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# Benefits of combining inspiratory muscle with 'whole muscle' training in children with cystic fibrosis: a randomised controlled trial

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## ABSTRACT

**Background** The purpose of this study (randomised controlled trial) was to assess the effects of an 8-week combined 'whole muscle' (resistance+aerobic) and inspiratory muscle training (IMT) on lung volume, inspiratory muscle strength ($PI_{max}$) and cardiorespiratory fitness ($VO_2$ peak) (primary outcomes), and dynamic muscle strength, body composition and quality of life in paediatric outpatients with CF (cystic fibrosis, secondary outcomes). We also determined the effects of a detraining period.

**Methods** Participants were randomly allocated with a block on gender to a control (standard therapy) or intervention group (initial n=10 (6 boys) in each group; age 10±1 and 11±1 years). The latter group performed a combined programme (IMT (2 sessions/day) and aerobic+strength exercises (3 days/week, in-hospital)) that was followed by a 4-week detraining period. All participants were evaluated at baseline, post-training and detraining.

**Results** Adherence to the training programme averaged 97.5%±1.7%. There was a significant interaction (group×time) effect for $PI_{max}$, $VO_{2peak}$ and five-repetition maximum strength (leg-press, bench-press, seated-row) (all $p<0.001$), and also for %fat ($p<0.023$) and %fat-free mass ($p=0.001$), with training exerting a significant beneficial effect only in the intervention group, which was maintained after detraining for $PI_{max}$ and leg-press.

**Conclusion** The relatively short-term (8-week) training programme used here induced significant benefits in important health phenotypes of paediatric patients with CF. IMT is an easily applicable intervention that could be included, together with supervised exercise training in the standard care of these patients.

## INTRODUCTION

Cystic fibrosis (CF) affects ~1:2500 Caucasian newborns. Owing to a defect in the CF transmembrane conductance regulator (CFTR) gene, excess mucous is produced in several organs including the lung.[1] Bronchioles are obstructed, and lung tissue is inflamed.[2] The main strategies for preserving lung function are mucous clearance, eradicating inflammation and gas exchange optimisation by applying chest physiotherapy,[3] oral corticosteroids[4] and non-invasive ventilation.[5] A more recent intervention is supervised physical exercise,[6] including inspiratory muscle training (IMT).

IMT involves the training of muscles that act to expand the chest in order to take air into the lungs.[7] It is designed to directly improve the performance of these muscles, which are skeletal in nature and thus trainable.[7] The specific training loads to the inspiratory muscles can be applied with either a non-linear resistive device, a threshold or targeted loading device or normocapnic hyperpnoea; and the training regimens vary in terms of intensity and duration or both.[8 9] IMT with threshold loading devices involves a series of forced inspirations up to a certain percentage (≥20%) of maximal inspiratory pressure ($PI_{max}$) to enhance inspiratory muscle strength; this in turn would theoretically improve pulmonary function and airway clearance in CF patients and ultimately, exercise tolerance.[7] Since lung deterioration starts during early childhood, IMT should begin at young age. Four controlled/quasi-controlled IMT studies have been conducted with children/adolescents, with positive changes usually reported in inspiratory muscle strength (eg, $PI_{max}$).[10–13] Yet, these benefits have not been consistently paralleled by improvements in exercise capacity, that is, no change in peak oxygen uptake ($VO_{2peak}$).[10 13]

In most CF child patients, $VO_{2peak}$ inevitably decreases over time,[14] with this variable being an important mortality predictor.[14 15] Although previous research has shown the benefit of exercise training on the $VO_{2peak}$ of children/adolescents with CF,[16–19] no published paper has reported the effects of combining both exercise training and IMT in this patient population. The purpose of this study (randomised controlled trial, RCT) was to assess the effects of an 8-week combined IMT and exercise (resistance+aerobic) programme on lung volume, inspiratory muscle strength ($PI_{max}$) and cardiorespiratory fitness ($VO_{2peak}$) (primary outcomes) and dynamic muscle strength, body composition and quality of life (QoL) in paediatric outpatients with CF (secondary outcomes). We also determined the effects of a detraining period. We hypothesised that the combined training programme would significantly benefit most of the aforementioned variables (especially, primary outcomes).

## METHODS

### Study design

Our RCT was compliant with the recommendations of the Consolidated Standards of Reporting Trials (CONSORT) statement of 2010 (32).[20] The Ethics Committee of the Children's *Hospital Infantil Universitario Niño Jesús* (HIUNJ, Madrid, Spain)

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approved the study, which was performed following the ethical guidelines of the Declaration of Helsinki. Participants and their parents/caregivers provided written informed consent. After baseline measurements, children were randomly allocated to one of the two study groups, that is, control (standard therapy) or intervention (exercise). Randomisation to either group was performed with a block on gender based on a randomisation sequence. The staff in charge of outcome assessment was blinded to the participant randomisation assignment, but the staff involved in training was not. The participants and their parents/caregivers were explicitly informed into which group (ie, control or exercise) they were assigned as well as on the study hypotheses, and told not to discuss their randomisation assignment with assessment staff.

The intervention group performed an 8-week training programme that was followed by a 4-week detraining period. All participants were evaluated at baseline and at post-training and detraining in the same setting (HIUNJ) by the same investigators. The study was performed between September 2011 and July 2012, that is, after a recent RCT by our group with other CF children (performed between January 2010 and January 2011) had ended.[19] Our previous RCT included a similar exercise intervention (resistance+aerobic exercises) and most study outcomes assessed here, but without IMT.[19]

## Participants

The potential participants included 95 outpatient children previously diagnosed with a genetic test detecting CF and treated at the HIUNJ. The inclusion criteria were be a boy/girl aged 6–17 years and living in the Madrid area (in order to be able to attend training sessions). Exclusion criteria were having severe lung deterioration (forced expiratory volume ($FEV_1$) <50% of expected), unstable clinical condition (ie, hospitalisation within the previous 3 months), *Burkholderia cepacia* infection or any disorder (eg, muscloskeletal) impairing exercise.

During the intervention period, the controls were instructed on the positive effects of regular physical activity and IMT, and maintained their usual chest physiotherapy sessions (2/day, consisting of postural drainage and chest percussion/vibration manually performed by parents/caregivers); they also performed IMT following the same protocol as the intervention group (see below) but at 10% only of baseline $PI_{max}$.

Besides performing the aforementioned physiotherapy sessions, the intervention group enrolled in three exercise sessions/week (Monday-Wednesday-Friday) during 8 weeks (total=24 sessions). All sessions took place during the afternoon/evening (16:00–20:00) in the in-hospital gymnasium of HIUNJ, equipped with weight-training machines (Strive Inc, McMurray, Pennsylvania, USA) specifically built for the body size of children/adolescents. Each exercise session was individually supervised by trained fitness specialists (1 supervisor/child). In order to minimise infection risk, the gymnasium was well ventilated, the equipment was cleaned before each session, and each child trained alone. Children stayed hydrated during the sessions (≥500 ml of water or sport drink/session).

The aerobic training started with a 10 min warm-up on a cycle-ergometer (Rhyno Magnetic H490, BH Fitness Proaction, Vitoria, Spain), followed by 20–40 min of cycle-ergometer training exercise and 'active playing' (running and soccer playing, for ~15 min). All children wore a portable heart rate (HR) monitor during training to control exercise intensity, which corresponded to the HR at the ventilatory threshold (VT) during the baseline evaluation (see below). The second part of the training session consisted of three circuits of the following strength exercises (listed in the order they were performed): leg press, pull down, leg extension, bench press, leg curl, seated row and abdominal crunch (the latter performed on the floor). The participants performed 1 set of 12–15 repetitions per exercise (~20 s duration) with no rest periods between exercises. The load increased gradually (by 2.25 kg after three training sessions with a given weight) and independently for each exercise, starting at 50% of the baseline five-repetition maximum (5RM).

To reduce participant dropout and to maintain adherence to the programme, all exercise sessions were accompanied with music. We considered a session completed when at least 90% of the prescribed exercises were successfully performed. Make-up sessions were allowed in case of hospitalisation.

Each child performed two IMT sessions/day (morning and evening), except for Monday-Wednesday-Friday (in which the evening IMT session was performed in the gymnasium, after aerobic training and before strength exercises). Each session lasted ~5 min and included 30 inspirations through a specific threshold loading device (Power breathe, Biocorp Europa, Andoain, Basque Country, Spain) against a load corresponding to 40% (weeks 1–2) and 50% of the baseline $PI_{max}$ (weeks 3–4), and to 40% of the 'new' $PI_{max}$ assessed after week 4 (weeks 5–8).

## Detraining

Following the intervention period, participants in the intervention group underwent a 4-week detraining period, during which they performed no exercise/IMT sessions. All participants continued with the aforementioned chest physiotherapy sessions (2/day) and were instructed on the positive effects of regular physical activity.

## Outcome measures

### Primary outcomes

Spirometry tests preceded $VO_{2peak}$ evaluations. We determined the participants' forced vital capacity (FVC), $FEV_1$ and $PI_{max}$ at the residual volume using a mouth pressure meter (Micro Medical Inc, Chatham, Kent, UK) in accordance with established standards.[21 22] The best result from three attempts (interspersed with rest periods of ≥1 min duration) was taken.

Children's $VO_{2peak}$ (as well as VT) was assessed in the paediatric exercise physiology laboratory of HIUNJ, using the equipment and protocol that are also detailed in our companion paper.[19] A finger pulse oximeter (Trusat, General Electric Finland Oy, Helsinki, Finland) was used for the determination of peripheral oxygen saturation ($SpO_2$).

### Secondary outcomes

We measured the children's dynamic upper body and lower body muscle strength with the same seated bench press, seated row and seated leg press machines that were used for training as well as for both strength training and assessment in our previous RCT.[19] The 5RM (kg) was defined as the maximum strength capacity to perform five repetitions until momentary muscular exhaustion, and was measured as detailed elsewhere.[23] Repetitions that were not performed with a full range of motion were not counted.

Standing height was measured to the nearest 0.1 cm with a clinical stadiometer (Asimed T2, Barcelona, Spain). Body mass was determined to the nearest 0.05 kg using a balance scale (Ano Sayol SL, Barcelona, Spain) with the participant in their underwear. Body mass index was calculated as body mass/height ($kg/m^2$). Skinfold thickness was measured with a Harpenden caliper (Holtan Crymych, UK) at the biceps, triceps, subscapular, abdominal, suprailiac, thigh and calf area on the left side of

the body.[24] We estimated the children's body fat percentage (and thus fat-free mass percentage, both relative to total body mass) from their body density values using age-specific and gender-specific equations,[25] that is, for boys and girls aged ≤11,[26] 12–15[27] and 16–18 years.[28]

We determined the children's QoL with the Spanish version (1.0) of the Cystic Fibrosis Questionnaire-Revised (CFQ-R).[29] The ≤11-year-olds group completed the CFQ-R by means of an interview, whereas the 12-year-old to13-year-old group completed the same CFQ-R themselves and adolescents aged ≥14 years completed the CFQ-R V.14+. Response choices included frequency, likelihood or difficulty on four-point scales of different domains (physical, social or emotional functioning, treatment burden, eating disturbances, body image, digestive symptoms and respiratory symptoms). We computed a total QoL score based on the sum of the scores (0–100) of each domain. In order to minimise the risk of children memorising the responses to the questionnaire in the detraining evaluation (just 4 weeks after the post-training evaluation), we only recorded pretraining and post-training data.

### Statistical analysis

We analysed the data according to the intention-to-treat principle.[30] For parametric data (ie, all except QoL scores), we used a two-factor (group, time), repeated-measures ANOVA. To minimise the risk of type-I error, we only performed within-group comparisons when a significant group×time interaction effect existed. For QoL scores, we compared the mean change over time (post-training *minus* pretraining) in the two groups with the Mann-Whitney's U test. The level of significance was set to=0.05. Data are shown as mean±SEM.

## RESULTS

The study's flow diagram is shown in figure 1. Baseline demographic characteristics did not differ between the two groups (six boys and four girls in each) age 11±1 and 10±1 years in intervention group and controls, respectively (p=0.446), and body mass index 16.6±0.7 and 15.6±0.7 kg/m$^2$ (p=0.309). Their Tanner's maturation stage was n=7 and=5 for stages I–II, and n=3 and=5 for ≥III. The main clinical characteristics were similar between the two groups, that is, no participant had

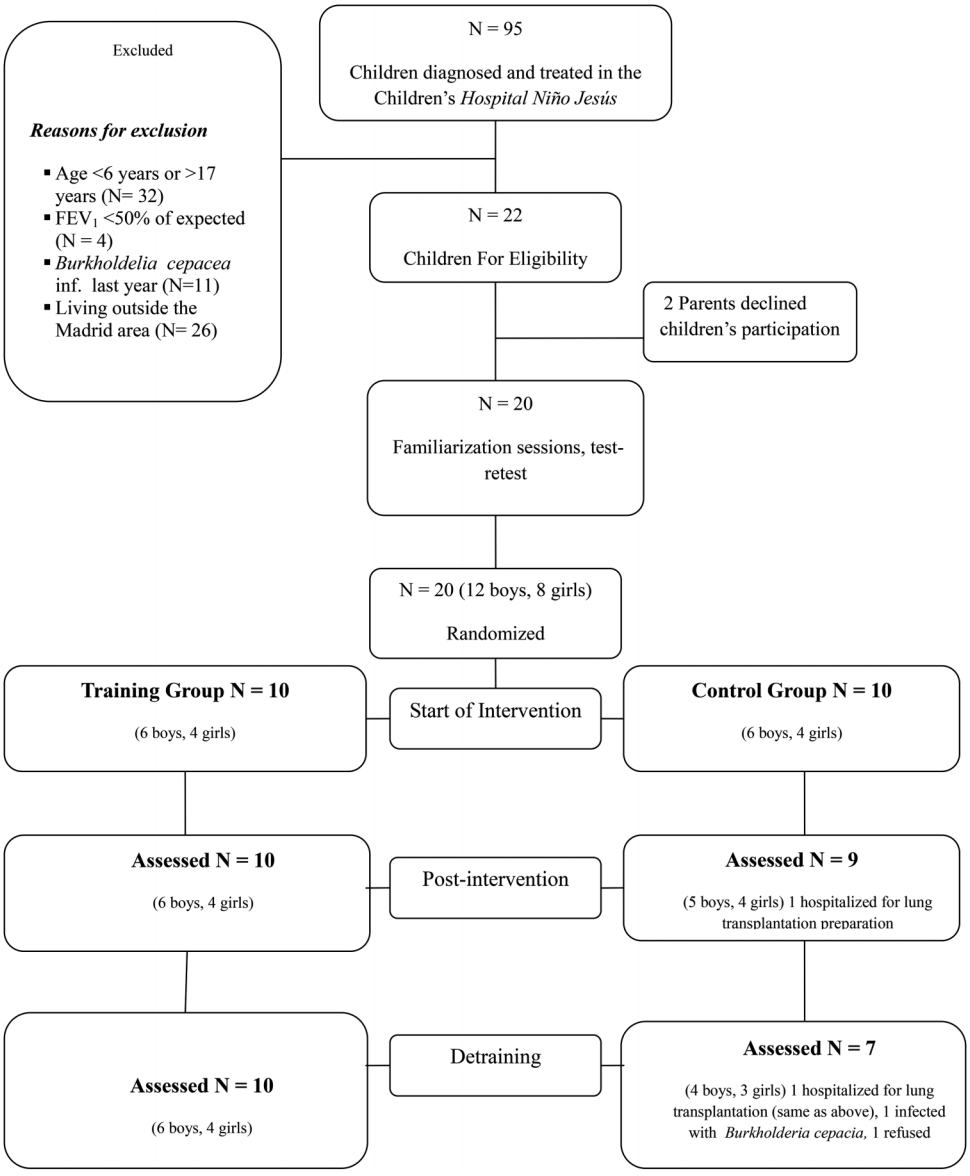


**Figure 1** Flow diagram of the study.

major conditions such as allergic bronchopulmonary aspergillosis, biliar lithiasis, *cor pulmonale*, dehydration, diabetes, *mecolium ileum*, pancreatitis, rectal prolapse, portal hypertension, pneumothorax or infection by *Escherichia coli*, and the proportion of children with asthma, atelectasis, gastrostromy, liver affectation or infection by *Pseudomonas aeruginosa*, *Staphilococcus aereus* and *Streptomonas maltophilia* was similar in the intervention (10%, 10%, 20%, 40%, 50%, 20%, and 70%, respectively) and control group (10%, 10%, 30%, 60%, 20% and 60%). As for the main drugs administered on the children at the start of the study, these included inhaler-delivered bronchodilators before chest physiotherapy (100% in both groups), nebulised 7% hypertonic saline (intervention 80%, control 90%), nebulised antibiotics (usually tobramycin+colistin) (intervention 70%, control 80%), pancreatic digestive enzyme replacement (80% in both groups), ursodesoxycholic acid (intervention 30%, control 40%) and vitamin (100% in both groups) and mineral supplements (intervention 30%, control 20%).

Adherence to the training programme averaged 97.5%±1.7%. Seven of the 10 children completed all sessions as originally planned. Reasons for missing one or more sessions were school examination (one boy (once) and one girl (twice)) and family commitments (one boy (once)). Make-up sessions were possible in one boy who was hospitalised at the beginning of the programme and was able to restart and complete it. We noted no major adverse effect or health problem attributable to the testing sessions or prescribed training sessions.

## Primary outcomes

The results of parametric primary and secondary outcomes are shown in table 1. We found no significant group×time interaction effect for FVC (p=0.156) or $FEV_1$ (p=0.486), and no significant between-group differences at baseline (p=0.435 and 0.439, respectively). We observed a significant interaction effect for $PI_{max}$ (p<0.001), with not between-group differences at baseline. In the intervention group, $PI_{max}$ significantly increased with training (by 36.5%, p<0.001), and it remained essentially unchanged after the detraining period (−4.1%, p=0.171). No significant changes were observed during the study period within the control group (p=0.444 for pretraining vs post-training, p=0.824 for post-training vs detraining).

Baseline $VO_{2peak}$ was significantly higher in controls than in the experimental group (p=0.034), and we observed a significant interaction effect for this variable (p<0.001). In the intervention group, $VO_{2peak}$ increased with training by 6.9 ml/kg/min on average (95% CI 3.4 to 10.5 ml/kg/min, p=0.002), whereas it decreased over the detraining period by a lesser magnitude (−1.5 ml/kg/min; 95% CI −2.7 to −0.4 ml/kg/min, p=0.014). No significant changes were observed within the control group (p>0.1 for both pretraining vs post-training and post-training vs detraining). No child showed desaturation during the tests, with $SpO_2$ values averaging 96.4±0.4, 96.2±0.5 and 96.1±0.6% (controls) and 94.7±0.7, 94.5±0.7 and 93.1±0.8% (intervention group).

## Secondary outcomes

We found significantly higher values of leg-press (p=0.046), but not of bench-press (p=0.438) and seated-row at baseline in the intervention group, compared to their controls (p=0.136). We observed a significant interaction effect for all strength tests (all p<0.001). In the intervention group, bench-press and seated-row performance significantly increased with training (both p<0.001) and decreased with detraining (p=0.001 and

**Table 1** Results of study outcomes by group

| | Group | Pretraining | Post-training | Detraining | p Value for group effect | p Value for time effect | p Value for interaction (group×time) effect |
|---|---|---|---|---|---|---|---|
| Primary outcomes | | | | | | | |
| FVC (l/min) | Control | 1.90 (0.33) | 1.85 (0.32) | 1.92 (0.32) | 0.360 | 0.684 | 0.156 |
| | Training | 2.23 (0.27) | 2.34 (0.29) | 2.28 (0.28) | | | |
| $FEV_1$ (l/s) | Control | 1.57 (0.26) | 1.55 (0.26) | 1.59 (0.26) | 0.733 | 0.712 | 0.486 |
| | Training | 1.65 (0.19) | 1.74 (0.23) | 1.69 (0.24) | | | |
| $PI_{max}$ (mm Hg) | Control | 69.5 (9.7) | 71.8 (10.0) | 66.7 (9.4) | 0.033 | 0.001 | *<0.001* |
| | Training | 68.3 (6.3) | 107.6 (8.4) | 103.2 (8.1) | | | ($\eta^2$=0.502, power=0.999) |
| $VO_{2peak}$(ml/kg/min) | Control | 36.2 (2.1) | 35.6 (1.5) | 32.1 (1.4) | 0.485 | 0.072 | *<0.001* |
| | Training | 31.1 (0.9) | 38.0 (1.3) | 36.5 (1.2) | | | ($\eta^2$=0.508, power=1.000) |
| Secondary outcomes | | | | | | | |
| 5RM leg press (kg) | Control | 45.2 (4.7) | 43.9 (5.1) | 43.9 (5.4) | 0.002 | <0.001 | *<0.001* |
| | Training | 62.5 (6.5) | 89.5 (9.3) | 88.6 (9.2) | | | ($\eta^2$=0.615, power=1.000) |
| 5RM bench press (kg) | Control | 23.2 (2.9) | 21.6 (3.2) | 21.7 (3.6) | 0.018 | <0.001 | *<0.001* |
| | Training | 26.4 (2.7) | 38.4 (3.2) | 35.9 (2.9) | | | ($\eta^2$=0.715, power=1.000) |
| 5RM lateral row | Control | 23.2 (3.0) | 22.0 (3.1) | 21.7 (3.6) | 0.009 | <0.001 | *<0.001* |
| | Training | 30.5 (3.6) | 43.0 (4.2) | 35.9 (2.9) | | | ($\eta^2$=0.593, power=1.000) |
| Body mass (kg) | Control | 31.5 (4.6) | 32.4 (4.7) | 32.7 (4.5) | 0.002 | 0.355 | 0.342 |
| | Training | 36.4 (3.1) | 37.8 (3.2) | 38.3 (3.1) | | | |
| Fat mass (% of total) | Control | 17.1 (1.8) | 17.2 (1.8) | 17.5 (1.9) | 0.815 | 0.159 | *0.023* |
| | Training | 18.4 (1.3) | 17.4 (1.2) | 17.5 (1.1) | | | ($\eta^2$=0.211, power=0.704) |
| Fat-free mass (% of total) | Control | 82.9 (1.8) | 82.8 (1.8) | 82.5 (1.9) | 0.849 | 0.077 | *0.001* |
| | Training | 81.6 (1.3) | 82.6 (1.0) | 82.5 (1.0) | | | ($\eta^2$=0.337, power=0.940) |

Data are mean (SEM). Effect size ($\eta^2$) and statistical power are reported for those significant p values of interaction (group×time) interaction effect.
5RM, five-repetition maximum; FVC, forced vital capacity; $FEV_1$, forced expiratory volume; $PI_{max}$, maximal inspiratory muscle pressure; $VO_{2peak}$, peak oxygen uptake.
Significant p values of interaction effect are in italics. See text for significant post-hoc comparisons within each group for those outcomes showing a significant interaction effect.

p=0.005, respectively); yet, the significant training gains in leg-press (p<0.001) were virtually retained at detraining (p=0.168). No changes were found in controls over time (all p>0.1).

There were no significant between-group differences at baseline for mean values of body mass, body fat percentage and fat-free mass percentage (all p>0.1). We found a significant interaction effect for both body fat (p<0.023) and fat-free mass percentage (p=0.001), but not for body mass (p=0.342). In the intervention group, the fat-free mass percentage increased after training by 1.0% (p=0.033) and decreased with detraining (p=0.036), and a trend towards a significant change over time was found for body fat percentage (p=0.095 for pretraining vs post-training and p=0.078 for post-training vs detraining), whereas no within-group differences were found in the controls (all p>0.1).

We found a trend towards a beneficial training effect on the QoL (total score) reported by children (p=0.071), with the following median (min, max) values being found: 636 (626, 745) and 638 (626, 737) at pretraining and post-training (controls); 629 (505, 701) and 688 (609, 791) at pretraining and post-training (intervention group).

## DISCUSSION

A relatively short-term (8-week) combined IMT and exercise (aerobic+resistance) programme performed in-hospital induced significant benefits in the children's $VO_{2peak}$, inspiratory and 'whole body' muscle strength, which were accompanied with a shift towards a healthier body composition phenotype (decreased and increased fat and fat-free mass percentage, respectively). Further, some muscle strength gains (ie, in $PI_{max}$ and 5RM leg-press) were largely maintained after detraining, and a positive trend was observed for the training effects in children's QoL. The study was well-powered to detect significant training gains, that is, statistical power of ~100% for all training improvements in primary outcomes.

Our findings are of clinical relevance, especially those of $VO_{2peak}$, and corroborate and extend previous data.[16–19] The $VO_{2peak}$ of children with CF is usually lower compared to their healthy referents[31] and inevitably decreases over time.[14] $VO_{2peak}$ is an important mortality predictor in CF patients[14 15] with mortality rates over 60% after 8 years in children with $VO_{2peak}$ <32 ml/kg/min (vs no mortality if >45 ml/kg/min).[14] Our training programme increased the children's $VO_{2peak}$ from a mean value slightly below the 'high-risk' threshold of 32 ml/kg/min to a value clearly above it (38 ml/kg/min) after only 8 weeks, and $VO_{2peak}$ remained above 32 ml/kg/min after detraining. Thus, gains in $VO_{2peak}$ averaged ~18%, which is higher than the ~11% improvement we showed in this type of population after a similar type of exercise training protocol but without IMT.[19] Taken together, this supports the need to prescribe 'complete' (IMT+strength and aerobic) exercise interventions for patients with CF from early phases of life, including patients with stable clinical conditions and low–moderate disease severity as the ones we studied. An easy-to-apply (total daily duration ~10 min), largely home-based IMT intervention added to weekly exercise can maximise training benefits in $VO_{2peak}$. However, our experimental setting without an additional group of paediatric outpatients performing IMT, but no 'whole muscle' training, does not allow to determine to what extent the $VO_{2peak}$ improvements we found can be more attributable to central adaptations (eg, potential effects of IMT on maximal ventilatory muscle capacity) or peripheral adaptations (ie, higher leg muscle strength allowing to delay fatigue during testing).

Our findings showing a significant increase in the children's muscle strength and fat-free mass percentage is also of interest because muscle weakness is prevalent (56%) among CF adults and is in excess to that expected from physical inactivity only.[32] Thus, strength training interventions should be started as soon as possible in patients' lives. Despite earlier concerns regarding the safety and efficacy of youth strength training, current public health objectives now encourage this type of intervention—if appropriate training guidelines are followed, it has the potential to enhance the children's physical capacity as well as their overall health and fitness status.[33] The trend towards a QoL improvement with training is also interesting, with previous research suggesting that much longer interventions are needed to induce significant improvements in the QoL of CF children, that is, ≥6 months[15] or 2–3 years.[16 34] On the other hand, it also seems that long-term exercise interventions (ie, several years) are usually necessary to overcome or at least attenuate the declining effect that CF has on lung volumes,[34] which is consistent with the lack of changes we found in FVC or $FEV_1$ after training for 8 weeks.

In summary, the relatively short-term (8-week) training programme we applied induced significant benefits in important health phenotypes of child patients with CF, especially $VO_{2peak}$ and both inspiratory and 'whole body' muscle strength. We believe IMT is an easily applicable intervention that could be included in the standard care of these patients. Overall, our data provide scientific support for the use of in-hospital exercise training in the armamentarium against chronic, debilitating paediatric diseases, of which CF is a good example.

### What are the new findings?

- Short-term combined inspiratory and 'whole muscle' (strength + aerobic) training improved important health phenotypes in children with cystic fibrosis, included a strong mortality predictor as is $VO_{2peak}$.
- This type of training was well-tolerated by the patients, who showed good adherence.
- Some training gains were partially maintained after detraining.

### How might it impact on clinical practice in the near future?

- The proposed training intervention is very easy to apply and thus could be incorporated into the overall treatment armamentarium against cystic fibrosis.
- We provide further support for the use of exercise interventions mostly based on hospital for the standard care of paediatric patients.
- Interventions previously tested in athletes or in the field of performance and sports medicine (eg, inspiratory muscle training) can be applied to patient populations.

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AL and IFG have drafted the article, while ES-S, LG-S, JRV-A, MIBGA, SJF, LML-M and MP revised it critically for important intellectual content. All the authors have given final approval of the version to be published.

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**Competing interests** None.

**Patient consent** Obtained.

**Ethics approval** Comité Etico (CEIC) Hospital Infantil Universitario Niño jesús.

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