# QUESTION

| Should respiratory strength training vs. no intervention be used for for people with respiratory weakness and restrictive lung disease with Friedreich ataxia? | |
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| **POPULATION:** | for people with respiratory weakness and restrictive lung disease with Friedreich ataxia |
| **INTERVENTION:** | respiratory strength training |
| **COMPARISON:** | no intervention |
| **MAIN OUTCOMES:** | Respiratory function; Respiratory function; Respiratory function; Respiratory function; Respiratory function; Respiratory function; Respiratory function; Respiratory function; Respiratory function; Respiratory function; Prevalence of chest infections; Dyspnea; Exercise tolerance; Exercise tolerance; |

# ASSESSMENT

## Problem

Is the problem a priority?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ No<br>○ Probably no<br>● Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | There is a single case report (Botez et al, 1997) documenting a patient with severe FA and ”arduous” breathing and O2 desaturation together with SDB at night.<br><br>Preliminary data collected by one of the authors indicates decline in respiratory volumes in severe FA and also impaired cough mechanisms. | The Friedreich’s ataxia Clinical Management Guideline Patient and Parent Advisory Panel were interviewed on the consequences, urgency and priority of pulmonary function.<br><br>6/7 indicated that the problem was serious, 1/7 indicated they didn’t know if serious.<br><br>6/7 indicated that the problem was urgent, 1/7 indicated they didn’t know if urgent.<br><br>6/7 indicated that the problem was a priority, 1/7 indicated they didn’t know if a priority. (Aug 2020) |

## Desirable Effects

How substantial are the desirable anticipated effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ Trivial<br>● Small<br>○ Moderate<br>○ Large<br>○ Varies<br>○ Don't know | There are no published data of this intervention in FA. In comparable disorders (Duchenne, Pompe disease, other neuromuscular disorders, and ataxia telangiectasia) there is low level evidence for benefit in selected respiratory parameters with aquatic therapy or inspiratory muscle training, such as in cough flow, MIP, TV, chest expansion, MIP. These studies had limited number of subjects and lacked controls. | |

| Outcomes | № of participants (studies) Follow-up | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects* (95% CI) | |
|---|---|---|---|---|---|
| | | | | Risk with no intervention | Risk difference with respiratory strength training |
| Respiratory function assessed with: Chest expansion | 3 (1 observational study)[1] | ⨁◯◯◯ Very low[a,b,c,d,e,f] | - | 3 male pediatric patients with Duchenne muscular dystrophy underwent an 8-week individualised aquatic therapy program focussing on chest expansion and respiratory muscle strength. There was a clinically meaningful change in 1/3 in chest measurements (0.750 inches pretest vs 1.000 inches posttest for upper chest expansion; 0.375 inches pretest vs 1.000 inches posttest for mid/lower chest expansion). (Adams et al 2017). | |
| Respiratory function assessed with: Inspiratory capacity | 3 (1 observational study)[1] | ⨁◯◯◯ Very low[a,b,c,d,e,f] | - | 3 male pediatric patients with Duchenne muscular dystrophy underwent an 8-week individualised aquatic therapy program focussing on chest expansion and respiratory muscle strength. 1/3 showed an improvement in inspiratory volume (750ml pretest to 875ml posttest). (Adams et al 2017). | |
| Respiratory function assessed with: Peak flow | 3 (1 observational study)[1] | ⨁◯◯◯ Very low[a,b,c,d,e,f] | - | 3 male pediatric patients with Duchenne muscular dystrophy underwent an 8-week individualised aquatic therapy program focussing on chest expansion and respiratory muscle strength. 2/3 showed a positive trend in peak flow (147 vs 160 L/min, and 98 vs 119 L/min). (Adams et al 2017) | |
| Respiratory function assessed with: Peak cough flow | 11 (1 observational study)[2] | ⨁◯◯◯ Very low[a,b,c,d,e] | - | 11 patients with neuromuscular disorders aged 4-18 years underwent a 10-week aquatic exercise program. Comparisons were made using the ANOVA statistical test of 6 × 2 repeated measurements, with six measurement moments (PRE/POST during the 1st session + PRE/POST at 5 sessions + PRE/POST at 10 sessions). Clinical, statistically insignificant changes were found for peak cough flow ($p>0.05$) | |

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| | | | | (Huguet-Rodriguez et al 2020) |
| Respiratory function assessed with: Forced expiratory volume | 22 (2 observational studies)[2,3] | ⊕◯◯◯ Very low[a,b,c,d,e,g] | - | 11 patients with neuromuscular disorders aged 4-18 years underwent a 10-week aquatic exercise program. Comparisons were made using the ANOVA statistical test of 6 × 2 repeated measurements, with six measurement moments (PRE/POST during the 1st session + PRE/POST at 5 sessions + PRE/POST at 10 sessions). Clinical, statistically insignificant changes were found for expiratory pressures ($p$>0.05). (Huguet-Rodriguez et al 2020)<br><br>11 patients with late onset Pompe disease underwent a 6-week repetitive inspiratory muscle training (IMT) followed by a 6-week non-training period and an optional training period of 40 weeks. The total study duration was 52 weeks. There were no statistically significant differences after training, after the non-training period, and in the comparison between baseline to week 52 for forced expiratory volume. (Wenninger et al 2019). |
| Respiratory function assessed with: Minute Volume | 11 (1 observational study)[4] | ⊕◯◯◯ Very low[b,c,d,h] | - | 11 patients with ataxia telangiectasia underwent inspiratory muscle training (IMT) along with 9 healthy volunteers. Assessments were completed before and after a 24-week IMT programme. The paired t-test was used to analyze the data before and after IMT. To compare data obtained after IMT, a two-way analysis of variance (ANOVA) with repeated measures was used. There were no significant changes in minute volume pre- and post-IMT ($p$=0.741). (Felix et al 2014). |
| Respiratory function assessed with: Tidal Volume | 11 (1 observational study)[4] | ⊕◯◯◯ Very low[b,c,d,h] | - | 11 patients with ataxia telangiectasia underwent inspiratory muscle training (IMT) along with 9 healthy volunteers. Assessments were completed before and after a 24-week IMT programme. The paired t-test was used to analyze the data before and after IMT. To compare data obtained after IMT, a two-way analysis of variance (ANOVA) with repeated measures |

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| | | | | was used. There was an increase in tidal volume ($p$=0.015) when comparing pre-and post-IMT data in patients with AT (Felix et al 2014). |
| Respiratory function assessed with: Maximum inspiratory pressure | 22 (2 observational studies)[3,4] | ⊕◯◯◯ Very low[b,c,d,e,g,h] | - | 11 patients with ataxia telangiectasia underwent inspiratory muscle training (IMT) along with 9 healthy volunteers. Assessments were completed before and after a 24-week IMT programme. The paired t-test was used to analyze the data before and after IMT. To compare data obtained after IMT, a two-way analysis of variance (ANOVA) with repeated measures was used. MIP increased after IMT ($p$ < 0.001). Statistical significance was also reached for the age-predicted values after IMT, with MIP increasing from 29% to 50% ($p$ < 0.001). When evaluated over the 24-week study period, MIP indicated that respiratory muscle strength increased after the second month of IMT. However, after the fifth month of IMT, the MIP plateaued. Therefore, the gain in strength was maintained. (Felix et al 2014). 11 patients with late onset Pompe disease underwent a 6-week repetitive inspiratory muscle training (IMT) followed by a 6-week non-training period and an optional training period of 40 weeks. The total study duration was 52 weeks. MIP showed a statistically significant increase after 6 weeks of IMT ($p$ =0.024). 9 subjects showed an increase of MIP (82%). 3 of them achieved a large increase of ≥15 cmH2O. The mean increase after 6 weeks of training was +7.6 cmH2O (+ 15.7%) with a moderate effect size in cross-sectional analysis (d =0.402). 1 patient showed a decline of -8 cmH2O (-14%), and a second one remained stable (-1 cmH2O ). Overall, the patients achieved a significant improvement in MIP both after the short-term IMT of 6 weeks and after the extended IMT of 40 weeks. (Wenninger et al 2019). |

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| Respiratory function assessed with: Vital capacity | 22 (2 observational studies)[3,4] | ⨁◯◯◯ Very low[b,c,d,e,g,h] | - | 11 patients with ataxia telangiectasia underwent inspiratory muscle training (IMT) along with 9 healthy volunteers. Assessments were completed before and after a 24-week IMT programme. The paired t-test was used to analyze the data before and after IMT. To compare data obtained after IMT, a two-way analysis of variance (ANOVA) with repeated measures was used. There was an increase in vital capacity ($p$=0.002) when comparing pre- and post-IMT data in patients with AT (Felix et al 2014). 11 patients with late onset Pompe disease underwent a 6-week repetitive inspiratory muscle training (IMT) followed by a 6-week non-training period and an optional training period of 40 weeks. The total study duration was 52 weeks. There were no statistically significant differences after training, after the non-training period, and in the comparison between baseline to week 52 for forced vital capacity. (Wenninger et al 2019) | |

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|---|---|---|---|---|---|
| Prevalence of chest infections - not measured | - | - | - | - | - |
| Dyspnea assessed with: MMRC-Dyspnea scale | 11 (1 observational study)[3] | ⨁◯◯◯ Very low[b,c,d,e,g] | - | 11 patients with late onset Pompe disease underwent a 6-week repetitive inspiratory muscle training (IMT) followed by a 6-week non-training period and an optional training period of 40 weeks. The total study duration was 52 weeks. There were no statistically significant differences after training, after the non-training period, and in the comparison between baseline to week 52 for the MMRC-Dyspnea scale. (Wenninger et al 2019) | |
| Exercise tolerance assessed with: 6-minute walk test | 11 (1 observational study)[3] | ⨁◯◯◯ Very low[b,c,d,e,g] | - | 11 patients with late onset Pompe disease underwent a 6-week repetitive inspiratory muscle training (IMT) followed by a 6-week non-training period and an optional training period of 40 weeks. The total study duration was 52 weeks. There were no statistically significant differences after training, after the non-training period, and in the comparison between baseline to week 52 for the 6-minute walk test. (Wenninger et al 2019) | |
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a. Participants with muscular dystrophy (no participants diagnosed with FRDA).
b. Small sample size.
c. No confidence intervals reported with low absolute numbers of participants and events.
d. Potential selection bias.
e. Lack of control group.
f. Participants at different stages of disease.
g. Participants with Pompe disease (no participants with a diagnosis of FRDA).
h. Participants with ataxia telangiectasia (no participants with a diagnosis of FRDA).

## Undesirable Effects

How substantial are the undesirable anticipated effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ Large<br>○ Moderate<br>● Small<br>○ Trivial<br>○ Varies<br>○ Don't know | | |

| Outcomes | № of participants (studies) Follow-up | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects* (95% CI) | |
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| | | | | Risk with no intervention | Risk difference with respiratory strength training |
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| Prevalence of chest infections - not measured | - | - | - | - | - |
| Dyspnea assessed with: MMRC-Dyspnea scale | 11 (1 observational study)[3] | ⨁◯◯◯ Very low[b,c,d,e,g] | - | 11 patients with late onset Pompe disease underwent a 6-week repetitive inspiratory muscle training (IMT) followed by a 6-week non-training period and an optional training period of 40 weeks. The total study duration was 52 weeks. There were no statistically significant differences after | |

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a. Participants with muscular dystrophy (no participants diagnosed with FRDA).
b. Small sample size.

| | | |
|---|---|---|
| | c. No confidence intervals reported with low absolute numbers of participants and events.<br>d. Potential selection bias.<br>e. Lack of control group.<br>f. Participants at different stages of disease.<br>g. Participants with Pompe disease (no participants with a diagnosis of FRDA).<br>h. Participants with ataxia telangiectasia (no participants with a diagnosis of FRDA). | |

## Certainty of evidence

What is the overall certainty of the evidence of effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | Very low certainty of the evidence of effects 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<br>○ Possibly important uncertainty or variability<br>● Probably no important uncertainty or variability<br>○ No important uncertainty or variability | <table><tr><th>Outcomes</th><th>Importance</th><th>Certainty of the evidence (GRADE)</th></tr><tr><td>Respiratory function<br>assessed with: Chest expansion</td><td>CRITICAL[a]</td><td>⨁◯◯◯<br>VERY LOW[b,c,d,e,f,g]</td></tr><tr><td>Respiratory function<br>assessed with: Inspiratory capacity</td><td>CRITICAL[a]</td><td>⨁◯◯◯<br>VERY LOW[b,c,d,e,f,g]</td></tr></table> | |

| | | |
|---|---|---|
| Respiratory function<br>assessed with: Peak flow | CRITICAL[a] | ⊕◯◯◯<br>VERY LOW[b,c,d,e,f,g] |
| Respiratory function<br>assessed with: Peak cough flow | CRITICAL[a] | ⊕◯◯◯<br>VERY LOW[b,c,d,e,f] |
| Respiratory function<br>assessed with: Forced expiratory volume | CRITICAL[a] | ⊕◯◯◯<br>VERY LOW[b,c,d,e,f,h] |
| Respiratory function<br>assessed with: Minute Volume | CRITICAL[a] | ⊕◯◯◯<br>VERY LOW[c,d,e,i] |
| Respiratory function<br>assessed with: Tidal Volume | CRITICAL[a] | ⊕◯◯◯<br>VERY LOW[c,d,e,i] |
| Respiratory function<br>assessed with: Maximum inspiratory pressure | CRITICAL[a] | ⊕◯◯◯<br>VERY LOW[c,d,e,f,h,i] |
| Respiratory function<br>assessed with: Maximum expiratory pressure | CRITICAL[a] | ⊕◯◯◯<br>VERY LOW[c,d,e,f,h,i] |
| Respiratory function<br>assessed with: Vital capacity | CRITICAL[a] | ⊕◯◯◯<br>VERY LOW[c,d,e,f,h,i] |
| Prevalence of chest infections - not measured | CRITICAL[j] | - |
| Dyspnea<br>assessed with: MMRC-Dyspnea scale | CRITICAL[j] | ⊕◯◯◯<br>VERY LOW[c,d,e,f,h] |
| Exercise tolerance<br>assessed with: 6-minute walk test | IMPORTANT[k] | ⊕◯◯◯<br>VERY LOW[c,d,e,f,h] |
| Exercise tolerance<br>assessed with: Borg scale | IMPORTANT[k] | ⊕◯◯◯<br>VERY LOW[c,d,e,f,h] |

a. Identified as critical (4/6), important (1/6) and low importance (1/6) by people with FA and critical by expert authors on this topic.
b. Participants with muscular dystrophy (no participants diagnosed with FRDA).
c. Small sample size.

| | | |
|---|---|---|
| | d. No confidence intervals reported with low absolute numbers of participants and events.<br>e. Potential selection bias.<br>f. Lack of control group.<br>g. Participants at different stages of disease.<br>h. Participants with Pompe disease (no participants with a diagnosis of FRDA).<br>i. Participants with ataxia telangiectasia (no participants with a diagnosis of FRDA).<br>j. Identified as critical (3/6), important (1/6) and low importance (2/6) by people with FA and critical by expert authors on this topic<br>k. Identified as important (5/6) and low importance (1/6) by people with FA and important by expert authors on this topc | |

## 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<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>● Favors the intervention<br>○ Varies<br>○ Don't know | A majority of FA experts did not have any information on outcome measures or intervention. A small % reported positive benefit from assessing pulmonary function and cough flow testing, assessing prevalence of chest infections and evaluating exercise tolerance. Also, among the experts providing information, all or nearly all thought that respiratory strength training was beneficial. | 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 **assessing pulmonary function test (cough flow) measures** as a management strategy for people with respiratory weakness.<br><br>Reflecting on the impact of assessing Pulmonary Function Test (cough flow) measures on respiratory function, 16% (4/25) clinical experts reported a benefit (large, moderate or small), 4% (1/25) reported no effect and, 0% (0/25) reported observing a harm (large, moderate or small). 20 clinicians could not provide any information on this outcome. Reflecting on the impact on prevalence of chest infections, 12% (3/25) clinical experts reported a benefit, 8% (2/25) reported no effect. 20 expert clinicians could not provide any information on this outcome. Reflecting on the impact on dyspnea, 16% (4/25) clinical experts reported a benefit, 4% (1/25) reported no effect. 20 expert clinicians could not provide any information on this outcome. Reflecting on the impact on exercise tolerance, 16% (4/25) clinical experts reported a benefit, 4% (1/25) reported no effect. 20 expert clinicians could not provide any information on this outcome.<br><br>Clinical experts were asked to consider the harms/benefits of **respiratory strength training** as a management strategy for |

| | | |
|---|---|---|
| | | people with respiratory weakness.<br><br>Reflecting on the impact of respiratory strength training on respiratory function, 32% (8/25) clinical experts reported a benefit (large, moderate or small), and 0% (0/25) reported observing a harm (large, moderate or small). 17 clinicians could not provide any information on this outcome. Reflecting on the impact on prevalence of chest infections, 32% (8/25) clinical experts reported a benefit, 0% (0/25) reported no effect. 17 expert clinicians could not provide any information on this outcome. Reflecting on the impact on dyspnea, 32% (8/25) clinical experts reported a benefit, 0% (0/25) reported no effect. 17 expert clinicians could not provide any information on this outcome. Reflecting on the impact on exercise tolerance, 28% (7/25) clinical experts reported a benefit, 0% (0/25) reported no effect. 18 expert clinicians could not provide any information on this outcome. |

## Acceptability

Is the intervention acceptable to key stakeholders?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ No<br>○ Probably no<br>● Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | No published evidence. | The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were asked if using respiratory strength training in people with weak breathing and restrictive lung disease was acceptable (weighing up the balance between benefits, harms and costs).<br><br>2/3 indicated the intervention was acceptable, 1/3 indicated probably acceptable. (Aug 2020). |

# 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 | | | |

| | JUDGEMENT | | | | | | |
|---|---|---|---|---|---|---|---|
| **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 cannot recommend either respiratory strength training or no respiratory strength training for people with Friedreich ataxia and respiratory weakness and restrictive lung disease. We suggest that in selected patients with respiratory weakness, supervised respiratory training be considered with monitoring of respiratory parameters and for adverse effects such as exhaustion.

### Justification

Respiratory weakness can lead to symptoms of sleep disordered breathing such as fatigue, excessive daytime sleepiness and dyspnoea and nocturnal abnormalities in blood gases with deleterious effects. However, there are no published data regarding monitoring methods or respiratory strength training in FRDA. Based on limited low-level evidence in small studies and meta-analysis in some similar disorders, there is little objective evidence for respiratory strength training as an intervention for respiratory weakness (Silva et al, 2019; Williamson et al, 2019). However, FRDA expert opinion suggests that respiratory strength training may be considered for individuals with later stage FRDA with impaired pulmonary function tests indicating respiratory weakness.

### Subgroup considerations

This intervention could be considered for individuals with later stage Friedreich ataxia with impaired pulmonary function tests indicating respiratory weakness.

## Research priorities

There is a need for prospective data on aspects of respiratory muscle function and prevalence of sleep disordered breathing and chest infections in individuals with FRDA. Factors that contribute to impairments in these domains should be identified and the effect of respiratory strength training in improving respiratory function, quality of life should be studied.

**Reference**

Botez MI, Mayer P, Bellemare F, Couture J. Can we treat respiratory failure in Friedreich ataxia? Archives of Neurology. 1997;54(8):1030-3.

Silva IS, Pedrosa R, Azevedo IG, Forbes AM, Fregonezi GA, Dourado Junior ME, et al. Respiratory muscle training in children and adults with neuromuscular disease. Cochrane Database Syst Rev. 2019;9:CD011711

Williamson E, Pederson N, Rawson H, Daniel T. The effect of inspiratory muscle training on Duchenne muscular dystrophy: a meta-analysis. Pediatr Phys Ther. 2019;31(4):323-30.