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Intensive physical training in children with heritable connective tissue disorders is feasible and safe: a pilot study

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ABSTRACT

Purpose: This pilot study assessed the feasibility, safety, and acceptability of a physical training program combined with parental meetings for children with heritable connective tissue disorders (HCTD), including Marfan syndrome (MFS), Loeys-Dietz syndrome (LDS), and Ehlers-Danlos syndromes (EDS). Secondary, it aimed to explore preliminary observations regarding the program's impact on individual training goals and physical fitness, including aerobic and anaerobic capacity, strength, agility, pain, fatigue, and disability.

Materials and methods: The intervention comprised functional power training (FPT) and high-intensity interval training (HIIT) conducted three times a week over 12 weeks. Data on feasibility, safety, and acceptability were collected, along with preliminary observations on physical fitness performance.

Results: The intervention was feasible and safe, with no serious adverse events reported. However, acceptability was limited, with a participation rate of 27.8%. Preliminary findings revealed that 80% of participants achieved their training goals, 75% improved their aerobic capacity, and 70% showed gains in strength and agility, alongside reported reductions in pain and fatigue.

Conclusion: This study highlights the potential benefits of tailored physical training for children with HCTD. Despite acceptability challenges, the intervention demonstrated feasibility and safety, providing a foundation for larger-scale effectiveness studies that include systematic feedback mechanisms to enhance participant engagement.

➤ IMPLICATIONS FOR REHABILITATION

- The physical training program for children with heritable connective tissue disorders was feasible, providing a foundation for further research.
- The intervention was safe, with no serious adverse events, supporting its potential for future studies.
- Low participation emphasizes the need for strategies to enhance engagement in future interventions.
- Preliminary observations suggest potential benefits in fitness and symptom reduction, warranting further investigation.

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Heritable connective tissue disorders; high intensity interval training; functional power training; physical fitness; pediatric physical therapy

Introduction

Health problems in children with heritable connective tissue disorders (HCTD) are diverse and complex, characterized by multisystemic involvement [1–5]. The phenotypes of the most common HCTD's, including Marfan syndrome (MFS) [2], Loeys-Dietz syndrome (LDS) [3], and Ehlers-Danlos syndromes (EDS) [4] exhibit similarities in musculoskeletal changes (e.g., scoliosis, foot deformities, and joint hypermobility), cutaneous features (e.g., skin hyperextensibility and tissue fragility), and cardiovascular issues (e.g., aortic aneurysm and mitral valve prolapse), particularly in MFS and LDS. Children with HCTD often report challenges in keeping up with peer activities and participating in school, sports, and leisure activities due to fatigue, pain, and physical impairment [6–9]. Recent findings indicate that children with HCTD demonstrate lower endurance, muscle strength, and daily mobility compared to their healthy peers [10].

Despite the clear need for effective interventions, no multidisciplinary studies have specifically targeted on physical fitness in children with HCTD. However, previous studies have indicated

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that physical interventions may have positive outcomes in adolescents with generalized joint hypermobility (GJH) and hypermobile Ehlers-Danlos syndrome (hEDS), resulting in reduced disability and improved physical fitness [11]. Additionally, combining physical training with cognitive-behavioral therapy focused on pain-related fear has enhanced physical functioning in this population [12], with parental involvement being crucial for fostering positive behavioral changes regarding pain and fitness [13]. A review of randomized controlled trials on hEDS noted significant improvements in pain and proprioception through various exercise methods aiming at enhancing stability, muscle strength, and balance [14]. New training modalities like functional power training (FPT) and high-intensity interval training (HIIT) have also proven effective for improving muscle strength and exercise capacity in children with several chronic conditions [15,16]. FPT enhances gait and lower-extremity function through structured resistance training and is safe in children with disabilities [16–18], while HIIT effectively boosts aerobic capacity in children with conditions such as obesity and cerebral palsy [19–21].

Given the absence of research on the feasibility, safety, and effectiveness of FPT and HIIT in enhancing physical fitness among children with HCTD, this pilot intervention study was conducted to assess these parameters and provide valuable insights for future large-scale research [22,23]. Assessing feasibility is essential for determining if the intervention can be effectively implemented in a large-scale randomized controlled trial (RCT) [22]. This is supported by research that underscores the significance of pilot studies in optimizing interventions for specific population [23]. Assessing acceptability ensures that the intervention is well-received by both children and their parents, which is essential for adherence and long-term success [22–24]. Safety is particularly important in this population, as children with HCTD may have specific health concerns (eg. cardiovascular) that could affect their response to physical activity [1]. Understanding these aspects will not only help in tailoring the intervention to better fit the needs of children with HCTD but also facilitate the design of future studies by providing evidence of the intervention's feasibility and potential impact on health outcomes, as highlighted in the recommendations for developing effective interventions in other populations [22–24].

Therefore, the primary aim of this study was to investigate the feasibility, safety, and acceptability of a physical training program combined with parental meetings for children with MFS, LDS, and (genetically confirmed) EDS. Additionally, the secondary aim was to explore preliminary observations regarding the impact of the training program on individual training goals, physical fitness (aerobic and anaerobic capacity, strength, and agility), as well as on pain, fatigue, and disability.

Materials and methods

Study design and procedures

This pilot intervention study consisted of a 12-week training program and multidisciplinary parental meetings (Figure 1). A pre-post study design with standardized measurements was employed to evaluate feasibility, safety, and acceptability, as well as to explore preliminary observations on the program's impact. The measurements were conducted at the Amsterdam University Medical Center. The training sessions took place at a primary care pediatric physiotherapy practice. Two of the parental meetings were conducted online, while one took place onsite. The participants were recruited between May and August 2021. The study was conducted between August 2021 and January 2022 and was approved by the Medical Ethics Review Committee of Amsterdam UMC (NL76844.018.21).

Patient selection

The participants were recruited from the Amsterdam University Medical Center Expert Center for Marfan Syndrome and Related Disorders in the Netherlands. The inclusion criteria were as follows: (1) diagnosis of MFS, LDS, or genetically confirmed types of EDS (hereafter referred to as EDS), (2) aged 6–18 years, and (3)

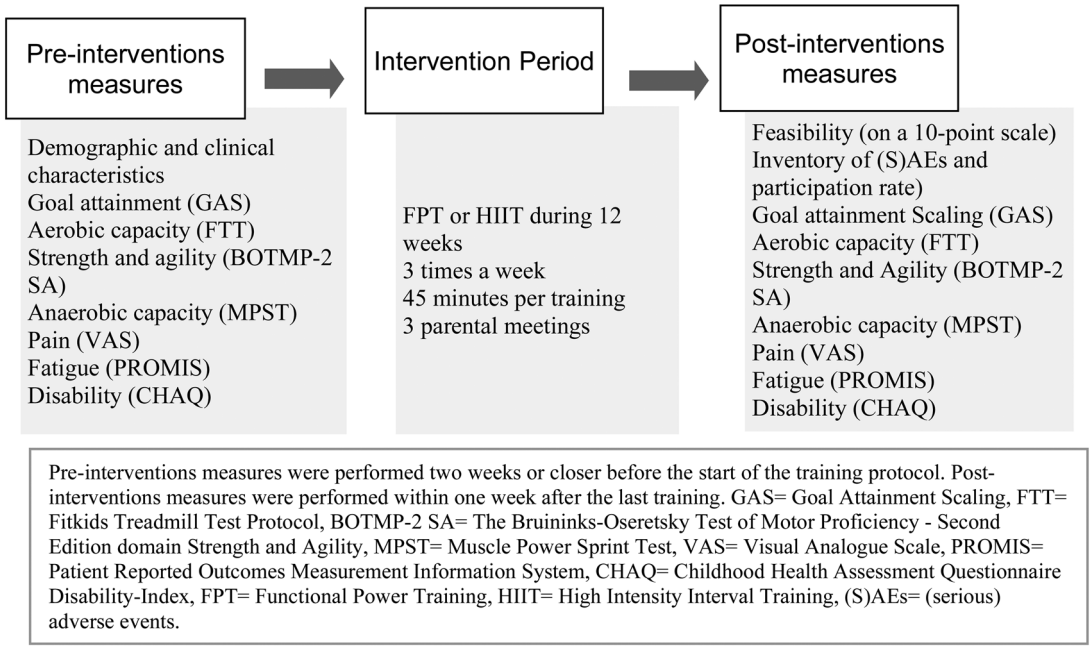

Figure 1. Research protocol.

indication for treatment to improve physical fitness. The exclusion criteria were as follows: (1) comorbid chronic diseases affecting physical fitness or activity, (2) indications for aortic root replacement, (3) cognitive impairment (IQ < 80), and (4) medical or psychiatric disorders that might reduce treatment adherence.

Participants eligible for inclusion and their parents were invited by letter and informed consent was signed by parents (children aged <12 years), both parents and children (children aged 12 to 16 years) or children (children aged ≥16 years).

Allocation of participants

The principal investigator (PI) allocated the participants to one of the two training programs based on their individual training goals (Figure 2). Participants who where taking prophylactic cardiovascular medication were excluded from participation in FPT program [25] but were allowed to participate in the HIIT program, with approval by the pediatric cardiologists. Example of self-formulated individual training goals were, for instance "I want to get to the ball faster when playing soccer" (participant 3) and "I want to get stronger in my legs and ankles to be able to play longer on the school playground" (participant 5). Training goals were further specified during the baseline measurement.

Intervention program

Two training methods, FPT and HIIT, were adapted into training programs for participants with HCTD. Both programs are based on recent literature [15,16] and designed according to the type, dose, and frequency principles of the training [26]. The training sessions were individualized by a multidisciplinary research team (MRT) consisting of pediatric physical therapists (PPTs), occupational therapists, pediatric rehabilitation physicians, pediatric cardiologists, social workers, and psychologists with expertise in HCTD. The PPTs of the MRT designed individual training programs based on defined training goals. Individualization involved training the specific skills that matched the individual child's training goal. Additionally, the child's physical capabilities were taken into account. Furthermore, PPTs were instructed to avoid intensive turning, twisting, and extended joint positions during the warming-up exercises and cooling down to prevent joint sprains and dislocations. Training sessions were conducted by a trained and intensively supervised local PPT who had completed a standardized two-day course on HCTD, exercise physiology, psychology, and an intervention program. Training sessions were conducted in a primary care setting within a participant's residential environment. Supervision of the local PPT consisted of online group sessions (five times during the 12-week training period) and individual guidance, both supervised by the MRT. The interventions were tightly protocolled, with the PPTs keeping track of progress and any adjustments in a logbook. Adjustments could only be made in consultation with the MRT.Independent of the training program, each training session had a maximum duration of 45 min and consisted of a warm-up phase (10 min), two out of four selected FPT or HIIT exercises, and a cooling-down phase (10 min).

In the FPT program, the training content and exercises were performed according to the FPT study protocol applied to children with cerebral palsy [27]. The key elements of power training were: (1) functional multi-joint exercises such as running and jumping, (2) high movement velocity (similar to the velocity used in daily/playing activities), and (3) the use of progressive training volume in terms of load (training weight in kg), movement velocity (m/s), and number of repetitions. For each power exercise, a baseline measurement of velocity and distance were obtained using a stopwatch and tapeline. At the start of the training period, the exercises were performed at 70% of the participant's individual maximum unloaded speed by retraining the movement with load. Exercises were performed on maximal effort with 30–50 s of rest.

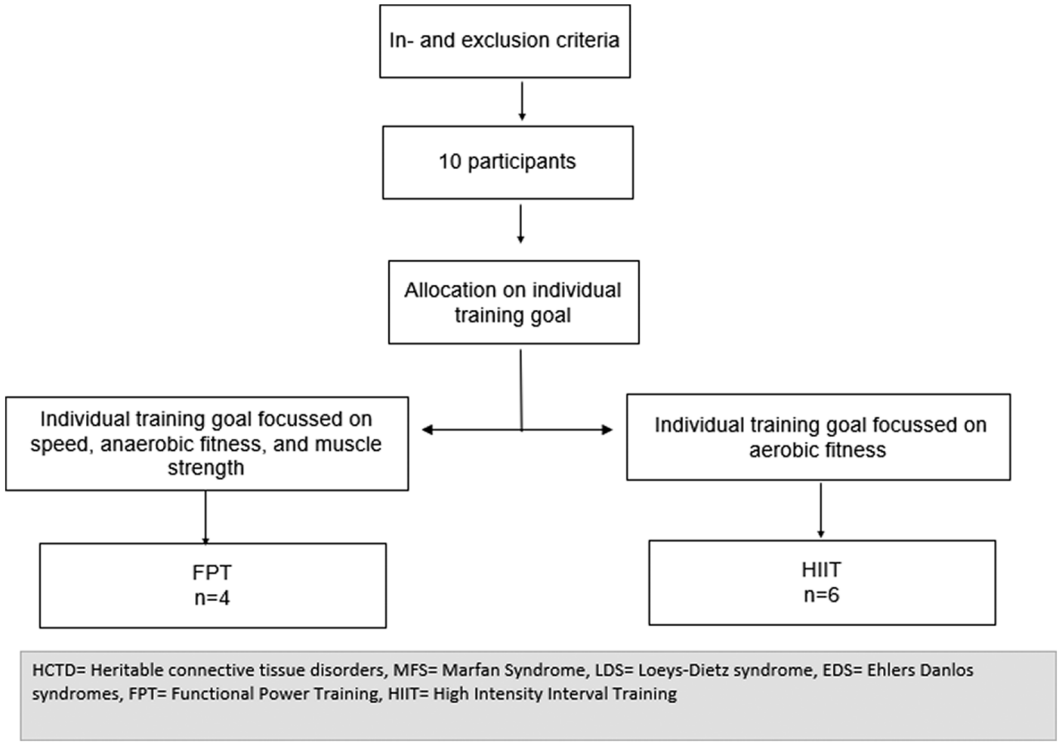

Figure 2. Allocation of participants.

Progression of the intensity of the program was secured by increasing the load. For each exercise, a target distance was calculated (for example; maximal running speed (m/s) × 25 *s* × 0.7, i.e., 70% of maximal unloaded speed). When the participant reached the target distance within 25 s, the load was increased (by steps of 10% of the current load). The number of repetitions of the power exercises increased during the 12 weeks from seven to nine repetitions of each exercise [27] (Appendix 1).

Regarding the HIIT program, exercises were performed based on prescribed intensity, volume, and time parameters, and participants were extensively encouraged to sprint with maximal effort. The key elements of HIIT were [1] functional multi-joint exercises such as running exercises, (2) the 30-s all-out approach [28–31], and (3) progressively shortening breaks between repetitions (work/rest ratio) and increasing the number of repetitions per exercise. The work/rest ratio was gradually reduced from 1:3 (30s work/3 min rest) to 1:1 (30s work/30 s rest). Between intervals, participants performed lower-intensity activities [30] (Appendix 2).

Parental meetings

In accordance with a recently performed multidisciplinary intervention study in adolescents with GJH and chronic musculoskeletal pain, the MRT organized three parental group meetings to assist parents in helping their children cope with their complaints [12]. Due to the COVID-19 pandemic, two sessions were organized online and one session was on site. During these two-hour sessions, the biopsychosocial model and cognitive behavioral therapy approaches were used to discuss three main themes: (1) pain and fatigue, (2) burden of disease, and (3) physical and psychological effects of training [32–34].

Measurements

Patient characteristics

Sociodemographic (sex and age) and diagnostic (diagnosis, cardiac status, and use of cardiovascular medication) data were collected from medical records and a custom-made questionnaire completed by the parents. The clinical characteristics assessed included body mass index (BMI; kg/m^2) converted to z-scores using Dutch reference data [35] and the presence of GJH, as assessed using the Beighton scale [36]. A Beighton score ≥ 6 out of 9 was defined as the cutoff value for the presence of GJH [4]. The Beighton score is a widely used tool and its validity and reliability for assessing GJH have been demonstrated in children ≥ 6 years of age [37].

Primary outcome measures

Feasibility. Feasibility was evaluated based on the percentage of participants who completed the intervention and their exercise adherence. The intervention was defined as "feasible" as 75% of the participants completed the intervention period. In addition, exercise adherence was calculated as the percentage of completed exercise sessions over the number of prescribed exercise sessions. Exercise adherence was registered by the local PPT, who recorded completed training sessions using a training log (maximum = 36). The exercise adherence of ≥80% was considered feasible.

Safety. Safety was defined as the incidence of exercise-related adverse events (AEs) and serious adverse events (SAEs). AEs, which are mild side effects of exercise that do not interrupt the training period, and SAEs, which are serious side effects that halt the training, were recorded in the training log by the local PPT and reported to the principal investigator PI. In the event of an SAE, the PI (LK) was immediately informed, and the safety monitoring board took appropriate action if required.

Acceptability. Acceptability, defined as the proportion of enrolled participants relative to the number of potentially eligible individuals, was assessed by calculating this percentage. Reasons for nonparticipation were collected when provided and described in numbers (n).

Secondary outcome measures

Goal attainment

The Goal Attainment Scaling (GAS) was used to specify individual training goals regarding gross motor functioning and evaluate progress in individual training goals. The goals were set by the PPT of the MRT in consultation with the parents and participant before the start of the intervention. The GAS goals were specific, measurable, achievable, realistic, and time-related. The achievement of the GAS goals was evaluated post-intervention using a six-point scale ranging from −3 to +2 (-3: deterioration, −2: a level that is unchanged from baseline, −1: less progress than expected, 0: the level of improvement that is expected, +1: more improvement than expected, and +2: much more improvement than expected) [38]. The GAS is a widely used tool in clinical practice and has shown good psychometric properties in healthy pediatric populations and patients with chronic conditions [39].

Physical fitness

Aerobic capacity. Pre- and post-intervention aerobic capacity were assessed using the standardized Fitkids Treadmill Test Protocol (FTT) [40]. The FTT is an incremental treadmill test consisting of 90-s stages with increments in speed and grade. After a warming-up period (3.5 km/h, 0% grade), the test starts at 3.5 km/h and 1% gradient, followed by incremental increases in speed (0.5 km/h) and incline (2%) until exhaustion [40]. The time to exhaustion (TTE) was defined as the point when the participant stopped the test despite verbal encouragement minus the 1.5-min warming-up and recorded in minutes and seconds. Participants with severe aortic dilatation were not allowed to perform this test (aortic z-score ≥ 3 [25]). The FTT has good validity and reproducibility in children aged 6–18 years of age [40].

Strength and agility. The Bruininks-Oseretsky Test of Motor Proficiency - Second Edition (BOTMP-2) was used to assess strength and agility pre- and post-intervention [41]. The motor area composite strength and agility (SA, further referred to as BOTMP-2 SA) comprised two subtests: (1) running speed and agility, and (2) strength. The running speed and agility subtest consisted of five items: a shuttle run, hopping on one and both feet, stepping over a balance beam, and a two-legged side hop. The strength subtest was designed to measure trunk, upper, and lower body strength, and consisted of five items: standing long jump, pushups, sit-ups, wall sit, and v-up (lying in the prone position and lifting legs and arms simultaneously). BOTMP-2 has been validated and is reliable for assessing motor performance in children and adolescents [42].

Anaerobic capacity. Pre-and post-intervention anaerobic capacity were assessed using the muscle power sprint test (MPST). The test consisted of 6 × 15-meter sprints with a 10-s rest between

the sprints. Participants were instructed to run as fast as possible from line to line with a static start and standardized rest. After crossing the line, they stopped running and turned around to prepare for the next sprint after a 10-s rest [43]. The time of every 15-meter sprint was recorded to the nearest 0.1 s with a stopwatch. Anaerobic power was defined as the mean power (Watt), which was the average power output of all six sprints determined by calculating the velocity (m/s = distance/time), acceleration (m/s^2 = velocity/time), force (kg/sf = body mass × acceleration), and power (Watt = force × velocity) of every sprint. The mean power was used in the analysis [44]. This test has demonstrated good validity and reliability in children [43,44].

Pain. Pain intensity over the last week was measured pre- and post-intervention using a Visual Analog Scale (VAS) [45] and scored on a 0–10 cm scale, with 0 cm referring to "no pain" and 10 cm to "very severe pain" [46]. The validity and reliability of this method for pain assessment have been demonstrated in children with chronic diseases [46].

Fatigue. Fatigue was assessed using the Patient-Reported Outcomes Measurement Information System (PROMIS) pre- and post-intervention. For participants < 8 years of age, the Fatigue 10a Parent Proxy v2.0 short form was used, and for participants 8–18 years of age, the self-reported Fatigue 10a Pediatric v2.0 short form was used. Both questionnaires contained ten fatigue statements pertaining to the degree of fatigue and the impact of fatigue on physical, mental, and social activities experienced during the last seven days. Each question had five response options (never = 1, rarely = 2, sometimes = 3, often = 4, always = 5). To calculate the total raw score, the values of the responses to each question were summed and compared to the available normative data and expressed as T-scores. Both questionnaires are widely used rating scales with excellent psychometric properties in childhood [47–49].

Disability. The Dutch version of the Childhood Health Assessment Questionnaire (CHAQ) [50] was used to assess functional disability in daily life activities and distinguish between the following domains of functioning: dressing, arising, eating, walking, hygiene, reach, grip, and activities. Items are scored on a four-point scale (0 = no difficulty, 1 = some difficulty, 2 = much difficulty, 3 = unable to do). Each domain was covered by a minimum of two and a maximum of five items. The highest score for an item within a domain determined the domain score. When assistance or aids were used, the domain score was increased by 1 point to a maximum of 3 points. The CHAQ disability index (CHAQ-DI) represents the mean score of the eight domains and ranges from 0 to 3 [50]. The CHAQ has been validated in several childhood populations and has shown high reliability, validity, and responsiveness to changes over time [51,52].

Statistical analysis

Data were exported from the Castor database (Electronic Data Capture, Ciwit BV, Amsterdam, The Netherlands, 2021) to the Statistical Package for Social Science (SPSS) version 26.0. Patient characteristics including sociodemographic (sex and age) and diagnostic (diagnosis, cardiac status, and use of cardiovascular medication) data were described at the individual level using means and standard deviations (SD) or medians and interquartile ranges (IQR).

The primary outcomes of feasibility, safety and acceptability were described at group level in percentages (participation completion, exercise adherence and acceptability) or numbers (safety). Data collected to assess preliminary effectiveness, the GAS goals were formulated pre-intervention, evaluated post-intervention, and described at the individual level. In addition, the FTT, BOTMP-2 SA, MPST, VAS, PROMIS Fatigue and CHAQ-DI scores were analyzed and described at individual level. Pre- and post-intervention FTT, BOTMP-2 SA, MPST, VAS, PROMIS Fatigue and CHAQ-DI scores were converted to sex- and age-adjusted z-scores using existing normative data [40,43,49,50]. Missing scores on FTT ($n = 2$, related to aortic status), pain intensity VAS ($n = 2$), PROMIS Fatigue ($n = 2$) and CHAQ ($n = 2$) were ≥ 15% and therefore complete case analysis was performed per measure. The change scores were calculated at an individual level using the Reliable Change Index (RCI) according to the method proposed by Jacobson and Truax [53]. The RCI reflects the absolute change in scores pre- and post-intervention that are required to be confident that the observed change was not due to random variations over time (at a probability level of <5% translating in a RCI ≥1.96). A positive RCI reflects an individual's improvement over time [53]. RCI ≥ .56 was interpreted as a positive trend. The RCI represents the ratio in which the numerator represents the actual observed difference score between two measurements and the denominator represents the standard error measurement (based on the standard deviation and coefficient alpha of the normative sample) of the difference score [54]. No coefficient alpha for reliability of the PROMIS Fatigue 10a Parent Proxy v2.0 short form has been published and therefore the RCI has only been calculated for the PROMIS Fatigue 10a Pediatric v2.0 short form (participants ≥ 8 years of age).

Results

Patient characteristics

Ten participants, with a mean (SD) age of 10.1 (2.7) years, participated of which seven were diagnosed with MFS, one with LDS, and two with EDS (one classical EDS, one arthrochalasia EDS). Three participants were female (Table 1). Two of the 10 participants had an aortic z-score ≥3 (25) and used cardiovascular medication (Losartan $n = 1$, Atenolol $n = 1$) (Table 1). The mean (SD) BMI was 16.9 (3.3) kg/m^2. The median (IQR) Beighton score was 5.5 (1–7) and five of the participants had a Beighton score ≥ 6 indicating the presence of GJH. Four participants participated in the FPT program and six in the HIIT program.

Primary outcome measures on feasibility, safety and acceptability

Regarding feasibility, all participants completed the training program. The mean (SD) number of training sessions completed was 32.4 (2.3) of the maximum possible 36. Nine of the ten participants attended at least 80% of the maximum number of training sessions (Table 2). One participant had psychosocial issues around the time of the intervention period and an episode of influenza and completed 77% of the training sessions (Participant 5, diagnosed with MFS). Interpreting safety, three participants experienced mild AE (slight dizziness or mild ankle sprain) during the first week of training. No SAE were observed during the study period (Table 2). In terms of acceptability, ten out of 36 potential participants (27.8%) enrolled in the study. Among the potential participants, 14 did not provide a reason for nonparticipation. The remaining nonparticipating potential participants cited various

Table 1. Patient characteristics.

Patient	Sex	Age (years)	Diagnosis	BMI	BMI z-score	Beighton score	CVM; type	Trainings method
1	M	9	aEDS	15.5	−0.3	6	no	HIIT
2	M	10	MFS	16.1	−0.3	6	no	HIIT
3	M	10	MFS	13.5	−2.3	1	Yes; *Atenolol*	HIIT
4	M	6	MFS	14.3	−0.9	8	no	FPT
5	F	7	MFS	21.5	3.4	0	no	FPT
6	M	12	LDS	23.8	2.4	5	no	HIIT
7	M	14	MFS	15	−2.5	1	Yes; *Losartan*	HIIT
8	M	12	MFS	17.3	−0.1	1	no	FPT
9	F	7	MFS	15	−0.2	7	no	FPT
10	F	9	cEDS	17.6	.8	8	no	HIIT

M = male; F = female; cEDS = classical Ehlers Danlos Syndrome; aEDS = Arthrochalasia Ehlers Danlos syndrome; MFS = Marfan Syndrome; LDS = Loeys Dietz Syndrome; HIIT = High Intensity Interval Training program; FPT = Functional Power Training program; BMI = Body Mass Index; CVM = Cardio-Vascular Medication.

Table 2. Feasibility and safety measures.

Participant	Age (years)	Completion of the program	Number of training sessions n(%)	Mild adverse events	Serious adverse events
1	9	Yes	34 (94)	No	No
2	10	Yes	33 (92)	No	No
3	10	Yes	36 (100)	Slight dizziness**	No
4	6	Yes	30 (83)	No	No
5	7	Yes	28 (77)*	No	No
6	12	Yes	32 (89)	No	No
7	14	Yes	32 (89)	Slight dizziness***	No
8	12	Yes	36 (100)	No	No
9	7	Yes	34 (94)	No	No
10	9	Yes	36 (100)	Mild ankle sprain****	No

*Participant participated in less than 80% of the trainings sessions.
**Slight dizziness was only present in the first two weeks of the training program.
***Slight dizziness was present in the transition to shorter rest breaks.
****One participant suffered a mild ankle sprain during training session, which recovered quickly and had no further impact on the training program.

reasons: moving to a different city ($n=1$), excessive study workload ($n=2$), changing school ($n=1$), parental divorce ($n=2$), work/family commitments ($n=1$), lack of motivation from the child ($n=3$), and excessive sports activities ($n=2$).

Secondary outcome measures on goal attainment, physical fitness, pain, fatigue and disability

Concerning training goals, eight out of ten participants achieved the predetermined GAS training goals, with seven of them exceeding their predetermined GAS training goals by achieving "more" or "much more" (Table 2). Regarding the FTT, eight participants performed the test, while two participants (Participants 3 and 7, both diagnosed with MFS) were excluded from this test due to aortic root dilation (z-score ≥ 3). Post- versus pre-intervention measures of six participants (75%) exhibited a positive tendency (RCI ≥1.56), and four out of eight participants showed significant improvement (RCI ≥1.96), indicating clinically meaningful enhancement in aerobic capacity for these participants (Table 3).

All participants demonstrated improved BOTMP-2 SA scores post-intervention compared to pre-intervention scores. Seven participants (70%) showed a positive tendency (RCI ≥1.56) on the BOTMP-2 SA scores post-intervention compared to pre-intervention. Six participants achieved significantly higher BOTMP-2 SA scores (RCI ≥1.96) post-intervention, indicating significant improvement in running strength and agility (Table 3). Eight out of ten participants showed progression in MPST scores post-intervention compared to pre-intervention measurements. Three of them (30%) achieved a reliable change (RCI > 1.96) in post- versus pre-intervention measures, indicating a significant improvement in anaerobic capacity in these participants (Table 3).

Pain intensity decreased in four of five participants who reported experiencing pain. Three of the five participants reported significantly reduced pain intensity post-intervention, indicating a clinically meaningful reduction in pain. However, one participant reported a significantly increased pain intensity post-intervention.

In terms of PROMIS Fatigue scores, three out of five participants reported reduced scores post-intervention, with two reporting significantly reduced scores, indicating a meaningful decrease in fatigue. Regarding the CHAQ-DI, four of eight participants reported unchanged or slightly decreased scores post- intervention. Two participants reported significantly increased CHAQ-DI scores, suggesting an improvement in disability (Table 4).

Discussion

This study primarily aimed to evaluate the feasibility, safety, and acceptability of an intensive physical training intervention designed to enhance physical fitness in children with HCTD within a pilot framework. The results indicate that the intervention is feasible and safe. However, acceptability was low due to a small enrollment percentage among potential participants. Furthermore, preliminary observations suggest effectiveness in reducing deconditioning and improving fitness levels.

To explore the feasibility, safety, and acceptability of the intervention, we defined preliminary success criteria. Our findings suggest that the physical intervention, conducted three times a week over 12 weeks and combined with an educational parental program, was feasible and safe, with no serious adverse events observed.However, the participation rate was only 27.8%, despite several strategies being implemented in advance, including an individualized goal-setting approach, the parent program, and delivering the intervention in the participant's residential environment. This low rate highlights significant barriers, such as time constraints and commitment, which potential participants identified beforehand. To enhance recruitment and engagement in future studies, strategies such as enhanced psychosocial support, clearer communication of condition-specific benefits, and offering flexible participation options should be considered [55].

Additionally, systematic feedback mechanisms—such as surveys, interviews, or focus groups—are essential for gaining a deeper understanding of participants' experiences. These qualitative approaches can help identify the most effective aspects of the intervention and areas for refinement, ultimately improving participant satisfaction and adherence. Finally, it is important to note that success criteria are not consistently defined across studies, which can make comparisons difficult [23,56,57].

Table 3. Individual measures on preliminary effectiveness.

Participant	Trainings method	Age (years)	GAS-score	FTT TTE z-score			BOTMP-2 SA z-score			MPST z-score		
				T0	T1	RCI	T0	T1	RCI	T0	T1	RCI
1	HIIT	9	2	−3.23	−0.65	3.82[a]	.70	1.20	1.52	−2.14	−1.75	.72
2	HIIT	10	2	−8.00	−6.90	.72	−1.10	−0.90	.60	−1.08	−0.97	.31
3	HIIT	10	1	−*	−*	−*	−0.10	.70	2.43[a]	−0.06	.39	1.18
4	Power	6	−3	−1.23	.14	1.56	.90	1.60	1.43	−1.32	−1.61	−0.67
5	Power	7	−3	−5.71	−7.09	−1.56	−1.50	.60	4.29[a]	−0.13	−0.78	1.52
6	HIIT	12	2	−37.30	−7.53	6.62[a]	−0.70	.10	2.43[a]	−0.69	.35	.87
7	HIIT	14	2	−*	−*	−*	−0.80	.10	1.88	−2.80	−0.54	5.04[a]
8	Power	12	2	−1.88	−1.23	1.56	−0.10	1.00	3.34[a]	−1.01	.98	2.03[a]
9	Power	7	2	−4.60	.99	7.80[a]	.60	2.60	4.88[a]	−1.62	−0.45	2.69[a]
10	HIIT	9	0	−0.44	1.24	3.21[a]	−0.20	1.70	5.77[a]	−1.15	−1.29	−0.40

T0 = represents measures pre-intervention; T1 = represents measures post-intervention; GAS = Goal attainment scaling score post intervention (-3: deterioration, −2: a level that is unchanged from the baseline, -1: less progress than expected, 0: the level of improvement that is expected, +1: more improvement than expected and +2: much more improvement than expected); FTT TTE = Fitkids Treadmill Test - Time to Exhaustion; BOTMP-2 SA = Bruininks-Oseretsky Test of Motor Proficiency domain Strength and Agility of; MPST = Muscle Power Sprint Test; RCI = Reliable change index were a positive score indicates progress over time and a negative score indicates decline over time.
[a]Represents a Reliable Change Index ≥1.96.
*Missing data as result of no consent from the cardiologist to perform the Fitkids Treadmill test (aortic z-score ≥3).

Table 4. Individual measures on pain, fatigue and disability.

Participant	Age (years)	VAS Pain z-score			PROMIS-fatigue z-score (≥8years)			CHAQ-DI z-score		
		T0	T1	RCI	T0	T1	RCI	T0	T1	RCI
1	9	–	–	n.a.	n.a	−0.06	n.a	–	.10	n.a.
2	10	2.05	.00	>10.0[a]	1.76	1.35	1.65	1.10	.85	1.22
3	10	00	.00	.00	−0.77	−0.77	.00	−0.40	−0.40	.00
4	6	.00	.00	.00				.60	.35	1.22
5	7	3.05	3.80	>-10.0[a]				.85	.85	.00
6	12	.00	.00	.00	−0.77	−0.77	.00	−0.40	−0.40	.00
7	14	–	–	n.a				–	–	n.a.
8	12	2.20	1.00	4.49[a]	1.19	.65	2.17[a]	−0.40	.10	−2.55[a]
9	7	3.05	1.50	>10.0[a]				.85	1.10	−1.22
10	9	.50	.45	1.02	1.60	.56	4.20 [a]	1.85	2.35	−2.55[a]

T0 = represents measures pre-intervention; T1 = represents measures post-intervention; VAS = visual analogue scale were a higher z-score indicates higher pain intensity; PROMIS-fatigue z-score (≥8years); scores on the ROMIS Fatigue questionnaire in children aged 8 years and older and where a higher z-score indicate higher level of fatigue; CHAQ-DI = Childhood Health Assessment Questionnaire Disability-Index where a higher z-score indicates more disability; RCI = Reliable Change Index were a positive score indicates progress over time and a negative score indicates decline over time, −= missing value, n.a.= not applicable, >= greater than, [a]= represents a Reliable Change Index ≥1.96.

Exploratory observations regarding effectiveness indicated that 75% of participants demonstrated a positive trend in improving aerobic capacity, while 70% showed improvements in strength and agility post-intervention. Notably, 80% achieved their individual established training goals, and most of the participants reported reductions in pain intensity and fatigue. However, two participants did not achieve their goals. One participant's engagement was influenced by psychosocial factors, while the other's result was possibly due to misaligned goal-setting; although this participant demonstrated progress across multiple variables, there was no improvement in the specific area directly linked to the target goal.

The tailor-made nature of the training protocol in the current study aimed to meet each child's individual and meaningful objectives. Although no similar studies specifically focus on children with HCTD, relevant insights can be drawn from interventions conducted in children with other conditions. For instance, Meulenbroek et al. implemented a multidisciplinary intervention that combined physical exercise, cognitive-behavioral therapy, and a parental program for adolescents with generalized joint hypermobility and chronic pain, resulting in significant improvements in physical fitness [12]. Similarly, a multidisciplinary treatment program for children and adolescents with chronic musculoskeletal pain effectively enhanced daily functioning. In line with these findings, the majority of participants in this study showed notable improvements in daily physical activities related to their personalized training goals [58]. These observations highlight the potential of tailored, multidisciplinary approaches for children and their parents to enhance physical fitness in children facing activity restrictions, although further research is needed to confirm these effects. For children with aortic root dilation, adherence to specific training restrictions is crucial to mitigate the risks associated with accelerated aortic root growth [25,59–61]. Nevertheless, recent evidence suggests a protective effect of physical exercise on arterial structures in MFS [62], indicating that physical activity may play a beneficial role in managing this condition and physical consequences.

This study possesses significant strengths, as it is the first to investigate the feasibility, acceptability, and safety of a multidisciplinary intervention for children with HCTD, providing a base for future large-scale effectiveness studies. However, several limitations should be acknowledged. First, in terms of feasibility, acceptability, and safety, the pilot study employed a small sample size with limited subgroups, recruited from a center of expertise within a university hospital, which may affect the generalizability of the findings. Additionally, the lack of feedback from the 10 participants and parents regarding the intervention limits our understanding of its acceptability. Furthermore, regarding the effectiveness of the intervention, the small sample size limited the ability to conduct a statistical comparison of pre- and post-intervention measures at the group level. To address this issue, RCIs were calculated at the individual level for physical

fitness parameters, as well as measures of pain, fatigue, and disability [53]. Lastly, no follow-up assessments were conducted to determine whether the observed positive effects were sustained over time. To address these limitations, future clinical trials should implement tailored physical exercise programs that include parental support, establish clear success criteria, and identify strategies to overcome barriers to participation. Additionally, gathering participant and parent feedback through surveys, interviews, or focus groups will be crucial for enhancing the program's overall acceptability. Conducting long-term follow-ups and utilizing larger sample sizes will also be essential for evaluating sustained benefits and improving the generalizability of the findings.

In summary, this study assessed the feasibility, safety, and acceptability of an intensive physical training intervention for children with HCTD, offering valuable insights into its potential impact on physical fitness. The findings indicate that while the intervention is feasible and safe, there are significant challenges related to participant acceptability, which require attention in future research. By implementing tailored exercise programs that incorporate parental support, establishing clear criteria for success, and actively seeking participant feedback, subsequent studies can enhance both the acceptability and effectiveness of such interventions. Long-term follow-up and larger sample sizes will be essential in validating the observed benefits and ensuring broader applicability of the results.

This study provides a foundation for future large-scale effectiveness studies on multidisciplinary interventions for children with HCTD. It highlights the potential benefits of tailored physical training in enhancing physical fitness and addressing the unique needs of this population. Ongoing research in this field is essential for developing effective strategies to reduce physical limitations in children with HCTD.

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