QUESTION

Should cardiovascular fitness and endurance exercises vs. no treatment be used for ambulant people with Friedreich ataxia?	
POPULATION:	ambulant people with Friedreich ataxia
INTERVENTION:	cardiovascular fitness and endurance exercises
COMPARISON:	no treatment
MAIN OUTCOMES:	Independence of ambulation ; Independence of ambulation ; Independence of ambulation; Independence of ambulation; Independence of ambulation; Independence of ambulation; Independence of ambulation; Balance; Balance; Balance; Balance; Balance; Falls; Walking capacity; Walking capacity; Walking capacity; Quality of life; Quality of life; Lower limb strength;

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Gait instability is the most frequently reported initial symptom in individuals with FRDA occurring as the first symptom in 76 - 88% of individuals (Reetz et al, 2015). Mobility typically declines, with loss of mobility for individuals with onset <15 years of age typically 11.5 years after first symptom onset; 18.3 years for individuals with onset 15-24 years of age and 23.5 years for individuals with onset >24 years (Rumney et al, 2020). In a cohort of 42 children with FRDA who could still ambulate exercise capacity was reduced (as measured by peak oxygen consumption (peak VO2) and peak work rate) compared with health individuals of a similar age (Drinkard et al, 2010).	The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were interviewed on the consequences, urgency and priority of the topic. 1/7 indicated the consequences of the disturbance of strength, balance, mobility and reduction of falls were probably serious, 5/7 indicated serious, 1/7 indicated didn't know if serious. 1/7 indicated the consequences of the disturbance of strength, balance, mobility and reduction of falls were probably not urgent, 1/7 indicated probably urgent, 5/7 indicated urgent. 1/7 indicated the consequences of the disturbance of strength, balance, mobility and reduction of falls were probably a priority, 6/7 indicated priority. (Aug 2020). In a public forum entitled "Voice of the patient", held on 2 June 2017 in the USA to inform the United States Food and Drug Administration approximately 400 attendees (in-person and online) were asked to choose top three symptoms that would be most meaningful to treat. 55% of people chose improving balance or improved walking as two of their top symptoms (weblink: http://curefa.org/pdf/news/FA-Voice-of-the-Patient.pdf).

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Trivial
○ Small
● Moderate
○ Large
○ Varies
○ Don't know

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no treatment	Risk difference with cardiovascular fitness and endurance exercises
Independence of ambulation assessed with: Functional Ambulation Category	0 (1 observational study)[1]	⨁◯◯◯ Very low[a,b,c,d]	-	37 people with Friedriech ataxia who received inpatient rehabilitation between Jan 2000 and Dec 2012 were included in this retrospective study. Mean rehabilitation duration was 4.7 weeks (SD 1.4 weeks). At the end of the rehabilitation program, a statistically significant difference was found in the FAC pre- and post- treatment (p=0.016).	
Independence of ambulation assessed with: Hoffer Ambulation Scale	0 (1 observational study)[1]	⨁◯◯◯ Very low[a,b,c,d]	-	37 people with Friedriech ataxia who received inpatient rehabilitation between Jan 2000 and Dec 2012 were included in this retrospective study. Mean rehabilitation duration was 4.7 weeks (SD 1.4 weeks). At the end of the rehabilitation program, a statistically significant difference was found in the Hoffer Ambulation scale pre- and post-treatment (p<0.05).	
Independence of ambulation assessed with: Barthel Index	0 (1 observational study)[1]	⨁◯◯◯ Very low[a,b,c,d]	-	37 people with Friedriech ataxia who received inpatient rehabilitation between Jan 2000 and Dec 2012 were included in this retrospective study. Mean rehabilitation duration was 4.7 weeks (SD 1.4 weeks). At the end of the rehabilitation program, a statistically significant difference was found in the Barthel Index pre- (mean 46.8, SD 8.8) and post- (mean 54.2, SD 10.3) treatment (p<0.001).	
Independence of ambulation assessed with: Friedreich	0 (1 RCT)[2]	⨁⨁◯◯ Low[a,b]	-	19 participants with Friedreich ataxia were randomised to a six-week outpatient rehabilitation programme immediately (intervention group) or	

A further case study examined the effects of 27 exercise sessions on the bike ergometer, 20 to 25 minutes each session, with a targeted exercising heart rate equal to 70% to 85% of pre-test maximum (Fillyaw et al, 1989). No functional measures were administered however, the patient's peak VO2 increased 27% and peak ventilation increased 21%.

Many of the studies included in the Evidence Profile table included cardiovascular/endurance training as a component of a multi-faceted exercise/rehabilitation program. Therefore, it is difficult to distinguish the impact of this specific intervention.

Ataxia Rating Scale				after a six-week delayed-start (control group). The rehabilitation was followed by a six-week home exercise programme. Paired t-tests were used to determine change in baseline and immediately post-rehab, and baseline and immedidately after post-home exercise programme (HEP). Significant improvements between baseline (mean 97.3, SD 22.2) and post-HEP (mean 94.0, SD 23.2) were found in the FARS (p=0.017). (Milne et al 2018).
Independence of ambulation assessed with: Functional Independence Measure	0 (1 RCT)[2]	-[a,b]	-	19 participants with Friedreich ataxia were randomised to a six-week outpatient rehabilitation programme immediately (intervention group) or after a six-week delayed-start (control group). The rehabilitation was followed by a six-week home exercise programme. Rehabilitation effectiveness was analysed using independent sample t-tests to compare change from baseline and six-week visit between groups. No significant difference was found in the FIM, between the groups from baseline to six-week visit. There was no significant between-group difference in the FIM motor domain, however there was a significant within-group increased for the intervention group. (Milne et al 2018).
Independence of ambulation assessed with: Scale for the Assessment and Rating of Ataxia	0 (2 RCTs)[3,4]	⨁◯◯◯ Very low[b,e,f,g,h]	-	8 individuals with spinocerebellar ataxia were recruited to this study and underwent a partial body weight support associated with gait training on a treadmill - 2 sessions of assessment with 1 week of interval between were completed. Wilcoxon matched-pairs test identified no significant differences in the SARA score before and after the training. (De Oliveira et al 2018).20 people with cerebellar degeneration in this single-blinded feasibility study were randomised to either aerobic (n=10, 4 weeks of cycling at home) or no training (n=10, no intervention). A mixed effect

				model with (group x time) was conducted and identified significant improvement in the SARA in the aerobic group (baseline score 9.1, SD 2.9; post training score 7.0, SD 2.8) compared to the control group (p<0.001). (Barbuto et al 2020).
Independence of ambulation assessed with: International Cooperative Ataxia Rating Scale	0 (1 RCT)[5]	-	-	20 people with spinocerebellar ataxia underwent either 4 weeks of cycling training (n=10) or no training (n=10). Wilcoxon signed-rank test identified significantly improved ICARS scores (pre score 13.5, SD 9.8; post score 11.3, SD 8.7, p=0.046) after 4 weeks of cycling training. No changes were found in the group that did not receive training. (Chang et al 2015).
Balance assessed with: Berg Balance Scale	0 (2 RCTs)[2,4]	⨁◯◯◯ Very low[b,g,h,i]	-	19 participants with Friedreich ataxia were randomised to a six-week outpatient rehabilitation programme immediately (intervention group) or after a six-week delayed-start (control group). The rehabilitation was followed by a six-week home exercise programme. Paired t-tests were used to determine change in baseline and immediately post-rehab, and baseline and immedidately after post-home exercise programme (HEP). Significant improvements between baseline and post-rehab were found in the Berg Balance Scale (p=0.039). as well as between baseline and post-HEP (p=0.026) for non-ambulant participants. (Milne et al 2018). 8 individuals with spinocerebellar ataxia were recruited and underwent a partial body weight support associated with gait training on a treadmill - 2 sessions of assessment with 1 week of interval between were completed: first stage was gait/conditioning and the second stage was dynamic balance training). Wilcoxon matched-pairs test identified significant improvements in the BBS before and after dynamic balance training (pre

				median score 48, range 44-54; post median score 54, range 47-55; *p*=0.04). (De Oliveira et al 2018).
Balance assessed with: Friedreich Ataxia Rating Scale	0 (1 RCT)[2]	⨁⨁◯◯ Low[a,b,j,k]	-	19 participants with Friedreich ataxia were randomised to a six-week outpatient rehabilitation programme immediately (intervention group) or after a six-week delayed-start (control group). The rehabilitation was followed by a six-week home exercise programme. Paired t-tests were used to determine change in baseline and immediately post-rehab, and baseline and immedidately after post-home exercise programme (HEP). Significant improvements between baseline (mean 97.3, SD 22.2) and post-HEP (mean 94.0, SD 23.2) were found in the FARS (*p*=0.017). (Milne et al 2018).
Balance assessed with: Scale for the Assessment and Rating of Ataxia	0 (1 RCT)[3]	⨁⨁◯◯ Low[b,e]	-	20 people with cerebellar degeneration in this single-blinded feasibility study were randomised to either aerobic (n=10, 4 weeks of cycling at home) or no training (n=10, no intervention). A mixed effect model with (group x time) was conducted and identified significant improvement in the SARA in the aerobic group (baseline score 9.1, SD 2.9; post training score 7.0, SD 2.8) compared to the control group (*p*<0.001). (Barbuto et al 2020).
Balance assessed with: Timed Up and Go test	0 (1 RCT)[3]	⨁⨁◯◯ Low[b,e]	-	20 people with cerebellar degeneration in this single-blinded feasibility study were randomised to either aerobic (n=10, 4 weeks of cycling at home) or no training (n=10, no intervention). A mixed effect model with (group x time) was conducted and identified significant improvement in the TUG in the aerobic group (baseline 13.2 sec, SD 8.0; post training 11.5 sec, SD 7.4) compared to the control group (*p*<0.007). (Barbuto et al 2020).

Balance assessed with: International Cooperative Ataxia Rating Scale	0 (1 RCT)[5]	⨁◯◯◯ Very low[b,c,g,l,m]	-	20 people with spinocerebellar ataxia underwent either 4 weeks of cycling training (n=10) or no training (n=10). Wilcoxon signed-rank test identified significantly improved ICARS scores (pre score 13.5, SD 9.8; post score 11.3, SD 8.7, *p*=0.046) after 4 weeks of cycling training. No changes were found in the group that did not receive training. (Chang et al 2015).	
Balance assessed with: Dynamic Gait Index	0 (1 RCT)[3]	⨁⨁◯◯ Low[b,e]	-	20 people with cerebellar degeneration in this single-blinded feasibility study were randomised to either aerobic (n=10, 4 weeks of cycling at home) or no training (n=10, no intervention). A mixed effect model with (group x time) was conducted and identified significant improvement in the Dynamic Gait Index in the aerobic group (baseline 17.5, SD 3.5; post training 19.0, SD 3.3) compared to the control group (*p*=0.006). (Barbuto et al 2020).	
Falls - not measured	-	-	-	-	-
Walking capacity assessed with: Dynamic gait index	0 (1 RCT)[3]	⨁⨁◯◯ Low[b,e]	-	20 people with cerebellar degeneration in this single-blinded feasibility study were randomised to either aerobic (n=10, 4 weeks of cycling at home) or no training (n=10, no intervention). A mixed effect model with (group x time) was conducted and identified significant improvement in the Dynamic Gait Index in the aerobic group (baseline 17.5, SD 3.5; post training 19.0, SD 3.3) compared to the control group (*p*=0.006). (Barbuto et al 2020).	
Walking capacity assessed with: Timed Up and Go test	0 (1 RCT)[3]	⨁⨁◯◯ Low[b,e]	-	20 people with cerebellar degeneration in this single-blinded feasibility study were randomised to either aerobic (n=10, 4 weeks of cycling at home) or no training (n=10, no intervention). A mixed effect model with (group x time) was conducted and identified significant	

				improvement in the TUG in the aerobic group (baseline 13.2 sec, SD 8.0; post training 11.5 sec, SD 7.4) compared to the control group (p<0.007). (Barbuto et al 2020).
Walking capacity assessed with: International Cooperative Ataxia Rating Scale	0 (1 RCT)[5]	⊕◯◯◯ Very low[b,c,g,l,m]	-	20 people with spinocerebellar ataxia underwent either 4 weeks of cycling training (n=10) or no training (n=10). Wilcoxon signed-rank test identified significantly improved ICARS scores (pre score 13.5, SD 9.8; post score 11.3, SD 8.7, p=0.046) after 4 weeks of cycling training. No changes were found in the group that did not receive training. (Chang et al 2015).
Quality of life assessed with: Friedreich Ataxia Impact Scale	0 (1 RCT)[2]	⊕⊕⊕◯ Moderate[c]	-	19 participants with Friedreich ataxia were randomised to a six-week outpatient rehabilitation programme immediately (intervention group) or after a six-week delayed-start (control group). The rehabilitation was followed by a six-week home exercise programme. Rehabilitation effectiveness was analysed using independent sample t-tests to compare change from baseline and six-week visit between groups. There was a significant between-group difference in the FAIS body movement scale (p=0.003). Paired t-tests were used to determine change in baseline and immediately post-rehab, and baseline and immedidately after post-home exercise programme (HEP). Significant improvements between baseline (mean 35.2 SD 21.9) and post-rehab (mean 27.7, SD 19.7) were found in the FAIS body movement scale (p=0.009) and in the FAIS lower limb (mean 65.2, SD 28.5 to mean 48.5, SD 31.5, p=0.033) and upper limb subscales (mean 29.3, SD 23.7 to mean 25.2, SD 20.4, p=0.044). (Milne et al 2018).
Quality of life assessed with:	0 (1	⊕◯◯◯	-	8 individuals with spinocerebellar ataxia were recruited and underwent a partial

Katz index of independence	observational study)[4]	Very low[b,c,l,n]		body weight support associated with gait training on a treadmill - 2 sessions of assessment with 1 week of interval between were completed: first stage was gait/conditioning and the second stage was dynamic balance training). Wilcoxon matched-pairs test identified no significant differences in the Katz index of independence score before and after the training. (De Oliveira et al 2018).	
Lower limb strength - not measured	-	-	-	-	-

1. Dogan-Aslan M., Buyukvural-Sen S.,Nakipoglu-Yuzer G.F.,Ozgirgin N. Demographic and clinical features and rehabilitation outcomes of patients with Friedreich ataxia: A retrospective study. Turkish Journal of Physical Medicine and Rehabilitation; 2018.
2. Milne S.C., Corben L.A.,Roberts M.,et al. Can rehabilitation improve the health and well-being in Friedreich's ataxia: a randomized controlled trial?. Clinical Rehabilitation; 2018.
3. Barbuto S., Martelli D. Omofuma I.B. et al. Phase I randomized single-blinded controlled study investigating the potential benefit of aerobic exercise in degenerative cerebellar disease. Clinical Rehabilitation; 2020.
4. De Oliveira L.A.S., Martins C.P. Horsczaruk C.H.R. et al. Partial Body Weight-Supported Treadmill Training in Spinocerebellar Ataxia. Rehabilitation Research and Practice; 2018.
5. Chang, Y. J.,Chou,C. C.,Huang,W. T.,Lu,C. S.,Wong,A. M.,& Hsu,M. J. Cycling regimen induces spinal circuitry plasticity and improves leg muscle coordination in individuals with spinocerebellar ataxia.. Archives of physical medicine and rehabilitation; 2015.

a. Intervention included other aspects of rehabilitation (i.e. strengthening, balance exercises) in the program as well as cardio-vascular exercise.
b. Small sample size.
c. Confidence intervals not reported.
d. No control gorup.
e. No participants with a diagnosis of FRDA (combined spinocerebellar ataxia, idiopathic ataxia, multiple system atrophy).
f. Outcome measure not specific to independence of ambulation.
g. Allocation not blinded.
h. One study an observational study.
i. Eight participants with a non-FRDA diagnosis (total participants n=27).
j. Outcome measure evaluates other aspects of function, not solely balance.
k. Outcome measure not specific to balance.
l. No participants had a diagnosis of FRDA (all spinocerebellar ataxia).
m. No short or long term follow up.
n. Single study published only.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT

○ Large
○ Moderate
● Small
○ Trivial
○ Varies
○ Don't know

RESEARCH EVIDENCE

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no treatment	Risk difference with cardiovascular fitness and endurance exercises
Independence of ambulation assessed with: Functional Ambulation Category	0 (1 observational study)[1]	⨁◯◯◯ Very low[a,b,c,d]	-	37 people with Friedriech ataxia who received inpatient rehabilitation between Jan 2000 and Dec 2012 were included in this retrospective study. Mean rehabilitation duration was 4.7 weeks (SD 1.4 weeks). At the end of the rehabilitation program, a statistically significant difference was found in the FAC pre- and post- treatment (p=0.016).	
Independence of ambulation assessed with: Hoffer Ambulation Scale	0 (1 observational study)[1]	⨁◯◯◯ Very low[a,b,c,d]	-	37 people with Friedriech ataxia who received inpatient rehabilitation between Jan 2000 and Dec 2012 were included in this retrospective study. Mean rehabilitation duration was 4.7 weeks (SD 1.4 weeks). At the end of the rehabilitation program, a statistically significant difference was found in the Hoffer Ambulation scale pre- and post-treatment (p<0.05).	
Independence of ambulation assessed with: Barthel Index	0 (1 observational study)[1]	⨁◯◯◯ Very low[a,b,c,d]	-	37 people with Friedriech ataxia who received inpatient rehabilitation between Jan 2000 and Dec 2012 were included in this retrospective study. Mean rehabilitation duration was 4.7 weeks (SD 1.4 weeks). At the end of the rehabilitation program, a statistically significant difference was found in the	

ADDITIONAL CONSIDERATIONS

No adverse events were reported as significant in the published studies; however, fatigue (muscle-fatigue and general fatigue) and cardiac status should be monitored.

				Barthel Index pre- (mean 46.8, SD 8.8) and post- (mean 54.2, SD 10.3) treatment (p<0.001).
Independence of ambulation assessed with: Friedreich Ataxia Rating Scale	0 (1 RCT)[2]	⊕⊕◯◯ Low[a,b]	-	19 participants with Friedreich ataxia were randomised to a six-week outpatient rehabilitation programme immediately (intervention group) or after a six-week delayed-start (control group). The rehabilitation was followed by a six-week home exercise programme. Paired t-tests were used to determine change in baseline and immediately post-rehab, and baseline and immedidately after post-home exercise programme (HEP). Significant improvements between baseline (mean 97.3, SD 22.2) and post-HEP (mean 94.0, SD 23.2) were found in the FARS (p=0.017). (Milne et al 2018).
Independence of ambulation assessed with: Functional Independence Measure	0 (1 RCT)[2]	-[a,b]	-	19 participants with Friedreich ataxia were randomised to a six-week outpatient rehabilitation programme immediately (intervention group) or after a six-week delayed-start (control group). The rehabilitation was followed by a six-week home exercise programme. Rehabilitation effectiveness was analysed using independent sample t-tests to compare change from baseline and six-week visit between groups. No significant difference was found in the FIM, between the groups from baseline to six-week visit. There was no significant between-group difference in the FIM motor domain, however there was a significant within-group increased for the intervention group. (Milne et al 2018).
Independence of ambulation assessed with: Scale for the Assessment and Rating of	0 (2 RCTs)[3,4]	⊕◯◯◯ Very low[b,e,f,g,h]	-	8 individuals with spinocerebellar ataxia were recruited to this study and underwent a partial body weight support associated with gait training on a treadmill - 2 sessions of assessment with 1 week of interval between were

Ataxia				completed. Wilcoxon matched-pairs test identified no significant differences in the SARA score before and after the training. (De Oliveira et al 2018).20 people with cerebellar degeneration in this single-blinded feasibility study were randomised to either aerobic (n=10, 4 weeks of cycling at home) or no training (n=10, no intervention). A mixed effect model with (group x time) was conducted and identified significant improvement in the SARA in the aerobic group (baseline score 9.1, SD 2.9; post training score 7.0, SD 2.8) compared to the control group (p<0.001). (Barbuto et al 2020).
Independence of ambulation assessed with: International Cooperative Ataxia Rating Scale	0 (1 RCT)[5]	-	-	20 people with spinocerebellar ataxia underwent either 4 weeks of cycling training (n=10) or no training (n=10). Wilcoxon signed-rank test identified significantly improved ICARS scores (pre score 13.5, SD 9.8; post score 11.3, SD 8.7, p=0.046) after 4 weeks of cycling training. No changes were found in the group that did not receive training. (Chang et al 2015).
Balance assessed with: Berg Balance Scale	0 (2 RCTs)[2,4]	⨁◯◯◯ Very low[b,g,h,i]	-	19 participants with Friedreich ataxia were randomised to a six-week outpatient rehabilitation programme immediately (intervention group) or after a six-week delayed-start (control group). The rehabilitation was followed by a six-week home exercise programme. Paired t-tests were used to determine change in baseline and immediately post-rehab, and baseline and immedidately after post-home exercise programme (HEP). Significant improvements between baseline and post-rehab were found in the Berg Balance Scale (p=0.039). as well as between baseline and post-HEP (p=0.026) for non-ambulant participants. (Milne et al 2018). 8 individuals with spinocerebellar ataxia were recruited and underwent a partial body weight

				support associated with gait training on a treadmill - 2 sessions of assessment with 1 week of interval between were completed: first stage was gait/conditioning and the second stage was dynamic balance training). Wilcoxon matched-pairs test identified significant improvements in the BBS before and after dynamic balance training (pre median score 48, range 44-54; post median score 54, range 47-55; *p*=0.04). (De Oliveira et al 2018).
Balance assessed with: Friedreich Ataxia Rating Scale	0 (1 RCT)[2]	⊕⊕◯◯ Low[a,b,j,k]	-	19 participants with Friedreich ataxia were randomised to a six-week outpatient rehabilitation programme immediately (intervention group) or after a six-week delayed-start (control group). The rehabilitation was followed by a six-week home exercise programme. Paired t-tests were used to determine change in baseline and immediately post-rehab, and baseline and immedidately after post-home exercise programme (HEP). Significant improvements between baseline (mean 97.3, SD 22.2) and post-HEP (mean 94.0, SD 23.2) were found in the FARS (*p*=0.017). (Milne et al 2018).
Balance assessed with: Scale for the Assessment and Rating of Ataxia	0 (1 RCT)[3]	⊕⊕◯◯ Low[b,e]	-	20 people with cerebellar degeneration in this single-blinded feasibility study were randomised to either aerobic (n=10, 4 weeks of cycling at home) or no training (n=10, no intervention). A mixed effect model with (group x time) was conducted and identified significant improvement in the SARA in the aerobic group (baseline score 9.1, SD 2.9; post training score 7.0, SD 2.8) compared to the control group (*p*<0.001). (Barbuto et al 2020).
Balance assessed with: Timed Up and Go test	0 (1 RCT)[3]	⊕⊕◯◯ Low[b,e]	-	20 people with cerebellar degeneration in this single-blinded feasibility study were randomised to either aerobic (n=10, 4 weeks of cycling at home) or no

				training (n=10, no intervention). A mixed effect model with (group x time) was conducted and identified significant improvement in the TUG in the aerobic group (baseline 13.2 sec, SD 8.0; post training 11.5 sec, SD 7.4) compared to the control group (p<0.007). (Barbuto et al 2020).	
Balance assessed with: International Cooperative Ataxia Rating Scale	0 (1 RCT)[5]	⨁◯◯◯ Very low[b,c,g,l,m]	-	20 people with spinocerebellar ataxia underwent either 4 weeks of cycling training (n=10) or no training (n=10). Wilcoxon signed-rank test identified significantly improved ICARS scores (pre score 13.5, SD 9.8; post score 11.3, SD 8.7, p=0.046) after 4 weeks of cycling training. No changes were found in the group that did not receive training. (Chang et al 2015).	
Balance assessed with: Dynamic Gait Index	0 (1 RCT)[3]	⨁⨁◯◯ Low[b,e]	-	20 people with cerebellar degeneration in this single-blinded feasibility study were randomised to either aerobic (n=10, 4 weeks of cycling at home) or no training (n=10, no intervention). A mixed effect model with (group x time) was conducted and identified significant improvement in the Dynamic Gait Index in the aerobic group (baseline 17.5, SD 3.5; post training 19.0, SD 3.3) compared to the control group (p=0.006). (Barbuto et al 2020).	
Falls - not measured	-	-	-	-	-
Walking capacity assessed with: Dynamic gait index	0 (1 RCT)[3]	⨁⨁◯◯ Low[b,e]	-	20 people with cerebellar degeneration in this single-blinded feasibility study were randomised to either aerobic (n=10, 4 weeks of cycling at home) or no training (n=10, no intervention). A mixed effect model with (group x time) was conducted and identified significant improvement in the Dynamic Gait Index in the aerobic group (baseline 17.5, SD 3.5; post training 19.0, SD 3.3) compared to the control group (p=0.006). (Barbuto	

				et al 2020).
Walking capacity assessed with: Timed Up and Go test	0 (1 RCT)[3]	⨁⨁◯◯ Low[b,e]	-	20 people with cerebellar degeneration in this single-blinded feasibility study were randomised to either aerobic (n=10, 4 weeks of cycling at home) or no training (n=10, no intervention). A mixed effect model with (group x time) was conducted and identified significant improvement in the TUG in the aerobic group (baseline 13.2 sec, SD 8.0; post training 11.5 sec, SD 7.4) compared to the control group (p<0.007). (Barbuto et al 2020).
Walking capacity assessed with: International Cooperative Ataxia Rating Scale	0 (1 RCT)[5]	⨁◯◯◯ Very low[b,c,g,l,m]	-	20 people with spinocerebellar ataxia underwent either 4 weeks of cycling training (n=10) or no training (n=10). Wilcoxon signed-rank test identified significantly improved ICARS scores (pre score 13.5, SD 9.8; post score 11.3, SD 8.7, p=0.046) after 4 weeks of cycling training. No changes were found in the group that did not receive training. (Chang et al 2015).
Quality of life assessed with: Friedreich Ataxia Impact Scale	0 (1 RCT)[2]	⨁⨁⨁◯ Moderate[c]	-	19 participants with Friedreich ataxia were randomised to a six-week outpatient rehabilitation programme immediately (intervention group) or after a six-week delayed-start (control group). The rehabilitation was followed by a six-week home exercise programme. Rehabilitation effectiveness was analysed using independent sample t-tests to compare change from baseline and six-week visit between groups. There was a significant between-group difference in the FAIS body movement scale (p=0.003). Paired t-tests were used to determine change in baseline and immediately post-rehab, and baseline and immedidately after post-home exercise programme (HEP). Significant improvements between baseline (mean 35.2 SD 21.9) and post-rehab (mean 27.7, SD 19.7) were found in the FAIS

				body movement scale (p=0.009) and in the FAIS lower limb (mean 65.2, SD 28.5 to mean 48.5, SD 31.5, p=0.033) and upper limb subscales (mean 29.3, SD 23.7 to mean 25.2, SD 20.4, p=0.044). (Milne et al 2018).	
Quality of life assessed with: Katz index of independence	0 (1 observational study)[4]	⨁◯◯◯ Very low[b,c,l,n]	-	8 individuals with spinocerebellar ataxia were recruited and underwent a partial body weight support associated with gait training on a treadmill - 2 sessions of assessment with 1 week of interval between were completed: first stage was gait/conditioning and the second stage was dynamic balance training). Wilcoxon matched-pairs test identified no significant differences in the Katz index of independence score before and after the training. (De Oliveira et al 2018).	
Lower limb strength - not measured	-	-	-	-	-

1. Dogan-Aslan M., Buyukvural-Sen S.,Nakipoglu-Yuzer G.F.,Ozgirgin N. Demographic and clinical features and rehabilitation outcomes of patients with Friedreich ataxia: A retrospective study. Turkish Journal of Physical Medicine and Rehabilitation; 2018.
2. Milne S.C., Corben L.A.,Roberts M.,et al. Can rehabilitation improve the health and well-being in Friedreich's ataxia: a randomized controlled trial?. Clinical Rehabilitation; 2018.
3. Barbuto S., Martelli D. Omofuma I.B. et al. Phase I randomized single-blinded controlled study investigating the potential benefit of aerobic exercise in degenerative cerebellar disease. Clinical Rehabilitation; 2020.
4. De Oliveira L.A.S., Martins C.P. Horsczaruk C.H.R. et al. Partial Body Weight-Supported Treadmill Training in Spinocerebellar Ataxia. Rehabilitation Research and Practice; 2018.
5. Chang, Y. J.,Chou,C. C.,Huang,W. T.,Lu,C. S.,Wong,A. M.,& Hsu,M. J. Cycling regimen induces spinal circuitry plasticity and improves leg muscle coordination in individuals with spinocerebellar ataxia.. Archives of physical medicine and rehabilitation; 2015.

a. Intervention included other aspects of rehabilitation (i.e. strengthening, balance exercises) in the program as well as cardio-vascular exercise.
b. Small sample size.
c. Confidence intervals not reported.
d. No control gorup.

	e. No participants with a diagnosis of FRDA (combined spinocerebellar ataxia, idiopathic ataxia, multiple system atrophy). f. Outcome measure not specific to independence of ambulation. g. Allocation not blinded. h. One study an observational study. i. Eight participants with a non-FRDA diagnosis (total participants n=27). j. Outcome measure evaluates other aspects of function, not solely balance. k. Outcome measure not specific to balance. l. No participants had a diagnosis of FRDA (all spinocerebellar ataxia). m. No short or long term follow up. n. Single study published only.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies	There is moderate to very low certainty of evidence as per the evidence profile table.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability		

Outcomes	Importance	Certainty of the evidence (GRADE)
Independence of ambulation assessed with: Functional Ambulation Category	IMPORTANT[a]	⨁◯◯◯ Very low[b,c,d,e]
Independence of ambulation	IMPORTANT[a]	⨁◯◯◯

assessed with: Hoffer Ambulation Scale		Very low[b,c,d,e]
Independence of ambulation assessed with: Barthel Index	IMPORTANT[a]	⨁◯◯◯ Very low[b,c,d,e]
Independence of ambulation assessed with: Friedreich Ataxia Rating Scale	IMPORTANT[a]	⨁⨁◯◯ Low[b,c]
Independence of ambulation assessed with: Functional Independence Measure	IMPORTANT[a]	_[b,c]
Independence of ambulation assessed with: Scale for the Assessment and Rating of Ataxia	IMPORTANT[a]	⨁◯◯◯ Very low[c,f,g,h,i]
Independence of ambulation assessed with: International Cooperative Ataxia Rating Scale	IMPORTANT[a]	-
Balance assessed with: Berg Balance Scale	IMPORTANT[j]	⨁◯◯◯ Very low[c,h,i,k]
Balance assessed with: Friedreich Ataxia Rating Scale	IMPORTANT[j]	⨁⨁◯◯ Low[b,c,l,m]
Balance assessed with: Scale for the Assessment and Rating of Ataxia	IMPORTANT[j]	⨁⨁◯◯ Low[c,f]
Balance assessed with: Timed Up and Go test	IMPORTANT[j]	⨁⨁◯◯ Low[c,f]
Balance assessed with: International Cooperative Ataxia Rating Scale	IMPORTANT[j]	⨁◯◯◯ Very low[c,d,h,n,o]
Balance assessed with: Dynamic Gait Index	IMPORTANT[j]	⨁⨁◯◯ Low[c,f]
Falls - not measured	CRITICAL[p]	-

Walking capacity assessed with: Dynamic gait index	IMPORTANT[q]	⊕⊕◯◯ Low[c,f]
Walking capacity assessed with: Timed Up and Go test	IMPORTANT[q]	⊕⊕◯◯ Low[c,f]
Walking capacity assessed with: International Cooperative Ataxia Rating Scale	IMPORTANT[q]	⊕◯◯◯ Very low[c,d,h,n,o]
Quality of life assessed with: Friedreich Ataxia Impact Scale	CRITICAL[r]	⊕⊕⊕◯ Moderate[d]
Quality of life assessed with: Katz index of independence	CRITICAL[r]	⊕◯◯◯ Very low[c,d,n,s]
Lower limb strength - not measured	IMPORTANT[t]	-

a. Identified as critical (1/6), important (3/6), low importance (2/6) by people with FA and critical by expert authors on this topic
b. Intervention included other aspects of rehabilitation (i.e. strengthening, balance exercises) in the program as well as cardio-vascular exercise.
c. Small sample size.
d. Confidence intervals not reported.
e. No control group.
f. No participants with a diagnosis of FRDA (combined spinocerebellar ataxia, idiopathic ataxia, multiple system atrophy).
g. Outcome measure not specific to independence of ambulation.
h. Allocation not blinded.
i. One study an observational study.
j. Identified as critical (2/5), important (3/5) by people with FA and important by expert authors on this topic
k. Eight participants with a non-FRDA diagnosis (total participants n=27).
l. Outcome measure evaluates other aspects of function, not solely balance.
m. Outcome measure not specific to balance.
n. No participants had a diagnosis of FRDA (all spinocerebellar ataxia).
o. No short or long term follow up.
p. Identified as critical (3/5) and important (2/5) by people with FA and important by expert authors on this topic.
q. Identified as critical (2/6), important (3/6), low importance (1/6) by people with FA and important by expert authors on this topic
r. Identified as critical (3/6), important (3/6) by people with FA and critical by expert authors on this topic
s. Single study published only.
t. Identified as critical (1/6) and important (5/6) by people with FA and important by expert authors on this topic

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		A survey designed to systematically collect expert-based opinions from clinicians involved in the development of these guidelines and providing clinical care for individuals with Friedreich ataxia, was conducted. Clinical experts from Australia, Europe, UK, South America, Canada and the USA were asked to consider the harms/benefits of Cardiovascular fitness and endurance exercises as a management strategy for ambulant individuals. Reflecting on the impact of Cardiovascular fitness and endurance exercises on Independence of ambulation, 57.69% (15/26) clinical experts reported a benefit (large, moderate or small), 3.85% (1/26) reported no effect and, 3.85% (1/26) reported observing a harm (large, moderate or small). 9 clinicians could not provide any information on this outcome. Reflecting on the impact on Balance, 42.31% (11/26) clinical experts reported a benefit, 23.08% (6/26) reported no effect and, 0% (0/26) reported observing a harm. 9 expert clinicians could not provide any information on this outcome. Reflecting on the impact on Falls, 44% (11/25) clinical experts reported a benefit, 16% (4/25) reported no effect and, 4% (1/25) reported observing a harm. 9 expert clinicians could not provide any information on this outcome. Reflecting on the impact on Walking capacity, 57.69% (15/26) clinical experts reported a benefit, 7.69% (2/26) reported no effect and, 0% (0/26) reported observing a harm. 9 expert clinicians could not provide any information on this outcome. Reflecting on the impact on Quality of life, 69.23% (18/26) clinical experts reported a benefit, 0% (0/26) reported no effect and, 0% (0/26) reported observing a harm. 8 expert clinicians could not provide any information on this outcome. Reflecting on the impact on Lower limb strength, 65.38% (17/26) clinical experts reported a benefit, 0% (0/26) reported no effect and, 0% (0/26) reported observing a harm. 9 expert clinicians could not provide any information on this outcome. There is currently no recommended dosage or intensity of cardiovascular or endurance training for individuals with FRDA.

		In clinical practice, cardiovascular exercise or endurance training appear to have beneficial effects for those individuals who choose this type of exercise. Unfortunately, due to the lack of evidence for recommended dosage, it is difficult to determine if the potential beneficial effects outweigh the potential detrimental effects.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No published evidence.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

We suggest cardiovascular and endurance exercise training be used over no cardiovascular exercise in ambulant individuals with Friedreich ataxia. Gradual onset and increase in the level of activity, with monitoring for any adverse symptoms, is likely to be a safe approach in those with and without cardiac abnormalities.

Justification

Many of the studies included cardiovascular/endurance training as a component of a multi-faceted exercise/rehabilitation program, making it hard to determine the effects of individual components of the programs. However, clinical practice and the few studies examining cardiovascular training alone suggest cardiovascular training provides beneficial effects. Although we are providing a conditional recommendation, there is no evidence to suggest cardiovascular training is superior to other targeted exercises and there is no evidence to suggest a particular dosage or intensity of exercise.

Subgroup considerations

This recommendation is for individuals with Friedreich ataxia who are ambulant.

Research priorities

There is a lack of published evidence focusing on dosage and intensity of cardiovascular or endurance training for individuals with FRDA who are ambulant. Outcomes from a currently recruiting randomised, placebo-controlled trial 'NAD+ and Exercise in FA' may provide further evidence for the effectiveness of aerobic exercise in ambulant individuals with FRDA (https://clinicaltrials.gov/ct2/show/NCT04192136).

References

Drinkard BE, Keyser RE, Paul SM, Arena R, Plehn JF, Yanovski JA, et al. Exercise capacity and idebenone intervention in children and adolescents with Friedreich ataxia. Arch Phys Med Rehabil. 2010;91(7):1044-50.

Fillyaw MJ, Ades PA. Endurance exercise training in Friedreich ataxia. Arch Phys Med Rehabil. 1989;70(10):786-8.

Reetz K, Dogan I, Costa AS, Dafotakis M, Fedosov K, Giunti P, et al. Biological and clinical characteristics of the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS) cohort: a cross-sectional analysis of

baseline data. Lancet Neurol. 2015;14(2):174-82.

Rummey C, Farmer JM, Lynch DR. Predictors of loss of ambulation in Friedreich's ataxia. EClinicalMedicine. 2020;18:100213.