and YHL). Discrepancies were resolved by discussion until consensus was reached. A manual search of the reference lists of all included studies was also conducted to identify any additional studies that met the inclusion criteria. Two independent reviewers (CYH and HKC) extracted the following data from the included studies: 1) author and year of publication; 2) study type; 3) diagnosis, sample size and participant characteristics; 4) type of exercise and dosage(s) of intervention(s); 5) outcome measures of interest; 6) assessment time points; and 7) major findings.

Based on the classification by Lieto et al. (2019) and Manto and Marmolino (2009), we categorized the studies conducted among participants with degenerative cerebellar ataxia, multiple system atrophy (MSA), and idiopathic late-onset cerebellar ataxia (ILOCA) within the non-hereditary degenerative group; those studies including participants with autosomal recessive and dominant ataxia, including the sub-types of spinocerebellar ataxia and Friedreich's ataxia, were classified as the hereditary group and those studies including participants with cerebellar ataxia secondary to stroke, multiple sclerosis, toxicity, immune-mediated causes, infection, trauma, neoplasms, or endocrine or structural diseases were classified as the acquired group.

We considered standardized and commonly used outcome measures for assessing the disease severity, balance, and functional independence. We considered the SARA (Schmitz-Hübsch et al., 2006) or ICARS (Cano et al., 2005) for assessing the severity of ataxia, the BBS, SARAbal (Winser et al., 2017), or posture and gait disturbance subscale of the ICARS (Cano et al., 2005) for assessing balance, and FIM (Fahey et al., 2007) for assessing functional independence.

The methodological quality of the included randomized controlled trials were assessed using the Physiotherapy Evidence Database (PEDro) Scale (Sherrington, Herbert, Maher, and Moseley, 2000). Available methodological quality scores were obtained from the website (<https://www.pedro.org.au/>). For those studies that were not prescored on the website, two independent reviewers were involved in the scoring process. The scale includes 10 items, with each item scored as 0 for 'no' and 1 for 'yes.' In this review, we interpreted scores of 6 and above as being high-quality and scores of 5 or below as being 'low-quality,' in line with a previous systematic review (Kannan and Claydon, 2014). The methodological quality of studies with designs other than randomized controlled trials was assessed using the Newcastle-Ottawa Scale (NOS) (Lo, Mertz, and Loeb, 2014). The NOS adopts a 'star system' to rate three perspectives including selection, comparability and exposure. The studies were scored a maximum of four stars for selection, three for exposure and two stars for comparability. In total, the methodological quality of each study was rated between 0 and 9 stars with higher stars indicating higher methodological quality.

The quality of the evidence presented by those studies that were included in the meta-analyses was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) tool. The GRADE quality of evidence was rated using the GRADEprofiler 3.6 software (<https://gradeprofi>

[ler.software.informer.com/3.6/](https://www.gradeprofi.com/3.6/)). The quality of evidence was classified according to four levels: 'very low,' 'low,' 'moderate,' or 'high' (Guyatt et al., 2008). The overall quality of evidence was based on the lowest quality of evidence level reported for any measured outcome in a given study. According to the GRADE system, the quality of evidence derived from the studies can be downgraded for several reasons, including study limitations (risk of bias); the inconsistency of findings; the indirectness of evidence; imprecision; and reporting or publication bias (Guyatt et al., 2008). The reasons for downgrading GRADE scores have been detailed in a previous systematic review (Kannan, Winser, Fung, and Cheing, 2018). Independent reviewers conducted the quality appraisals using the GRADE tool, NOS and the PEDro scale, and discrepancies between the reviewers were resolved by discussion. No study was excluded based on their quality scores. However, the quality was considered when interpreting the findings.

### Data analysis

Independent reviewers synthesized the extracted data from the included studies. The inter-rater agreement for rating the PEDro and the NOS was estimated using Cohen's Kappa. The coefficients Kappa of 0 was interpreted as poor agreement, 0.01 to 0.20 as slight agreement, 0.21 to 0.40 as fair agreement, 0.41 to 0.60 as moderate agreement, 0.61 to 0.80 as substantial agreement and 0.81 to 0.99 as almost perfect agreement (Landis and Koch, 1977). The findings of randomized controlled trials and non-randomized study designs reporting the data of a control group and an experimental group that assessed similar domains (i.e. disease severity, balance, or functional independence) using similar outcome measures and underlying cause categories (i.e. hereditary, non-hereditary or acquired) were grouped and pooled for meta-analysis. The Comprehensive Meta-Analysis software (CMA version 3.0, Biostat Inc., Englewood, New Jersey, USA) was used to conduct all meta-analyses. All outcome measures of interest were ordinal data, and differences in means and 95% confidence intervals (CIs) were estimated. A Chi-square test was used to determine heterogeneity. A heterogeneity of 0 to 40% was considered not important, 30 to 60% as moderate, 50 to 90% as substantial and 75% to 100% as considerable. A p-value of  $\leq 0.05$  indicated significance (Higgins and Green, 2011). To obtain pooled estimates of differences between groups, based on the low Chi-square value (minimal heterogeneity)



the weighted mean difference (WMD) was calculated using a fixed-effect model. The findings of those studies that were not included in the meta-analyses were synthesized narratively.

## Results

### Characteristics of the included studies

The electronic searches yielded 16,846 studies, among which 20 met our inclusion criteria. Figure 1 illustrates a flow chart outlining the screening process that was applied, including the reasons for exclusions. Six additional studies were identified after a manual search of the reference lists of the included studies. Overall, 26 studies were included in this systematic review, including eight that were eligible for meta-analysis. Eight randomized controlled trials (Ali, Darwish, Shalaby, and Abbas, 2021; Barbuto et al., 2020; Belas Dos Santos et al., 2018; Chang et al., 2015; Milne et al., 2012, 2018; Rodríguez-Díaz et al., 2018; Salcı et al., 2017), and one intra-individual control design (İlg et al., 2009) were

included in the meta-analysis. A summary of all included studies is reported in Table 1. All included studies were published between 2009 and 2021. The sample sizes of the included studies ranged from eight (De Oliveira et al., 2018) to 42 (Miyai et al., 2012; Salcı et al., 2017). The studies included a total of 427 participants, with an average of 16 participants per study. Among the included studies five studies recruited participants with: non-hereditary degenerative ataxia (Barbuto et al., 2020; Burciu et al., 2013; İlg et al., 2009; Keller and Bastian, 2014; Miyai et al., 2012); 13 included hereditary cerebellar ataxia including spinocerebellar ataxia (Ahmedy, Neoh, and Latiff, 2020; Bunn, Marsden, Giunti, and Day, 2015; Chang et al., 2015; De Oliveira et al., 2015, 2018; Im et al., 2017; Leonardi et al., 2017; Rodríguez-Díaz et al., 2018; Santos et al., 2017; Song et al., 2019; Toktaş, Yaman, Ulaşlı, and Dündar, 2015) and Friedreich's ataxia (Milne et al., 2012, 2018); and eight included acquired ataxia including multiple sclerosis (Ali, Darwish, Shalaby, and Abbas, 2021; Salcı et al., 2017), cerebellar stroke (Belas Dos Santos et al., 2018; Bultmann et al., 2014; High and Andrews, 2020),

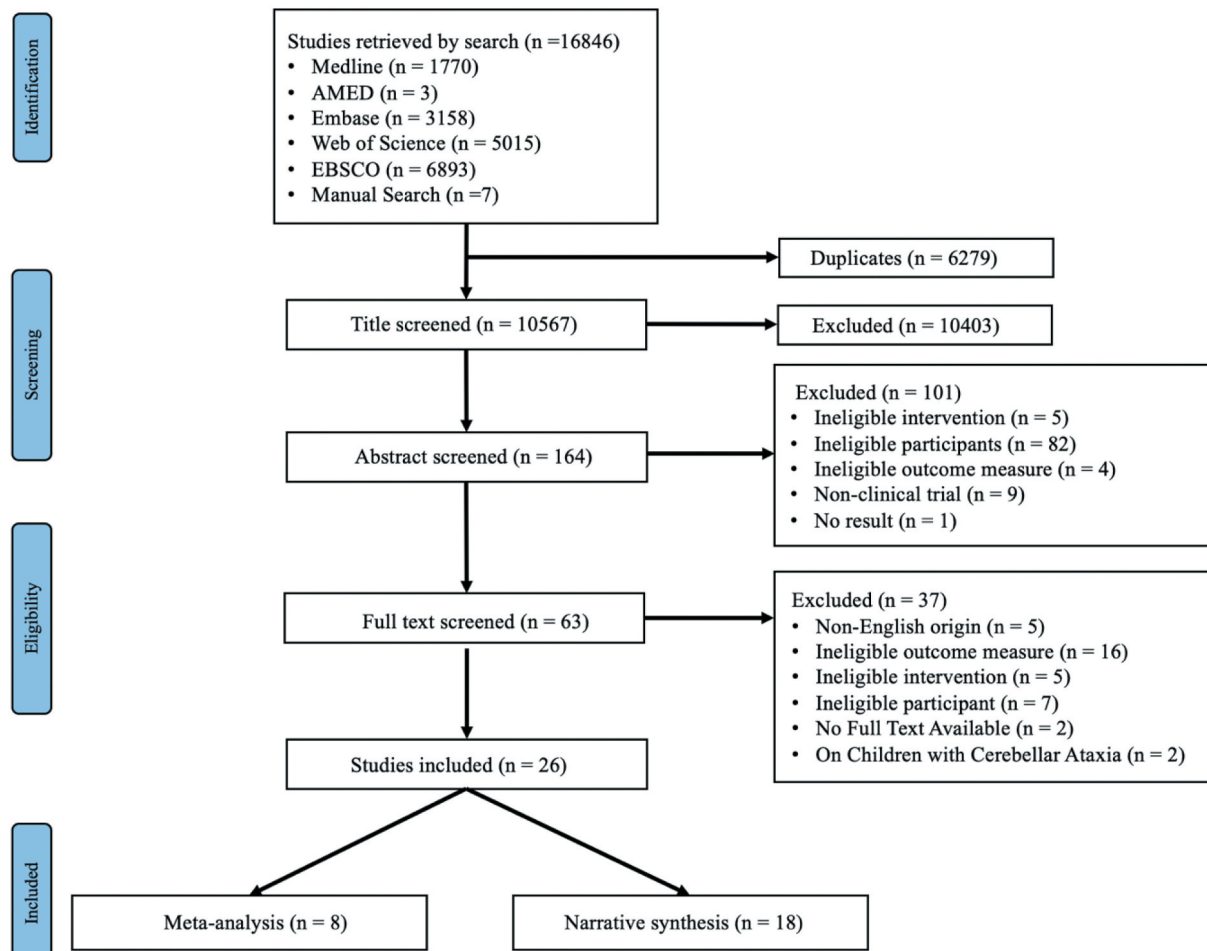


Figure 1. Screening of studies for inclusion.

**Table 1.** Summary of the included studies (n = 26).

Study	Study design	Participants	Exercises delivered	Outcome measures		Major findings
				Dosage	Group-specific intervention	
Ahmedy, Neoh, and Latiff, 2020 Malaysia	Case report	SCA n = 2 Age (years) = 25 and 38 Gender = 1 M, 1 F	Balance and coordinative training including functional tasks in standing position; sit-to-stand movements; core trunk flexibility and strengthening exercises; weight-supported gait training; fall prevention exercises Dosage = 1 hour/day, 5/week, 4 weeks	BBS SARA	Baseline (one-off, pre-intervention) and immediately post-intervention	No significant improvement in any domain of interest
Ali, Darwish, Shalaby, and Abbas, 2021 Egypt	RCT	MS n = 30 Age (years) = 20-45 Gender = both sexes	Lower limb mobilization: passive ankle mobilization; muscle stretch standing position: static postural control exercise; weight shifting exercise; perturbation exercise Core stability exercises including modified clinical Pilates training (performed in supine, prone, side lying, sitting and up-right positions) Task-oriented exercises (resistance exercise) = VR-based balance training program Dosage = 55 minutes/session, 2/week, 6 weeks Exp 1 = Exercise program and core stability exercises. Exp 2 = Exercise program and task-oriented exercises	BBS	Baseline (one-off, pre-intervention) and immediately post-intervention	Improvement in balance
Barbuto et al., 2020 USA	RCT	Degenerative cerebellar disease n = 20 Age (years) = 50 (SD, 15.65) Gender = 13 M, 7 F	Monitored aerobic training using stationary bicycle training Dosage = 30 minutes/session, 5/week, 4 weeks Exp = Aerobic training at 65-80% HRmax Con = No intervention	SARA	Baseline (one-off, pre-intervention) and immediately post-intervention	Improvement in disease severity
Belas Dos Santos et al., 2018 Brazil	RCT	Cerebellar stroke n = 15 Age (years) = 50.8 (SD, 11.8) Gender = 11 M, 4 F	Intensive physical therapy including conventional physiotherapy, gait training, muscle stretching and strengthening, balance training postural stability control, sensory techniques, functional daily activities, and prescribed home exercise. Dosage = 1 hour/session, 3/week, 5 months Exp = Intensive physical therapy delivered with a robot-driven exoskeleton orthosis equipment Con = Intensive physical therapy delivered without robot-driven exoskeleton.	BBS FIM SARA	Baseline (one-off, pre-intervention) and immediately post-intervention	Improvements in disease severity, balance and functional independence
Bultmann et al., 2014 Germany	One-group pretest-posttest design with healthy control	Cerebellar stroke n = 23 Age (years) = 58.6 (SD, 13.5) Gender = 17 M, 6 F Healthy control group n = 13 Age (years) = 59.3 (SD, 10.5) Gender = 9 M, 4 F	Gait training on a treadmill with progressively increasing velocity according to patients' ability. Dosage = 30 minutes/session, 7/week, 2 weeks Exp = Treadmill training (30 mins, 7/week x 2 weeks) Con = No intervention	ICARS	Baseline (one-off, pre-intervention) and immediately post-intervention Follow-up = 3 months	No significant improvement in any domain of interest

(Continued)

Table 1. (Continued).

Study	Study design	Participants	Exercises delivered	Dosage	Group-specific intervention	Outcome measures	Assessment timeline	Major findings
Bunn, Marsden, Giunti, and Day, 2015 UK	Randomized controlled feasibility study	SCA Total: n = 12 Age (years) = 59.25 (SD, n/s) Gender = 4 M, 8 F	Home-based balance exercises including balance control engagement at home under functionally relevant daily scenarios while looking at projected images (optokinetic stimuli) Exp = Home-based balance exercises with optokinetic stimuli Con = No intervention	Dosage = 15 minutes/session, 5/week, 4–8 weeks		FIM SARA	Baseline (4 weeks and immediately pre-intervention) and immediately post-intervention	Improvement in disease severity
Burciu et al., 2013 Germany	One-group pretest-posttest design with healthy control	Degenerative cerebellar disease n = 19 Age (years) = 56.3 (SD, 12) Gender = 13 M, 6 F Healthy control group n = 19 Age (years) = 53.5 (SD, 12.9) Gender = 11 M, 8 F	Postural training program including standing position on a force plate while facing a visual surround and displace center of gravity to reach cued locations (forward, backward, left, right) Dosage = 60 minutes/day, 7/week, 2 week Exp = Postural training program with NeuroCom SMART EquiTest system. Con = Age-matched healthy adults performed the same set of exercises.			BBS ICARS SARA Number of falls	Baseline (2 weeks and immediately pre-intervention) and immediately post-intervention Follow-up = 3 months	Improvement in fall prevention
Chang et al., 2015 Taiwan	RCT	SCA n = 20 Age (years) = 48.9 (SD, 6.48) Gender = 8 M, 12 F	Home based long-term cycling training involving pedaling exercise on a static cycling ergometer and performance of isometric maximum voluntary contraction of plantarflexors. Dosage = 15 minutes/session, 3/week, 4 weeks Exp = Home-based long-term cycling training Con = Verbal health education and upper-extremity exercises in a sitting position			ICARS	Baseline (one-off, pre-intervention) and immediately post-intervention	Improvement in disease severity
De Oliveira et al., 2015 Brazil	One-group pretest-posttest study	SCA n = 11 Age (years) = 42 (median) Gender = 5 M, 6 F	Static and dynamic balance exercise; whole-body movements; falling and falling prevention strategies; movements for contracture prevention and treatment. Dosage = 45 minutes/session, 2/week, 4 weeks.			BBS Number of falls	Baseline (one-off, pre-intervention) and immediately post-intervention	Improvements in balance and fall prevention
De Oliveira et al., 2018 Brazil	One-group pretest-posttest study	SCA n = 8 Age (years) = 43.1 (SD, 11.0) Gender = 5 M, 3 F	Gait training using weight-supporting treadmill with progressively increased velocity to participants' threshold without running or losing coordination and dynamic balance training during walking. Dosage = 50 minutes/session, 2/week, 8 weeks Exp 1 = Gait training using partial body weight support system on treadmill Exp 2 = dynamic balance training during gait			BBS SARA	Baseline (1 week and immediately pre-intervention), during intervention (8th week) and immediately post-intervention	Improvement in balance

(Continued)

Table 1. (Continued).

Study	Study design	Participants	Exercises delivered	Dosage	Group-specific intervention	Outcome measures	Assessment timeline	Major findings
Freund and Stetts, 2010 USA	Case report	TBI n = 1 Age (years) = 23 Gender = M	Trunk stabilization exercise including gentle voluntary contraction of the lower abdominal wall (Abdominal Drawing in Maneuver); performed in supine, sidelying, quadruped, sitting, standing and during functional activities			BBS	Baseline (1, 3 and 6 weeks pre-intervention), during intervention (6th week) and immediately after intervention Follow-up = 6 weeks and 1 year	Improvement in balance
High and Andrews, 2020 USA	Case report	Cerebellar hemorrhage with obstructive hydrocephalus n = 1 Age (years) = 32 Gender = M	Gait training include walking on a weight-supported treadmill Dosage = 60–90 minutes/session, 2–3/week, 10 weeks. Inpatient rehabilitation program including physical therapy (ambulating, catching, throwing), occupational therapy (daily tasks simulations), and speech therapy program. Dosage = 3 hours/session, 7/week, 47 days.			BBS FIM	Varies during the intervention period	Improvements in balance and functional independence
Ilg et al., 2009 Germany	Intraindividual control design	Degenerative cerebellar disease or Affluent CA n = 16 Age (years) = 61.4 (SD, 10.8) Gender = 8 M, 8 F	Coordinative physiotherapy including static balance exercise, dynamic balance exercise, whole body movements, falling and falling prevention strategies and prevent contractures. Home exercise included unsupervised exercises including all the elements. Dosage = 1 hour/session, 3/week x 4 weeks (coordinative physiotherapy); 1 hour/session, 1/day, 8 weeks (home exercise) Exp = Coordinative physiotherapy + home exercise Con = No intervention (patients as self-control)			BBS ICARS SARA	Baseline (8 weeks and immediately pre-intervention) and immediately post-intervention Follow-up = 8 weeks	Improvements in disease severity and balance
Im et al., 2017 South Korea	One-group pretest-posttest study	SCA n = 19 Age (years) = 53.2 (SD, 13.8) Gender = 7 M, 12 F	Gait training program including body weight transfers, posture control, gait stance simulations and stepping kinematics Dosage = 1.5 hour/session, 2/week, 12 weeks.			ICARS	Baseline (one-off, pre-intervention) and immediately post-intervention Follow-up = 3 months	Improvement in disease severity
Keller and Bastian, 2014 USA	Intraindividual control design	Degenerative cerebellar disease n = 14 Age (years) = 52 (SD, 11) Gender = 7 M, 7 F	Static and dynamic balance exercise program including static position stabilization, dynamic arm and leg movements, and sitting and standing. Dosage = ≥ 20 minutes/session, 4–6/week, 6 weeks.			ICARS	Baseline (2 weeks and immediately pre-intervention), during intervention (3rd week) and immediately post-intervention Follow-up = 1 month	Improvement in disease severity
Leonardi et al., 2017 Italy	One-group pretest-posttest study	SCA or FRDA n = 9 Age (years) = 35.33 (SD, 6.3) Gender = 6 M, 3 F	Proprioceptive stabilizer prescription using three Equistasi device over the seventh cervical vertebra and on each soleus muscle tendons. Physical therapy including voluntarily reaching for limit of stability; training of postural response activation to external perturbation. Dosage = 3 hours/session, 5/week, 3 weeks (proprioceptive stabilizer prescription); 40 minutes/session, 5/week, 3 weeks (individualized physical therapy)			SARA	Baseline (one-off, pre-intervention) and immediately post-intervention Follow-up = 3 weeks	Improvement in disease severity

(Continued)



Table 1. (Continued).

Study	Study design	Participants	Exercises delivered	Outcome measures	Assessment timeline	Major findings
Stephan et al., 2011 Canada	Case series	CA n = 4 Age (years) = 37.25 Gender = n/s	Climbing and pointing task training, exercises involving body balance, movement accuracy, movement smoothness, movement velocity, movement planning, and integration of somatosensory information Pointing task training include arm and leg pointing movements toward a target ball. Dosage = 45–60 minutes/session, 2–3/week, 6 weeks	BBS	Baseline (2 weeks and immediately pre-intervention), during intervention (every 2 weeks), immediately after intervention Follow-up = 2 weeks Self-perception of motor control: every week during intervention Assessment time from intervention varies	Improvement in balance
Milne et al., 2012 Australia	Retrospective study	FRDA n = 29 Age (years) = 34.77 (SD, 10.71) Gender = 17 M, 12 F	Inpatient rehabilitation including strength and stretching exercises; education, functional and balance re-training; aquatic physiotherapy; development of a home or community program. Dosage = frequency and duration varied	FIM		Improvement in functional independence
Milne et al., 2018 Australia	RCT	FRDA n = 19 Age (years) = 36.9 (SD, n/s) Gender = 8 M, 11 F	Out-patient rehabilitation exercises involve: strengthening, postural control, coordination and control, functional mobility, balance training, stretching and mobilizing and cardiovascular fitness. Dosage = 2–3 hours/session, 3/week, 6 weeks (out-patient rehabilitation); 6 weeks (individualized home exercise) Exp = Out-patient rehabilitation + individualized home exercise Con = Same as Exp with 6 weeks delay	BBS FIM	Baseline (one-off, pre-intervention), after out-patient rehabilitation and after home exercise stage	Improvement in functional independence
Miyai et al., 2012 Japan	RCT	Degenerative cerebellar disease n = 42 Age (years) = 62.5 (SD, 1.7) Gender = 22 M, 20 F	General physical therapy exercises including general conditioning, range-of-motion exercise for trunk and limbs, muscle strengthening, spine mobilization in prone and supine positions, outdoor, ascending and descending gait training. Dosage = 2 hours/day (weekdays), 1 hour/day (weekends), 4 weeks Exp = General physical therapy and occupational therapy. Con = Same as Exp with 4-week delay.	FIM SARA Number of falls	Exp Baseline (one-off, pre-intervention) and immediately post-intervention Con Baseline (4 weeks and immediately post-intervention) and immediately post-intervention Follow-up = 4, 12 and 24 weeks	Improvements in disease severity, functional independence and fall prevention
Rodríguez-Díaz et al., 2018 Cuba	RCT	SCA n = 38 Age (years) = 39.2 (SD, n/s) Gender = 23 M, 15 F	Neurorehabilitation therapy including occupational therapy; general conditioning of motor control; psychotherapy; physical therapy (range-of-motion exercise for trunk and limbs; static and dynamic balance exercise; indoor, outdoor, ascending and descending gait movements; upper and lower limbs coordination and muscle strengthening). Dosage = 6 hours/session, 5/week, 24 weeks. Exp = Neurorehabilitation therapy Con = No intervention	SARA	Baseline (one-off, pre-intervention) and immediately post-intervention	Improvement in disease severity

(Continued)

**Table 1. (Continued).**

Study	Study design	Participants	Exercises delivered	Dosage	Group-specific intervention	Outcome measures	Assessment timeline	Major findings
Salci et al., 2017 Turkey	RCT	MS n = 42 Age (years) = 35.67 (SD, n/s) Gender = 17 M, 25 F	Balance training including sensory and motor strategy facilitation techniques. Lumbar training involving transversus abdominis and synergistic muscle contraction training Task-oriented training includes sitting-to-standing movements; forward, backward and sideways stepping movements; reaching movements from sitting position; gait movements on flat and tilted surfaces.	Dosage = 45 minutes/session, 3/week, 6 weeks. Exp 1 = Balance training and lumbar stabilization. Exp 2 = Balance training and task-oriented training. Con = Balance training alone.		BBS ICARS	Baseline (one-off, pre-intervention) and immediately post-intervention	Improvements in disease severity and balance
Santos et al., 2017 Brazil	Prospective observational study	SCA n = 28 Age (years) = 41.6 (SD, 16.9) Gender = 20 M, 8 F	Virtual reality rehabilitation involving head movements, static and dynamic balance, motor coordination, circular pelvis movements, bodyweight transfer while maintaining balance and postural instability correction.	Dosage = 50 minutes/session, 2/week, 10 weeks.		BBS	Baseline (one-off, pre-intervention) and immediately post-intervention	Improvement in balance
Sartor-Glittenberg and Brickner, 2014 USA	Case series	TBI n = 3 Age (years) = 16, 20 and 22 Gender: 2 M, 1 F	Physical therapy program involving bed mobility, sit-to-stand, gait training with and without assistive devices, on various surfaces, while carrying objects, at various speeds, in various directions; ascending and descending gait training.	Dosage = 40–45 minutes/session, 187 sessions (patient 1), 89 sessions (patient 2), 127 sessions (patient 3).		BBS	Baseline (one-off, pre-intervention), during intervention (monthly) and immediately post-intervention	Improvement in balance
Song et al., 2019 South Korea	Case report	SCA n = 1 Age (years) = 39 Gender = M	Designed dancing protocol including basic and simple movements of the tango (multi-directional steps, turns, rocking actions).	Dosage = 50 minutes/session, 3/week, 8 weeks		BBS ICARS SARA	Baseline (one-off, pre-intervention) and immediately post-intervention Follow-up = 4 week	Improvement in balance
Toktaş, Yaman, Ulaşlı, and Dündar, 2015 Turkey	Case report	SCA n = 1 Age (years) = 55 Gender = M	Virtual reality rehabilitation including sports games (bowling, darts, tennis, football) on an Xbox Kinect system.	Dosage = ≥1 hour/session, 5/week, 6 weeks.		BBS FIM	Baseline (one-off, pre-intervention) and immediately post-intervention	Improvements in balance and functional independence

M: Male; F: Female; n/s: not stated; Exp: experimental group; Con: control group; BBS: Berg Balance Scale; FIM: Functional Independence Measure; FRDA: Friedreich Ataxia; ICARS: International Cooperative Ataxia Rating Scale; MS: Multiple Sclerosis; PT: Physical therapist; SARA: Scale for Assessment and Rating of Ataxia; SCA: SpinoCA; TBI: Traumatic Brain Injury; \*Only significant improvement (P < 0.05) is mentioned except for case report and case series

and traumatic brain injury (Freund and Stetts, 2010; Sartor-Glittenberg and Brickner, 2014; Stephan et al., 2011). The studies that did not enter meta-analysis either due to the heterogeneity in the health condition or the outcome measure used were narratively synthesized. The intervention frequency ranged from two (De Oliveira et al., 2015; Im et al., 2017; Santos et al., 2017) to seven sessions per week (Bultmann et al., 2014; Burciu et al., 2013; High and Andrews, 2018; Miyai et al., 2012), lasting for 2 weeks (Bultmann et al., 2014; Burciu et al., 2013) to 23 months (Sartor-Glittenberg and Brickner, 2014). When classified by study design we identified: randomized controlled trials (n = 9) (Ali, Darwish, Shalaby, and Abbas, 2021; Barbuto et al., 2020; Belas Dos Santos et al., 2018; Bunn, Marsden, Giunti, and Day, 2015; Chang et al., 2015; Milne et al., 2018; Miyai et al., 2012; Rodríguez-Díaz et al., 2018; Salcı et al., 2017); one-group pretest–posttest studies (n = 6), (Bultmann et al., 2014; Burciu et al., 2013; De Oliveira et al., 2015, 2018; Im et al., 2017; Leonardi et al., 2017) intraindividual control design studies (n = 2) (Ilg et al., 2009; Keller and Bastian, 2014), prospective observational study (n = 1) (Santos et al., 2017), retrospective study (n = 1) (Milne et al., 2012); and case reports or case series (n = 7) (Ahmedy, Neoh, and Latiff, 2020; Freund and Stetts, 2010; High and Andrews, 2020; Sartor-Glittenberg and Brickner, 2014; Song et al., 2019; Stephan et al., 2011; Toktaş, Yaman, Ulaşlı, and Dündar, 2015).

### Quality

The level of agreement between the two raters on the methodological quality assessed using the PEDro and NOS was > 0.90 indicating almost perfect agreement. The mean methodological quality score of included

randomized controlled trials according to the PEDro was 6 indicating high quality and the studies of non-randomized controlled designs scored between 4 and 8 out of 9 stars on the NOS. Studies eligible for the meta-analysis (n = 8) had a mean score of 6, ranging between 4 and 8, indicating high quality according to PEDro. Table 2 reports the PEDro quality scores and Table 3 reports the methodological quality score according to NOS. The GRADE quality of evidence ratings for the studies included in the meta-analysis ranged from ‘very low’ to ‘moderate’ (Appendix 2).

### Effects of therapeutic exercise on the severity of ataxia

The pooled analysis on the effects of therapeutic exercises on the disease severity included the outcomes reported by four studies (Barbuto et al., 2020; Ilg et al., 2009; Miyai et al., 2012; Rodríguez-Díaz et al., 2018) among 116 participants with one of the non-hereditary degenerative cerebellar ataxia assessed using the SARA. The types of exercises included aerobic training using a bicycle (Barbuto et al., 2020), range of motion and strengthening exercises for the extremities (Rodríguez-Díaz et al., 2018) and coordination exercises for the extremities and balance exercises (Ilg et al., 2009). The effects of exercise were found to be significant (WMD:  $-3.3$ ; 95% CI:  $-3.8$  to  $-2.8$ ;  $p < .001$ ) (Figure 2), and the quality of evidence for this comparison was low according to GRADE. The pooled analysis on the effects of therapeutic exercise among 42 participants with acquired cerebellar ataxia assessed using the ICARS showed no significant effect when the exercise intervention was compared with therapeutic exercises plus either lumbar stabilization or task-oriented training (WMD:  $-2.783$ ; 95% CI:  $-7.1$  to  $1.5$ ;  $p = .20$ ) (Figure 3). The

**Table 2.** Summary of methodological quality of the included studies according to the PEDro scale (n = 9).

PEDro Scale	Random allocation	Concealed allocation	Baseline similar	Subject blinding	Therapist blinding	Assessor blinding	Adequate follow-up	Intention-to-treat analysis	Between group comparison	Points estimate	Total Score/10
Ali, Darwish, Shalaby, and Abbas, 2021	Y	Y	Y	N	N	N	N	N	Y	Y	5
Barbuto et al., 2020	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8
Belas Dos Santos et al., 2018	N	N	Y	N	N	Y	N	N	Y	Y	4
Bunn, Marsden, Giunti, and Day, 2015	Y	Y	Y	N	N	N	Y	N	Y	Y	6
Chang et al., 2015	Y	N	N	N	N	Y	N	N	Y	Y	4
Miyai et al., 2012	Y	Y	Y	N	N	Y	Y	N	Y	Y	7
Milne et al., 2018	Y	N	Y	N	N	Y	Y	Y	Y	Y	7
Rodríguez-Díaz et al., 2018	Y	Y	Y	N	N	Y	Y	N	Y	Y	7
Salcı et al., 2017	Y	N	Y	N	N	N	Y	N	Y	Y	5

Key: 1, yes; 0, No.

**Table 3.** Summary of methodological quality of the included case studies, case series and cohort studies according to the New Castle Ottawa Quality Assessment Scale (n = 17).

Study and Year	Selection				Comparability/ Confounder		Outcome/Exposure			Total scores
	A	B	C	D	E	F	G	H		
<b>Case studies</b>										
Freund and Stetts, 2010	⊙	⊙	-	-	-	-	⊙	-	-	3/9
High and Andrews, 2020	⊙	⊙	-	-	-	-	⊙	-	-	3/9
Toktaş, Yaman, Ulaşlı, and Dündar, 2015	⊙	⊙	-	-	-	-	⊙	-	-	3/9
Mean score for case studies										3/9
<b>Case series</b>										
Ahmedy, Neoh, and Latiff, 2020	0	⊙	⊙	⊙	⊙	⊙	⊙	⊙	0	7/9
Stephan et al., 2011	⊙	⊙	-	-	-	-	⊙	-	-	3/9
Sartor-Glittenberg and Brickner, 2014	⊙	⊙	-	-	-	-	⊙	-	-	3/9
Song et al., 2019	⊙	⊙	-	-	-	-	⊙	-	-	3/9
Mean score for case series										4/9
	I	J	K	L	M		N	O	P	
<b>Cohort studies</b>										
Burciu et al., 2013	⊙	⊙	⊙	⊙	⊙	⊙	0	⊙	0	7/9
Bultmann et al., 2014	⊙	⊙	⊙	⊙	⊙	⊙	0	⊙	⊙	8/9
Ilg et al., 2009	⊙	⊙	⊙	⊙	⊙	0	⊙	⊙	⊙	8/9
Im et al., 2017	⊙	⊙	0	0	⊙	⊙	⊙	0	⊙	6/9
Keller and Bastian, 2014	⊙	⊙	0	0	⊙	⊙	⊙	⊙	⊙	7/9
Leonardi et al., 2017	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙	0	8/9
Milne et al., 2012	⊙	⊙	⊙	⊙	⊙	⊙	⊙	0	0	7/9
De Oliveira et al., 2018	⊙	0	⊙	⊙	⊙	⊙	⊙	⊙	0	7/9
Santos De Oliveira et al., 2015	0	⊙	⊙	⊙	⊙	0	⊙	⊙	⊙	7/9
Santos et al., 2017	0	⊙	⊙	⊙	⊙	⊙	0	⊙	⊙	7/9
Mean score for cohort studies										7.2/9
Total mean score for all included studies										6/9

Key: ⊙, yes; 0, no; -, not applicable; A) Case definition; B) Representativeness of cases; C) Selection of Controls; D) Definition of controls; E) Study controls for age and education; and controls for any additional factors; F) Ascertainment of exposure; G) Same method of ascertainment for cases and controls; H) Non-response rate; I) Representativeness of the exposed cohort; J) Selection of the non-exposed cohort; K) Ascertainment of exposure; L) Demonstration that outcome of interest was not present at start of the study; M) Compatibility of cohorts on the basis of the design or analysis; N) Assessment of outcome; O) Length of follow-up; P) Adequacy of follow-up.

GRADE quality of evidence was moderate for this comparison. The level of heterogeneity was low and not important ( $I^2 = 0.00$ ,  $p > .05$ ).

### Effects of therapeutic exercise on balance

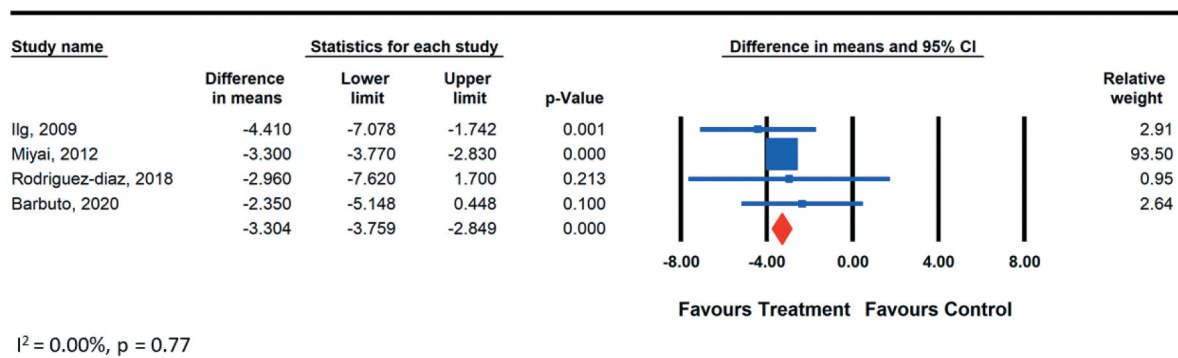
The pooled analysis on the effects of therapeutic exercises on balance included the outcomes reported in three studies (Ali, Darwish, Shalaby, and Abbas, 2021; Belas Dos Santos et al., 2018; Salcı et al., 2017). The meta-analysis including five comparisons among 102 participants with acquired cerebellar ataxia assessed using the BBS (WMD: 2.6; 95% CI: 1.1 to 4.2  $p < .01$ ) (Figure 4) showed a significant effect. The type of exercises included balance and coordination training (Ali et al., 2020), use of robot-driven exoskeleton orthosis (Belas Dos Santos et al., 2018) and lumbar stabilization exercise (Salcı et al., 2017). The quality of evidence for this comparison was low. The level of heterogeneity was low and not important ( $I^2 = 0.00$ ,  $p > .05$ ).

### Effects of therapeutic exercise on functional Independence

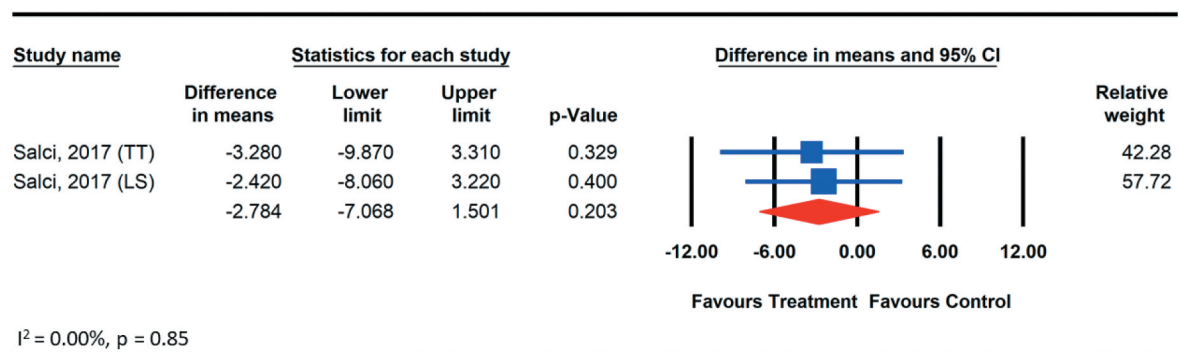
We did not find any significant effects of therapeutic exercise on functional independence assessed among 59 participants with hereditary ataxia using the FIM, compared with no treatment control (WMD: 1.6; 95% CI: -1.5 to 4.6;  $p = .3$ ) (Figure 5). The quality of evidence for the is comparison was moderate according to GRADE. The level of heterogeneity was low and not important ( $I^2 = 0.00$ ,  $p > .05$ ).

### Narrative synthesis

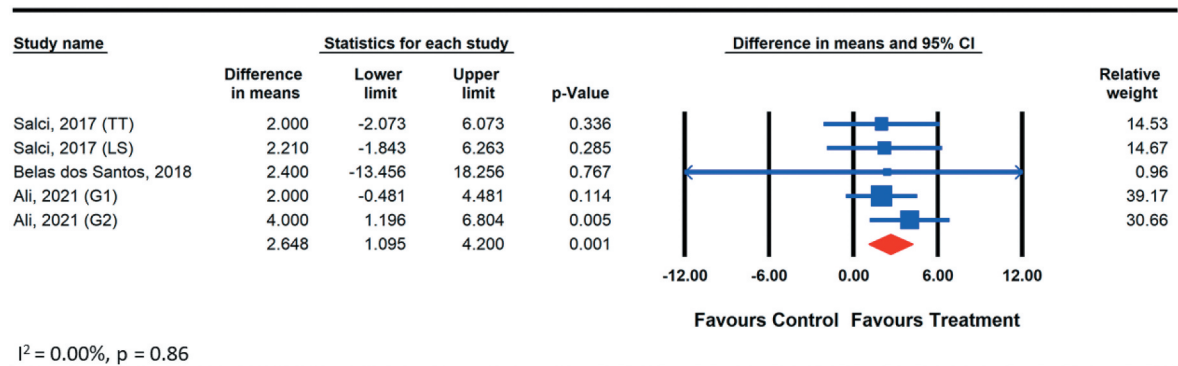
Among the studies that did not enter meta-analyses were narratively synthesized. Sixteen of the 17 studies demonstrated improvements in at least one outcome measure assessing disease severity, balance, or functional independence. The studies were grouped into one of the following five exercise categories: 1) general rehabilitation exercises (n = 8) (Ahmedy, Neoh, and Latiff, 2020;



**Figure 2.** Forest plot showing the effect of therapeutic exercise compared with no treatment measured with the scale for the assessment and rating of ataxia in patients with cerebellar ataxia.



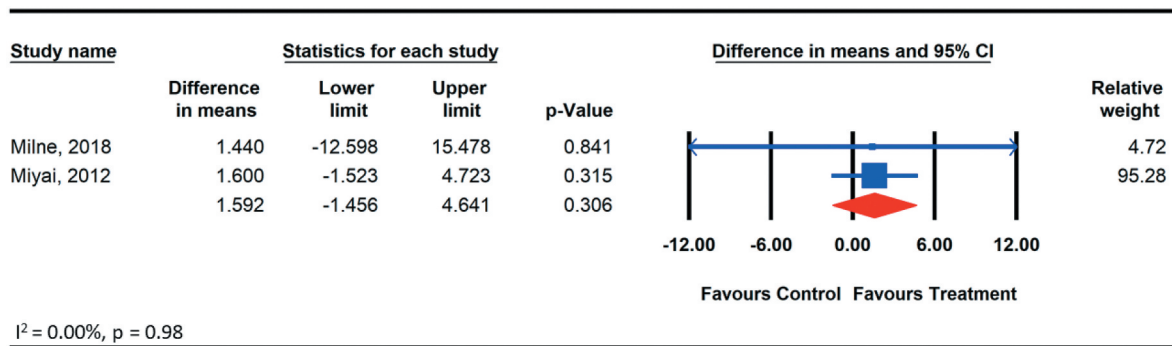
**Figure 3.** Forest plot showing the effect of therapeutic exercise compared with active therapies measured with International co-operative ataxia rating scale in patients with cerebellar ataxia.



**Figure 4.** Forest plot showing the effect of balance exercise compared with active therapies on balance measured with Berg Balance Scale in patients with cerebellar ataxia.

De Oliveira et al., 2015; High and Andrews, 2020; Ilg et al., 2009; Im et al., 2017; Keller and Bastian, 2014; Milne et al., 2012; Sartor-Glittenberg and Brickner, 2014); 2) computer-based training exercises ( $n = 4$ ) (Bunn, Marsden, Giunti, and Day, 2015; Burciu et al., 2013; Santos et al., 2017; Toktaş, Yaman, Ulaşlı, and Dündar, 2015); 3) treadmill training exercises ( $n = 3$ ) (Bultmann et al., 2014; De Oliveira et al., 2018; Freund

and Stetts, 2010); 4) sports-based training exercises ( $n = 2$ ) (Song et al., 2019; Stephan et al., 2011); and 5) training using an assistive device ( $n = 1$ ) (Leonardi et al., 2017). The summary of the included studies is reported in Table 4. The sample sizes of the studies ranged from eight (De Oliveira et al., 2018) to 28 (Santos et al., 2017). The intervention frequency ranged from two (De Oliveira et al., 2015; Im et al., 2017; Santos et al., 2017)



**Figure 5.** Forest plot showing the effect of therapeutic exercise compared with no treatment measured with Functional Independence Measure in patients with cerebellar ataxia.

to seven sessions per week (Bultmann et al., 2014; Burciu et al., 2013; High and Andrews, 2020) lasting for 2 weeks (Bultmann et al., 2014; Burciu et al., 2013) to 23 months (Sartor-Glittenberg and Brickner, 2014). The study designs included: one-group pretest–posttest studies ( $n = 6$ ) (Bultmann et al., 2014; Burciu et al., 2013; De Oliveira et al., 2015, 2018; Im et al., 2017; Leonardi et al., 2017); intraindividual control design study ( $n = 2$ ) (Ilg et al., 2009; Keller and Bastian, 2014); prospective observational study ( $n = 1$ ) (Santos et al., 2017), retrospective study ( $n = 1$ ) (Milne et al., 2012); and case reports or case series ( $n = 7$ ) (Ahmedy, Neoh, and Latiff, 2020; Freund and Stetts, 2010; High and Andrews, 2020; Sartor-Glittenberg and Brickner, 2014; Song et al., 2019; Stephan et al., 2011; Toktaş, Yaman, Ulaşlı, and Dündar, 2015)

### Computer-based training

Computer-based training included rehabilitation programs using optokinetic stimuli (Bunn, Marsden, Giunti, and Day, 2015) and virtual reality (Burciu et al., 2013; Santos et al., 2017; Toktaş, Yaman, Ulaşlı, and Dündar, 2015). Positive effects were found on the disease severity, balance, and functional independence. These effects can be attributed to the manipulatable features of virtual reality rehabilitation, which allows for both the intensity and feedback to be adjusted according to the ability of the individual (Betker, Szturm, Moussavi, and Nett, 2006; Bunn, Marsden, Giunti, and Day, 2015).

### Sports-based training

Sports-based training, including climbing, cycling, and dancing, were delivered to improve balance and reduce the severity of ataxia. Climbing is a complex task for the

whole motor system, as climbers are required to repeatedly shift their body weight to stabilize the trunk to advance. Adequate grip that requires precise reaching movements of both the hands and feet are also trained during climbing exercises (Stephan et al., 2011). Static cycling is a relatively safe form of coordination training.

### Assistive device

Assistive devices are adjuncts for therapeutic exercise. One study included in this review reported the benefits of a wearable proprioceptive stabilizer combined with therapeutic exercises (Leonardi et al., 2017). Patients with ataxia show an irregular gait pattern and deviations in body segmental movement during gait (Serrao et al., 2017). Therefore, devices that reduce body sway and improve trunk stability are effective for improving balance. The proprioceptive stabilizer triggers muscle contractions upon the detection of a muscle stretch and was found to be useful for increasing stability and improving balance in patients with ataxia (Leonardi et al., 2017).

### Discussion

This systematic review provides low to moderate GRADE-based quality of evidence from low to high methodological quality studies for the efficacy of therapeutic exercises to reduce the disease severity among adults with non-hereditary degenerative cerebellar ataxia and improve balance among adults with acquired cerebellar ataxia. The types of exercises included were either balance exercises, coordination training, aerobic exercises such as cycling, gait training, range of motion and strengthening exercises for the extremities, use of robotic-assisted exoskeleton orthosis, lumbar stabilization exercises or a combination of these exercises. Combining adjuncts, such as robotic-assisted gait



**Table 4.** Summary of studies narratively synthesized (n = 17).

Interventions	Study	Study design	Treatment summary	Domain of interest	Conclusion	
General rehabilitation	Ahmedy, Neoh, and Latiff, 2020	Case report	Multidimensional physical therapy program; static and dynamic balance exercises; fall prevention exercises; gait training and inpatient rehabilitation program 4 weeks – 23 months	Disease severity, balance, and functional independence	Two high methodological quality studies support the use of general rehabilitation for improving disease severity One study of high methodological quality and one of low quality support the use of general rehabilitation for improving balance One study of high methodological quality support the use of general rehabilitation for improving disease severity and balance One study of high methodological quality support the use of general rehabilitation for improving functional independence One study of low methodological quality support the use of general rehabilitation for improving balance and functional independence	
	High and Andrews, 2020	Case report				
	Im et al., 2017	One-group pretest-posttest study				
	Ilg et al., 2009	Intraindividual control design				
	Keller and Bastian, 2014	Intraindividual control design				
	De Oliveira et al., 2015	One-group pretest-posttest study				
	Milne et al., 2012	Retrospective study				
	Sartor-Glittenberg and Brickner, 2014	Case series				
	Burciu et al., 2013	One-group pretest-posttest design with healthy control		Rehabilitation program with the use of optokinetic stimuli and virtual reality 2–10 weeks	Fall prevention, balance, and functional independence	One study of high methodological quality supports the use of computer-based training for improving fall prevention One study of high methodological quality and one of low quality support the use of computer-based training for improving balance One study of low methodological quality supports the use of computer-based training for improving balance and functional independence
	Santos et al., 2017	Prospective observational study				
Computer-based training	Toktaş, Yaman, Ulaşlı, and Dündar, 2015	Case report				
	Bultmann et al., 2014	One-group pretest-posttest design with healthy control	Gait training on treadmill, some used body-weight support system 2–10 weeks	Balance	One study of high methodological quality and one of low quality support the use of treadmill training for improving balance	
Treadmill training	De Oliveira et al., 2018	One-group pretest-posttest study				
Sports-based training	Freund and Stettis, 2010	Case report				
	Stephan et al., 2011	Case series	Climbing, cycling and dancing 4–8 weeks	Balance	Two studies of low methodological quality support the use of sports-based training for improving balance	
Assistive device	Song et al., 2019	Case report				
	Leonardi et al., 2017	One-group pretest-posttest study	Wearable proprioceptive stabilizer with noninvasive focal mechanical vibrations 3–4 weeks	Disease severity	One study of high methodological quality support the use of assistive device for improving disease severity	

training, lumbar stabilization, and task-oriented approach to routine exercises, have been beneficial for improving balance among individuals with acquired ataxia. We found a non-significant effect of therapeutic exercises on functional independence in this population. The narratively synthesized studies reported benefits from non-randomized controlled trials of methodological quality scores between 4 and 8 out of 9 stars according to the NOS scale, for the use of general rehabilitation exercises, computer-based training, treadmill training, sports-based training and assistive devices for improving the disease severity or balance or functional independence. The findings of the present study are in line with those of previous reviews, which reported on the benefits of general rehabilitation, computer-based training, and treadmill training for improving balance among individuals with cerebellar ataxia (Marquer, Barbieri, and Pérennou, 2014; Milne et al., 2017).

The pooled analysis of four studies (Barbuto et al., 2020; Ilg et al., 2009; Miyai et al., 2012; Rodríguez-Díaz et al., 2018) of low to high methodological quality indicated a significant reduction in the disease severity, as assessed using SARA when therapeutic exercise was compared with the no treatment control. The items of SARA quantify the severity of the cardinal symptom of cerebellar ataxia, including walking ability; sitting and standing balance stability; speech; and limb coordination symptoms, such as dysmetria and dysdiadochokinesia. We speculate that an overall improvement in SARA scores indicates the beneficial effects of therapeutic exercises on all assessed symptoms other than speech. The exercises that were delivered included aerobic training using a stationary bicycle; exercises to improve static balance, such as standing on one leg; dynamic balance exercises, such as reaching, stair climbing, truck coordination training, general conditioning exercises and stretching exercises for key muscles. The exercises were delivered for an average of three sessions per week, with each session lasting for 60 minutes, and all of the included interventions lasted at least 4 weeks. Based on these findings, we recommend the use of therapeutic exercises for reducing the disease severity among individuals with degenerative and hereditary cerebellar ataxias. Future high-quality studies remain necessary to explore the benefits of exercises among individuals with acquired causes of ataxia.

The second interesting finding of this review highlights the benefits of therapeutic exercises on balance, as assessed using the BBS when comparing exercise interventions with active therapies. The studies included in this pooled analysis delivered conventional therapeutic exercises plus additional therapies, such as lumbar stabilization, task-oriented training, therapist-assisted gait

training, and robotic-assisted gait training, to the experimental group, whereas the control groups received conventional therapeutic exercises alone. The findings highlighted the additional benefits of adding adjuncts to conventional balance exercises for improving balance in this population. The additional improvement found among the experimental group using adjuncts to conventional therapeutic exercises could be accounted for the additional time spent during therapy. However, this recommendation should be interpreted with caution because all three included studies were of poor methodological quality, the GRADE evidence quality was low, and all three studies were restricted to individuals with acquired cerebellar ataxias. Future high-quality studies remain necessary to explore the additional benefits of adding adjuncts to conventional therapeutic exercises among individuals with non-hereditary degenerative and hereditary ataxias.

The pooled analysis showed a non-significant effect for therapeutic exercises on functional independence compared with both no treatment and active therapies. This finding has three potential explanations. First, unlike the traditional balance assessment scales, such as the BBS, which only focus on balance, the FIM assesses self-care, sphincter control, transfers, locomotion, communication, and social cognition (Milne et al., 2012). Exercise and balance training alone may not be sufficient to address domains other than balance. Second, the scale might not have been sensitive enough to detect subtle changes following treatment and lastly, the FIM is not disease-specific, and the lack of significance could indicate that this measure is not an appropriate outcome measure. Therefore, future studies may be necessary to develop disease-specific measures for the assessment of functional independence in this population.

Among the studies that used treadmill training, task-oriented training was delivered using adjustable levels of velocity, inclination, and weight support, providing individualized ambulatory opportunities for patients with varying degrees of mobility deficits to receive walking training. The effectiveness of treadmill exercise is, therefore, highly dependent on the exercise intensity and the functional level of the patients. In addition to the diverse baseline mobility levels of the included participants, the spectrum of modifications to the treadmill training protocol can explain the observed inconsistency in the results reported among the studies. Strict adherence to a task-oriented training protocol is suggested for better outcomes when using treadmill-based interventions (Cernak, Stevens, Price, and Shumway-Cook, 2008). Among the sports-based training exercises, despite the benefits reported from the included studies,

the results must be interpreted with caution as two of the studies reporting these effects were case studies with low methodological quality. Limited generalizability was identified because sports-based interventions might be limited to individuals with ataxia who are fit and ambulant. Future studies remain necessary to explore these benefits among a wider population. Lastly, among the studies on assistive devices, due to the study design and the poor methodological quality, we are unable to make any recommendations regarding the use of the wearable device. Future studies remain necessary to explore the benefits of using assistive devices as adjuncts for therapeutic exercises in this population.

Although most clinical studies include assessments at baseline and immediately after the intervention, evidence for the long-term effects of therapeutic exercise remains limited (Martin, Tan, Bragge, and Bialocerkowski, 2009). To address this gap in the literature, our review included studies with follow-up assessments beyond the intervention period. Despite some studies reporting sustained improvements, many gains were lost during the follow-up assessment period among patients with degenerative cerebellar ataxia (Im et al., 2017; Miyai et al., 2012; Song et al., 2019). The gains achieved from therapeutic exercises appear to gradually diminish during the follow-up period. This finding could be due to the nature of the disease (Ilg et al., 2010). Diseases resulting in ataxia due to non-hereditary and hereditary causes are commonly neurodegenerative and worsen over time. Despite natural disease progression, the positive effects of training can persist potentially reduce disease progression; however, these effects greatly depend on the type and frequency of home exercise. Secondly and importantly, the role of the cerebellum in learning and sustaining new tasks need to be considered. Patients with cerebellar lesions show limited improvement with practice and in addition, the movement performance decreases to prepractice level when the attention is diverted while performing (Ioffe, Chernikova, and Ustinova, 2007). This also explains the gradually diminishing performance following a lack of sufficient practice during the follow-up phase. Therefore, adherence to exercise interventions beyond the supervised training period is strongly recommended for sustained benefits (Keller and Bastian, 2014).

Our review has many strengths. First, we utilized a comprehensive search strategy, which included pertinent search terms and themes across five search engines, to identify studies on therapeutic exercises for improving disease severity, balance and functional independence in patients with ataxia. Second, to the best of our knowledge, this represents the first study to include a meta-analysis in this field of research. Third, the use

of a quantitative approach to analyze the overall effects using a meta-analysis increases the accuracy of the findings. Last, the use of psychometrically sound quality rating tools (i.e. PEDro scale, NOS and GRADE profile) provided thorough methodological quality and quality of evidence appraisals of the included studies.

This review has several limitations that should be considered when interpreting the findings. First, the meta-analyses were conducted on a small number of studies due to the limited number of randomized controlled trials published in this field; therefore, the statistical power of the evidence generated is limited. Second, considerable heterogeneity was detected across the examined studies, resulting in limited recommendations and insufficient information for recommending a standardized clinical protocol. Third, although the review included a wide range of participant ages, etiologies, and chronicity, most of the patients included in these studies were ambulant, with low ataxia severity. Thus, the findings of this review cannot be generalized to patients with more severe symptoms. Fourth, the generalizability of the study findings to all patients with ataxia is limited because disease progression and the response to treatment greatly varies between the ataxia presentation with different underlying causes. Last, the possibility of a language bias cannot be eliminated because studies published in languages other than English were not included in this review.

This review found low to moderate evidence from studies of low to high methodological quality that supports therapeutic exercises to reduce the disease severity among adults with non-hereditary degenerative cerebellar ataxia and improve balance among adults with acquired cerebellar ataxia. Future clinical trials with adequate sample sizes and robust methodologies are recommended to explore the benefits of therapeutic exercises on the disease severity, balance, and functional independence. The use of conventional therapeutic exercises plus additional therapies, such as lumbar stabilization, task-oriented training, therapist-assisted gait training, and robotic-assisted gait training, is found to be beneficial in improving balance among individuals with acquired cerebellar ataxia. Disease-specific tools for assessing functional independence are currently unavailable; therefore, future studies are warranted to develop such disease-specific tools. Adherence to exercise intervention beyond the supervised training period is strongly recommended for sustained benefits among people with

cerebellar ataxia. Last, future studies of high methodological quality are recommended to establish the benefits of computer-based training, treadmill training, sports-based training, and the use of assistive devices for improving balance in this population.

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## Disclosure statement

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## Appendix 1. Search term for databases

Database: Medline

- (1) Ataxia
- (2) Ataxic
- (3) "Cerebellar ataxia"
- (4) Stroke
- (5) "Multiple sclerosis"
- (6) "Spinocerebellar ataxia"
- (7) "Friedreich's ataxia"
- (8) "Traumatic brain injury"
- (9) "Cerebellar infarction"
- (10) "Degenerative cerebellar ataxia"
- (11) "Ataxic cerebral palsy"
- (12) "Balance problem"
- (13) Imbalance
- (14) "Postural instability"
- (15) Stability
- (16) Functional independence
- (17) "Poor postural control"
- (18) "Berg Balance Scale"
- (19) BBS
- (20) "Rating of Ataxia"
- (21) SARA
- (22) "Ataxia Rating Scale"
- (23) ICARS
- (24) "Functional independence measure"
- (25) FIM
- (26) Rehabilitation
- (27) "Rehabilitation program"
- (28) "Rehabilitation exercise"
- (29) Exercise
- (30) "Balance exercise"
- (31) "Balance training"
- (32) Gait
- (33) Physiotherapy
- (34) "Physical therapy"
- (35) Stability
- (36) "Fall prevention"
- (37) "Exercise-based therapy"
- (38) "Physiotherapy-related therapy"
- (39) "Non-pharmaceutical treatment"
- (40) 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
- (41) 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
- (42) 26 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39
- (43) 40 AND 41 AND 42

**Appendix 2.** GRADE evidence profile: summary of the findings for the effectiveness of interventions compared to control.

Quality assessment		Summary of findings								
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Number of patients		Absolute risk	Quality
							Intervention	Control		
<p><i>Outcome: Effect of therapeutic exercise compared with no treatment using the Scale for the Assessment and Rating of Ataxia (SARA)</i></p>										
4	3 randomized controlled trials (Barbuto et al., 2020; Rodriguez-Diaz et al., 2018; Miyai et al., 2012) and 1 observational study (Ilg et al., 2009)	Serious <sup>a</sup>	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	66	66	The mean effect of exercise in the intervention group was 3.30 lower (3.76 lower to 2.85 higher)	Low <sup>a</sup>
<p><i>Outcome: Effect of therapeutic exercise compared with active therapies using the International Co-operative Ataxia Rating Scale (ICARS)</i></p>										
1	Randomized controlled trial Salci et al., 2017 (TT) Salci et al., 2017 (LS)	Serious <sup>b</sup>	No serious inconsistency	No serious indirectness	Serious <sup>c</sup>	Undetected	14	14	The mean effect of exercise in the intervention group was 2.78 lower (7.07 lower to 1.50 higher)	Moderate <sup>b</sup>
<p><i>Outcome: Effect of balance exercise compared with active therapies using the Berg Balance Scale (BBS)</i></p>										
3	2 randomized controlled trials (Ali, Darwish, Shalaby, and Abbas, 2021; Salci et al., 2017) and 1 observational study (Belas Dos Santos et al., 2018)	Serious <sup>d</sup>	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	50	51	The mean effect of exercise in the intervention group was 2.60 higher (0.92 lower to 4.28 higher)	Low <sup>d</sup>
<p><i>Outcome: Effect of therapeutic exercise compared with no treatment using the Functional Independence Measure (FIM)</i></p>										
2	2 randomized controlled trials Milne 2018 Miyai, 2012	No serious limitations	No serious inconsistency	No serious indirectness	Serious <sup>c</sup>	Undetected	30	29	The mean effect of exercise in the intervention group was 1.59 lower (1.53 lower to 4.72 higher)	Moderate <sup>c</sup>