Received: 17 January 2023 | Revised: 8 March 2023 | Accepted: 28 March 2023

DOI: 10.1002/jimd.12607

ORIGINAL ARTICLE

JIMD SSIEM WILEY

Physical training and high-protein diet improved muscle strength, parent-reported fatigue, and physical quality of life in children with Pompe disease

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Funding information
Stichting Vrienden van het Sophia, Grant/Award Number: W.OK18-13; Stichting Prinses Beatrix Spierfonds

Communicating Editor: Saadet Mercimek-Andrews

Abstract

Exercise has proven to be an effective adjuvant treatment to enzyme replacement therapy (ERT) in mildly affected adult Pompe patients. The aim of this study was to investigate the effects of a 12-week tailored lifestyle intervention, consisting of physical training and a high protein diet (2 grams/kg), in children with Pompe disease. This randomized controlled semi-crossover trial investigated the effects of a lifestyle intervention on the primary outcome: exercise capacity. Secondary outcomes were: muscle strength, core stability, motor function, physical activity levels, quality of life, fatigue, fear of exercise, caloric intake, energy balance, body composition, and safety. Fourteen Pompe patients with a median age of 10.6 [IQR: 7.2–14.5], of whom six classic infantile patients, participated in the lifestyle intervention. At baseline, patients had a lower exercise capacity compared to healthy peers (median 70.3% [IQR: 54.8%–98.6%] of predicted). After the intervention, absolute Peak VO_2 improved significantly (1279 mL/min [1012.5–2006] vs. 1352 mL/min [1101.5–2069], $p = 0.039$), but not compared to the control period. Muscle strength of the hip

flexors, hip abductors, elbow extensors, neck extensors, knee extensors, and core stability improved significantly compared to the control period. Children reported a significant increase on the change in health domain of quality of life, parents reported significantly better scores on the quality of life domains: physical functioning, change in health, family cohesion, and fatigue. A 12-week tailored lifestyle intervention for children with Pompe disease seemed safe and led to improvements in muscle strength, core stability, quality of life, and parent-reported fatigue. Pompe patients with a stable disease trajectory seemed to benefit the most from the intervention.

KEYWORDS

endurance training, lifestyle intervention, muscle strength, physical exercise, Pompe disease

1 | INTRODUCTION

Pompe disease is a metabolic myopathy caused by the deficiency of the lysosomal enzyme acid-α-glucosidase (GAA). Pompe disease is characterized by progressive muscle weakness, which also affects the respiratory muscles.[2] The disease presents with a spectrum of severity, determined by the level of residual GAA activity. Classic infantile Pompe patients without any GAA activity, present shortly after birth with a hypertrophic cardiomyopathy, do not achieve major motor milestones, and demise within the first year of life due to cardiorespiratory failure if left untreated.[2–4] Patients with nonclassic infantile Pompe disease, with up to 20% residual GAA activity, present either during childhood (childhood onset Pompe disease including atypical onset Pompe disease) or adulthood (adult onset Pompe disease) with a more slowly progressive proximal muscle weakness including respiratory involvement.[2]

In 2006, enzyme replacement therapy (ERT) with alglucosidase alfa was approved. This has significantly improved clinical outcomes, including motor function, muscle strength, and survival.[2,5] However, ERT does not reverse all muscle-related problems and many Pompe patients still experience progressive muscle weakness.[4,6]

Physical exercise training has been proven as an effective adjuvant therapy to ERT in adults with lateonset Pompe disease. An earlier study published by our group showed that a 12-weeks program including aerobic, resistance and core-stability training could be performed safely in a large group of adult late-onset Pompe patients. This program led to an improvement in exercise capacity, maximum distance walked, core stability, and muscle function.[7] Other studies, investigating aerobic, resistance training, or respiratory muscle training in smaller groups of adult late onset Pompe patients, also showed that training is safe and can lead to improvements in muscle strength, muscle function, and walking distance.[8–10] Only two studies have investigated the effects of a combination of (high-protein) diet and physical exercise.[11,12] Sechi et al. showed that exercise in combination with high-protein diet resulted in a larger improvement in exercise capacity, pulmonary function, and quality of life than when only exercise was performed (total group $n = 10$).[11] Earlier, Slonim et al. found that late onset Pompe patients compliant to high-protein and low-carbohydrate diet and exercise therapy had slower muscle function deterioration (measured using the Walton scale) compared to patients who did not follow this regimen.[12] However, the latter study had limitations, as it was uncontrolled, and the duration of compliance to the diet and exercise intervention could not be verified with certainty.

In children with Pompe disease, evidence regarding favorable effects of physical exercise and diet is lacking. Trials investigating the effect of lifestyle interventions (i.e., a combination of an exercise and diet and/or psychological support program) have never been published before. The aim of this study was to investigate the safety and effect of a tailored exercise training program including high-protein diet, on the primary outcome of change in the exercise capacity. Secondary outcomes were: muscle strength, core stability, motor function, physical activity levels, quality of life, fatigue, fear of exercise, caloric intake, energy balance, and body composition in children with Pompe disease.

2 | METHODS

This was a prospective single-center randomized controlled semi-crossover trial investigating the effects of a 12-week tailored lifestyle intervention program in children with Pompe disease. This trial was conducted between December 2019 and May 2020 in the Centre for Lysosomal and Metabolic diseases at the Erasmus

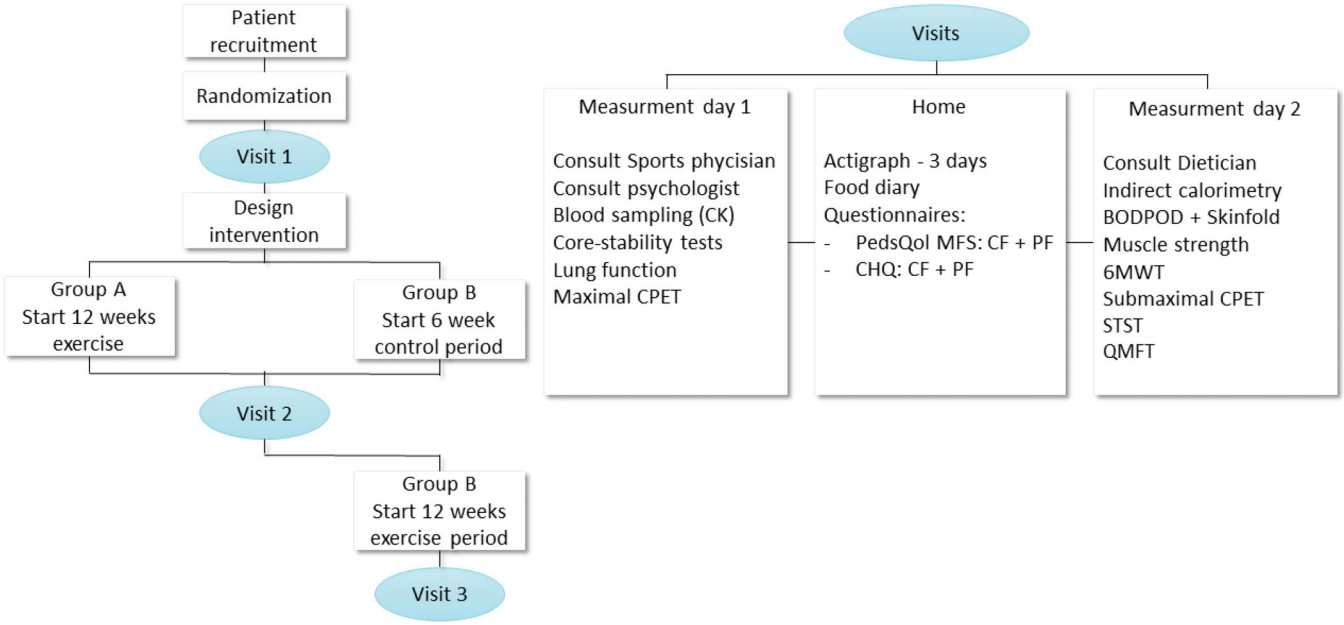

FIGURE 1 Study design, visits, and measurement assessments. The left figure shows the study design. Patients were randomized into two groups, group A started with 12 weeks of exercise and group B started with a 6-week control period, where after they also started 12 weeks of exercise. The right figure shows the measurements performed on each visit in detail. 6MWT, 6 minute walking test; BODPOD, body composition measurement system; CF, child form; CHQ, child health questionnaire; CK, Creatine Kinase; CPET, cardiopulmonary exercise test; MFS, Multi Fatigue Scale; PF, parents form; QMFT, quick motor function test; STST, supine to stand test.

MC—Sophia Children's Hospital in Rotterdam, The Netherlands. The study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Erasmus MC University Medical Centre (NL.70912.078.19) and registered at www.trialregister.nl as Trial NL8181. The detailed protocol of the exercise study was published before.[1]

2.1 | Participants

Children and adolescents with a diagnosis of classic infantile Pompe disease and nonclassic infantile Pompe disease (childhood onset Pompe disease including atypical Pompe disease) aged between 6 and 18 years could participate.[13] We define atypical Pompe disease patients as children that present with a hypertrophic cardiomyopathy after the first year of life. Pompe disease was confirmed by a demonstration of α-glucosidase-deficiency in leucocytes or fibroblasts and two pathogenic GAA variants (www.pompevariantdatabase.nl). All classic and atypical infantile patients participating in this trial received 40 mg/kg/week. All childhood onset patients participating in this study received 20 mg/kg per 2 weeks, besides from one patient who does not receive ERT yet (see for details Ref. [14]). Physical inability to perform a cardiopulmonary exercise test (CPET), participation in other exercise training programs, and contra-indications for exercise were exclusion criteria. Signed informed consent was obtained from all participants (and parents in patients aged less than 16 years old) before enrollment.

2.2 | Randomization

Randomization for group A or B (start control) was performed in Castor (Electronic Data Capture) using block sizes of 4 and 6.[15] Group B started the intervention after a control period of 6 weeks without intervention, while group A started the intervention immediately after the first assessment. Blinding of participants and physical therapists was not possible due to the nature of the intervention.

2.3 | Study design and intervention

Figure 1 shows the study design, visits, and measurements. Each study visit consisted of two assessment days with at least 3 days and maximum 7 days in between. The tailored lifestyle intervention was designed as previously described.[1] The intervention lasted 12 weeks and consisted of a tailored exercise program and high-protein diet. The tailored exercise program was performed three times per week lasting 45–60 minutes each (detailed training program, Table S1) and consisted of muscle endurance exercises, core stability exercises, and personalized aerobic training using hear trate (HR) zones 2, 3, and 4 based on the ventilator anaerobic threshold (VT2) measured during the CPET. Different

programs were designed for wheelchair patients, patients <12 years old, and patients aged 12–18 (Table S1). While the programs targeted the same muscle groups, more playful exercises were chosen for the younger children compared to the older children. Whenever a child could complete 3 sets of 15 repetitions of a certain exercise, the exercise was made more difficult. If a child could not perform an exercise, the exercise was adjusted per case. Patients trained under supervision of a physical therapist, LES visited all first training sessions and a training (either live or via video connection) of each patient every 2 weeks, to monitor uniform execution of the training program. During the intervention, LES telephoned patients weekly to monitor safety, side effects, and assure compliance. In addition to the tailored exercise program, all participants received a recommended caloric intake per day, TEE (calculated using the Schofield formula and based on measured REE and corrected for weight), a personalized high protein diet of 2 g/kg a day, and a brochure regarding healthy diet in children (designed by the "Voedingscentrum," the Dutch government supported nutritional center).[16]

2.4 | Outcome measurements

The primary study endpoint was the maximal exercise capacity measured by peak oxygen uptake (peak VO_2); the gold standard for aerobic fitness.

Secondary study endpoints include

1. Physical fitness: (submaximal) exercise capacity, muscle strength, motor function, core stability, and psychical activity levels.
2. Patient-reported outcomes: Quality of life, fatigue, and fear of exercise.
3. Nutritional status: caloric intake, energy balance, and body composition.
4. Safety

For detailed protocols of all measurements, see the previously published exercise study protocol.[1]

2.4.1 | Physical fitness

Exercise capacity

Exercise capacity was assessed by maximal CPET, submaximal CPET, and 6-minute walking test (6MWT). All patients underwent the maximal CPET (ramp protocol), and submaximal CPET on the same electrically braked bicycle ergometer. The 6MWT was performed in accordance with the American Thoracic Society guidelines; however, due to lack of space, the course was 8 m in length instead of 30 m.

Muscle strength, motor function, and core stability

All muscle strength measurements were performed in a standardized manner by either LJG or LES using Handheld dynamometry (HHD) and compared to normal values of Beenakker et al.[17] A sum score was calculated by averaging all measured muscle groups.[1] The motor function was measured using the QMFT, a specifically constructed tool to measure motor function of Pompe disease patients.[18] Scores of each item are summed with a maximum score of 64, indicating normal muscle functioning. Additionally, the required time to move from a supine to standing position (supine to stand test, STST) was assessed.

To assess core stability, we measured time in balance for each of the following four core-stability exercises: plank, back bridge, left side bridge, and right side bridge.

Physical activity levels

During the consultation with the sports physician, children and parents were asked about the amount of time spent on physical activity a week. Subsequently, physical activity levels were measured with a validated Actigraph GT3X+ accelerometer.[1] The subjects were asked to wear the accelerometer on their right hip for 2 weekdays and 1 weekend day.

2.4.2 | Patient-reported outcomes

Quality of life, fatigue, and fear of exercise

The validated child health questionnaire (CHQ) child form (CHQ-CF45 including 45 items and 11 domains) and parent form (PF) (CHQ-PF28 including 28 items and 13 domains) were used to assess health-related quality of life before and after the intervention.[19] Baseline outcomes were compared to previously published data in healthy Dutch children ($n = 737$) and their parents ($n = 4538$).[19–21] Higher scores indicate better quality of life. The PedsQL Multidimensional Fatigue Scale (MFS) CF and PF, consisting of 3 domains and 18 items, were used to evaluate fatigue, with a higher score indicating less fatigue.[22] Baseline outcomes were compared to previously published data in healthy Dutch children ($n = 366$) and their parents ($n = 497$).[23] During the semi-structured interview with the psychologist, children and parents were (separately) asked to score fear of exercise (and fear to let their child exercise) on the fear thermometer, 0 (no fears at all) up to 8 (high fear for exercise).

2.4.3 | Nutritional status

Body composition, intake, and energy balance

At each visit, patient'sheight and weight were measured, and body composition was assessed using a skinfold caliper (four skinfolds method) and air displacement plethysmography (ADP) on whole-body densitometry using the

BOD POD.[1] All patients filled in a detailed food diary for 3 consecutive days and underwent an indirect calorimetry during the consult with the dietician to measure rest expenditure (REE). Both measured REE and estimated REE, calculated using the Schofield equation, were then converted to total energy expenditure (TEE).[24]

2.4.4 | Safety

Plasma creatine kinase (CK) was measured at the start of each measurement moment as a safety marker for exercise-induced muscle damage.[25] Subsequently, all patients were contacted weekly to record the potential side effects and feedback to the training program.

Sample size calculation and statistical analysis

The power calculation was based on the primary study endpoint change in peak VO_2. The only previous study investigating exercise capacity in children with Pompe disease measured a 75% peak VO_2 of 37.7 mL/kg/min.[26] We considered an improvement in Peak VO_2 of at least 5% as clinically relevant. The difference of a 5% increase in Peak VO_2 can be observed with a power of 80% and an alpha of 0.05 at a number of 10 children with Pompe disease assuming a standard deviation of 2.19 VO2/kg. Anticipating on a dropout rate of 30%–40%, we calculated that 14 patients with Pompe disease should be included in our trial. Data were collected in Castor (Clinical Electronic Data Capture) and analysed using IBM SPSS Statistics 25.0 (IBM Corp, Armonk, NY). Patient characteristics were described using descriptive statistics. Baseline characteristics between groups were compared with the Mann–Whitney *U* and Chi-squared test for proportions. All data were analyzed as nonparametric due to the small sample size. Baseline quality of life domains and fatigue domains were compared to the healthy population using the Wilcoxon one sample test. Differences over the exercise period and control period were analyzed using the Wilcoxon signed ranks test. A generalized equations approach model was used to compare change over the control to the exercise period and account for the correlation of the repeated measurements in the active group. The working correlation matrix was set as unstructured. The significance level was determined at $p < 0.05$.

3 | RESULTS

3.1 | Patient characteristics

Fifteen patients were included. In total, five patients refused to participate, three parents found the study to be too burdensome especially combined with the already intensive medical care, and two parents (of childhood onset patients) felt that the burden did not outweigh the possible gain for their child. One patient dropped out immediately after inclusion as she had to have a burdensome medical treatment. The median age of the patients was 10.6 years (IQR: 7.2–14.5), 57% were female, six patients were diagnosed with classic infantile, six patients with childhood onset Pompe disease, and two with atypical infantile Pompe disease. All patients except one childhood onset patient received ERT. ERT doses were as described in the methods and did not change during or the year prior to this trial. Randomization groups were comparable expect for ERT duration in years, which was longer in patients in group A. Patient and disease characteristics can be found in Table 1 and Table S2.

3.2 | Compliance and drop-outs

All 14 patients successfully completed the exercise intervention. Compliance with the 36 training sessions was high, with a median training session attendance of 94.4% [91–97.2]. Table 2 shows the percentage of change for all outcomes after the tailored intervention per patient.

3.3 | Physical training

3.3.1 | Exercise capacity

At baseline, patients showed a lower exercise capacity of 70.3% [IQR: 54.8–98.6] of predicted Peak VO_2/kg compared to reference values. After 12 weeks of training, absolute peak VO2 increased significantly (1279 mL/min [1012.5–2006] vs. 1352 [1101.5–2069], $p = 0.039$), but not compared to the control period ($p = 0.643$). Peak VO_2/kg did not change. Figure 2 and Table S3 show all outcomes related to endurance. Walked distance on the 6MWT and average hear trate measured during the submaximal CPET did not change significantly after the intervention compared to the control period.

3.3.2 | Muscle strength, motor function, and core stability

Muscle strength of the hip flexors, hip abductors, elbow extensors, neck extensors, and knee extensors increased significantly, including the sum score of all muscle groups (before 77.7 newtons [66.58–136.9] vs. 84.2 newtons [68.3–153.3], $p = 0.001$ compared to the control period) (Table 3). Median QMFT score increased by +3 (59.5 [37.3–64] vs. 62.5 [33.3–64], $p = 0.950$), but did not reach significance

TABLE 1 Patient characteristics.

Subject	Age (years)	Gender (M/F)	Disease onset	CRIM status	Diagnose age (years)	ERT duration (years)	Age at start ERT (Years)	Current ERT dose / Frequency[a]	GAA variant 1	GAA variant 2	Breathing assist and/or walking aid
Group A—Start exercise											
1	755	F	Classic infantile	+	0.25	7,19	0,36	40 weekly	c.1551+1G>A	c.1551+1G>A	None
3	8.61	M	Atypical infantile	+	3.35	5.18	3.43	40 weekly	c.875A>G	c.379_380delTG	None
6	6.86	F	Classic infantile	−	0.14	6.70	0.16	40 weekly	c.525delT	c.525delT	Walker, no breathing assist
10	14.01	F	Childhood onset	+	12.44	1.08	1.57	20 biweekly	c.-32−13T>G	c.379_380delTG	None
11	12.15	F	Childhood onset	+	10.17	1.39	1.98	20 biweekly	c.-32–13T>G	c.379_380delTG	None
12	19.01	F	Childhood onset	+	4.27	10.80	8.21	20 biweekly	c.-32–13T>G	c.2331+2T>A	None
13	6.24	M	Atypical infantile	+	1.40	4.74	1.5	40 weekly	c.1115A>T	c.1115A>T	None
14	3.50	M	Childhood onset	+	3.50	1.93	1.57	20 biweekly	c.-32–13T>G	c.379_380delTG	None
Group B—Start control period											
2	9.42	M	Classic infantile	−	0.32	9.10	0.32	40 weekly	c.2481+102_2646	c.del525T	Wheelchair, no breathing assist
									+31del		
4	11.76	F	Childhood onset	+	7.60	No ERT	x	No ERT	c.-32–13T>G	c.525del	None
5	18.53	M	Childhood onset	+	9.37	8.06	10.47	20 biweekly	c.-32–13T>G	c.525delT	None
7	7.35	F	Classic infantile	+	0.25	7.08	0.27	40 weekly	c.2481+102_2646	c.2481+102_2646	None
									+31del538	+31del538	
8	12.95	M	Classic infantile	+	0.16	12.77	0.18	40 weekly	c.525delT	c.2481+102_2646	Wheelchair and Night ventilation
										+31del	
9	15.98	F	Classic infantile	+	0.02	15.95	0.03	40 weekly	c.2481+102_2646	c.2481+102_2646	Wheelchair, no breathing assist
									+31del	+31del	

Abbreviations: ERT, enzyme replacement therapy; F, female; M, male.

[a]Dosing of ERT changed over time for patients with classic infantile Pome disease. Treatment with recombinant human alpha-glucosidase applied were 15 or 20 mg/kg/week; 20 mg/kg/2 or 40 mg/kg/wk. After 2008, all patients received a dose of 40 mg/kg/week.[32,33]

TABLE 2 Change before and after of the tailored lifestyle intervention per patient.

Subject	Disease onset	VO_{2PEAK}	VO_{2PEAK} /kg	$Watt_{Max}$	$Watt_{Max}$/kg	6MWT (% change)	QMFT (score)	STST	Core Stability (s)	Muscle strength total increase (%)
1	Classic Infantile	↑+19,2%	↑+13,9%	↑+14,7%	↑+8.8%	↓-7,5%	↑3 (47–>50)	↓	↑21	n.a.
2	Classic infantile	↑+27,5%	↑+23,3%	↑+17,8%	↑+14.9%	↓-9,3%	↓-3 (39–>36)	n.a.	↑186	= 1.9%
3	Atypical onset	↑+5,7%	↓-8,2%	=+4,7%	↓-8.6%	↑6,7%	= (64–>64)	↓	↑240	↑14.2%
4	Childhood onset	↑+12,5%	↑+13,9%	↑+9,8%	↑9.1%	= 1,5%	↑3 (56–>59)	↓	↑72	↑6.4%
5	Childhood onset	↑+19,8%	↑+14,0%	↑+11,4%	↑7.6%	↑6,0%	0 (64–>64)	↓	↑16	↑31.8%
6	Classic infantile	↑+12,7%	↑+7,5%	↓-29,0%	↓33.26%	↓−9,2%	↓-7 (32–>25)	n.a.	↑25	↑19%
7	Classic infantile	↑+2,9%	↑+13,9%	↑+32,8%	↑20.9%	↓−15,6%	↑1 (57–>58)	↑	↑72	↑10.1%
8	Classic infantile	↑+17,2%	↑+17,0%	↑+9,7%	↑9.6%	n.a.	0 (21–>21)	n.a.	n.a.	↑23.8%
9	Classic infantile	↓−19,3%	↓−14,0%	↓-27,1%	↓−24%	↓−86,0%	↓-10 (31–>21)	n.a.	↑10	↓-6.0%
10	Childhood onset	↑+15,5%	↑+13,3%	↑+14,7%	↑+11.3%	↑7,1%	↑3 (61–>64)	↓	↑339	↑27.6%
11	Childhood onset	=+0,7%	=−4,0%	=+4,7%	=−1.9%	↑14,0%	↑3 (60–>63)	↓	↑399	↑23.0%
12	Childhood onset	↓−9,7%	↓−11,6%	=+2,0%	=+1.3%	=−4,5%	0 (64–>64)	↓	↑241	↑11,2%
13	Atypical onset	n.a.	n.a.	n.a.	n.a.	=−1,3%	0 (64–>64)	↓	↑57	= 2.1%
14	Childhood onset	↑+9,7%	↑+7,0%	↓−9,1%	↓−12.7%	=−4,4%	↑1 (63–>64)	=	↓−12	↑14.0%

Note: Percentage change before and after of the tailored lifestyle intervention per patient.

Abbreviation: kg, kilogram; Max, maximal; min, minutes; ml, milliliters; n.a., not available; QMFT, quick motor function; s, seconds; STST, supine to stand test; VO_2, oxygen uptake; Watt, wattage.

(Table 3). STST improved significantly −2.35 seconds [1.9–3.1] vs. 1.8 seconds [1.55–2.72], $p = 0.015$ but not compared to the control period. Core stability, assessed by measuring time in balance while performing the plank, back bridge, and side bridges, improved significantly in all four core-stability exercises compared to the control period (Table 3).

3.3.3 | Physical activity levels

Seven out of 14 children participated in sports activities (in addition to school-related physical exercise) before the start of the exercise program. Median percentage of time spent in sedentary activity measured with the Actigraph was 76.1% [65.5–83.4] at baseline and did not increase significantly after the intervention (Table S4). In total, 11 out of 14 children continued physical training at least once a week after the intervention had stopped.

3.4 | Patient-reported outcomes

3.4.1 | Quality of life, fatigue, and fear of exercise

At baseline, children reported worse quality of life scores for physical functioning, self-esteem, and general health perception domains compared to healthy children (Table S5). Parents reported a decreased quality of life in nine domains in their children compared to parents of healthy children. After training, children reported higher scores on the change in health domain compared to the control period score. Parents reported an increased quality of life on the physical function domain (77 [36–100] before the intervention vs. 83 [50–100] after the intervention, $p = 0.006$ compared to the control period) and better scores on the 'change in health' domain and family cohesion domain compared to the control period. Children reported a decreased score for the cognitive fatigue domain compared to healthy children (Table S6). Parent-reported fatigue in the children was worse for all domains compared to those of healthy children. After training, only the parent-MFS report showed significant improvements in both general fatigue (10 points improvement compared to the control period, $p = 0.014$) and total fatigue (16 points improvement compared to the control period, $p = 0.034$). Fear of exercise was low for both children and parents before the intervention. After the intervention, parent-reported fear was reduced even more on the anxiety thermometer ($p = 0.034$), child reported fatigue also reduced compared to the control period ($p = 0.043$). Most given reason for fear of exercise (by both children and parents) was fear of falling during training sessions.

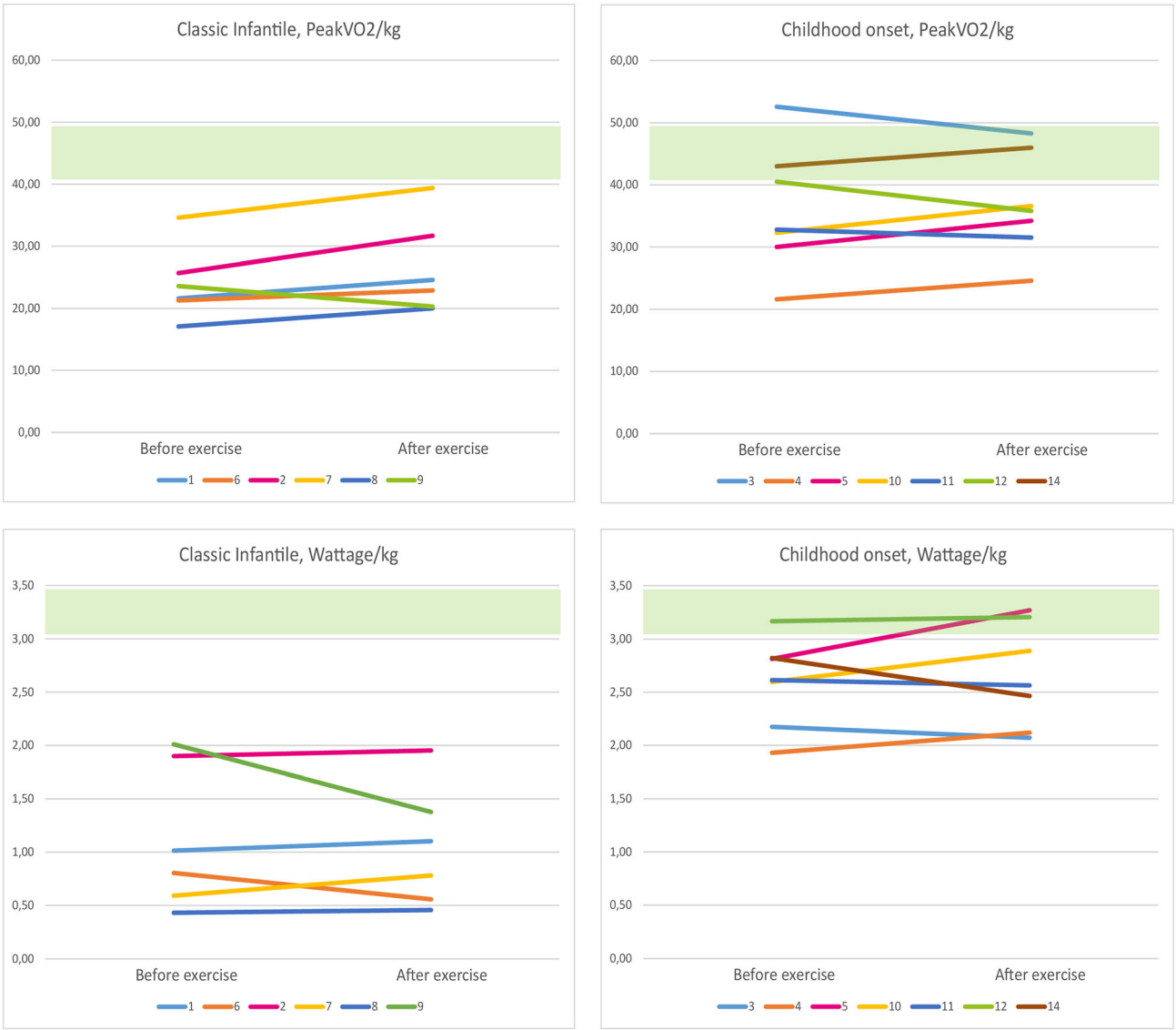

FIGURE 2 Change in Peak VO_2/kg and Wattage/kg before and after the tailored lifestyle intervention. Upper left: Change in Peak VO_2/kg before versus after the exercise intervention in classic infantile Pompe patients. Lower Left: Change in Wattage/kg before versus after the exercise intervention in classic infantile Pompe patients. Upper right: Change in Peak VO_2/kg in atypical and late onset Pompe patients. Lower right: change in wattage/kg in atypical and late onset Pompe patients. The Green-shaded area represents normal Peak VO_2/kg and Wattage/kg.

3.5 | Nutritional status

3.5.1 | Body composition and energy balance

Protein intake increased after the intervention (59 grams [54.4–80.2] to 70.4 grams [60.7–72.5], $p = 0.002$ compared to the control period). Absolute difference between recommended intake and actual intake decreased (333 calories [220–458] vs. 188 [116–315], $p = 0.010$ compared to the control period). Children had an increased REE (+10%) measured by indirect calorimetry before exercise compared to reference values (Schofield), which increased further but did not reach significance(110.4% [99.6–119] vs. 114.6% [108.7–118], $p = 0.594$).[24] BMI and percentage of body fat (and thus percentage of fat free mass) measured by skinfold caliper and air displacement plethysmography remained unchanged (Table S7).

3.6 | Safety

Plasma creatine kinase (CK) did not change after the intervention (421 Units/liter [302.8–578.5] vs. 350 Units/liter [195.8–579.8], $p = 0.245$). Patients did not complain about abnormal muscle strain (lasting for >2 days after training). One adverse event was reported by a physiotherapist. During one of the training sessions a classic infantile Pompe (number 9) fell, she did not have any injuries besides a bump on her head.

TABLE 3 Muscle strength, core stability, 6MWT, and motor function.

	Exercise Period ($n = 14$)[a]			Control Period ($n = 7$)				
	Before	**After**	***p*-values**	**Before**	**After**	***p*-values**	**Effects size exercise versus control period**	***p*-value difference exercise versus control period**
Muscle strength								
Neck flexion (*N*)	66 [56–72.5]	76 [51–92]	0.116	51 [35–107]	56 [40–71]	0.463	16 [−5–36]	0.128
Neck extension (*N*)	115 [70–148]	119 [81–170]	**0.019***	105 [78–123]	129 [91–146]	0.116	-1 [−26–23]	0.904
Shoulder abduction (*N*)	69 [50–99]	56 [36–108]	0.807	62 [43–115]	59 [43–117]	0.674	7 [−10–24]	0.424
Elbow flexion (*N*)	84 [71–135]	82 [73–177]	**0.021***	76 [62–147]	76 [66–123]	0.528	23 [2–44]	**0.035***
Elbow extension (*N*)	68 [46–141]	44 [69–120]	0.272	66 [34–103]	59 [35–147]	0.462	-9 [−29–10]	0.348
Squeezing strength (*N*)	31 [22–83]	36 [22–80]	0.294	25 [20–88]	25 [20–88]	0.753	0 [−6–6]	0.969
Hip flexion (*N*)	124 [97–201]	146 [94–146]	**0.016***	105 [96–193]	105 [92–194]	0.225	24 [7–42]	**0.005***
Hip abduction (*N*)	95 [78–160]	105 [89–178]	**0.005***	91 [79–191]	90 [78–178]	0.116	29 [15–44]	**<0.001***
Knee flexion (*N*)	79 [53–143]	87 [48–125]	0.108	81 [39–137]	57 [42–169]	0.600	18 [−8–44]	0.183
Knee extension (*N*)	82 [59–176]	108 [56–218]	**0.003***	82 [42–225]	74 [44–190]	0.500	34 [18–68]	**<0.001***
Total Strength (*N*)	**78 [67–137]**	**84 [68–153]**	**0.003***	**68 [60–145]**	**68 [62–142]**	0.917	15 [6–23]	**0.001***
Core-stability tests								
Plank (s)	10 [0.5–36]	30 [4.5–96]	**0.005***	4.5 [0–25]	5 [0–29]	0.197	22 [8–35]	**0.001***
Side plank left side (s)	3 [0–16.5]	13 [0–46]	**0.038***	1 [0–26.5]	1 [0–19.5]	0.317	12 [4–20]	**0.003***
Side plank right side (s)	3 [0–13.5]	13 [0–46]	**0.033***	1 [0–16]	1.5 [0–16.5]	0.564	12 [3–30]	**0.008***
Back bridge (s)	35 [11.5–54.5]	91 [30.5–160]	**0.006***	16.5 [3.8–50.5]	1.5 [0–16.5]	0.223	61 [13–109]	**0.013***
Motor function								
QMFT	59.5 [37.3–64]	62.5 [33.3–64]	0.950	48 [28.3–60.3]	48 [28.5–60.3]	0.564	-1 [−2.6–1.5]	0.617
STST (s)[b]	2.35 [1.9–3.1]	1.8 [1.55–2.72]	**0.015***	3.29 [2.7–14.49]	3.04 [2.23–11.04]	0.144	−1.1 [−0.7–3]	0.213
6MWT								
Walked distance (m)	456 [348–488]	401 [304–540]	0.675	350 [222–451]	366 [218–476]	0.686	4 [−41–49]	0.857

Note: Data are presented as median [IQR]. Differences over the exercise period and control period were analyzed using the Wilcoxon signed ranks test. A generalized equation approach model was used to compare change over the control to the exercise period (described as the effect size including 95% confidence interval and matching *p*-value). * and bold means significant $p < 0.05$.

Abbreviations: QMFT, Quick Motor Function Tests; N, newton; n, number; s, seconds; STST, supine to stand test.

[a]$N = 14$ for squeezing strength and $N = 13$ for other muscle groups (one patient lacked cognitive skills to perform the hand-held measurements).

[b]STST control group ($n = 4$) one patient could not perform the STST anymore after the control period of 6 weeks, STST exercise group ($n = 10$). One patient did not perform the STST as he was in a wheelchair.

4 | DISCUSSION

This study is the first study to investigate effects of a tailored intervention including physical exercise training and a high protein diet in children with Pompe disease. The 12-week tailored intervention led to improvements in muscle strength, core-stability, physical quality of life, and parent-reported fatigue in children with Pompe disease.

4.1 | Physical Fitness

As Pompe disease is characterized by progressive muscle weakness and respiratory failure often leading to a sedentary lifestyle, physical training in patients with Pompe disease should target endurance and muscle strength and ultimately transfer this into motor function and performance. At baseline, children in our cohort had a decreased endurance, of 70.3% of predicted compared to

healthy peers measured by Peak VO_2. As expected, classic infantile patients had a lower Peak VO_2 compared to the more mildly affected atypical and childhood onset patients. This was in accordance to earlier published studies in children with Pompe disease (four infantile-onset and one childhood onset patient aged 10–19 years) which also reported a reduced Peak VO_2, ranging from 52% to 67% of predicted.[26,27] The tailored intervention significantly improved the absolute exercise capacity measured by Peak VO2, with the largest improvements seen in the children with the lowest Peak VO_2 at the start. However, Peak VO2 did not improve compared to the control period. Muscle strength increased and core stability improved in almost all patients. The largest improvements were seen in the less severely affected patients, this was subsequently reflected in the motor function outcomes. The STST and QMFT improved in all atypical and childhood onset Pompe patients (if not already scoring maximum points). Classic infantile Pompe patients who had a stable disease trajectory also seemed to improve on QMFT, whereas patients that already had a rapidly progressive course of disease, still deteriorated in QMFT points during the intervention. When looking at distance walked on the 6MWT, only classic infantile patients showed decreases in distance walked, whereas all atypical and childhood onset patients at least remained stable (<5% improvement). However, when looking at the walked distance over time in classic infantile patients, we commonly see high inconstancy in the walked distance (often of >5% variance), possibly explaining our results. Despite the lack of improvement in some outcomes in classic infantile patients, almost all children (and parents) during the structured interview reported feeling stronger and fitter. The improved core stability and strength seemed especially important in the more severely affected classic infantile patients, as after training they were clearly sitting more straight in their wheelchairs, and also claimed that independent transfers (which contributes to their self-reliance) became easier during the 12-week training course. Most children continued some form of exercise training after the intervention; however, this was not reflected by the unchanged measured physical activity levels. As we measured the physical activity levels directly after the "intensive" program, we think possibly children took a "rest" week of exercise.

4.2 | Patient-reported outcomes

Exercise has been proven to increase quality of life and improve fatigue in healthy children.[28] Adult late onset Pompe disease patients are known to have a decreased quality of life, and high levels of fatigue.[29,30] No study has investigated the quality of life and fatigue in children with Pompe disease yet. In this study, children and parents clearly scored worse on both quality of life and fatigue compared to healthy children. Both children and parents reported a significant improvement on the "change in health domain" of the CHQ. This domain asks the question whether a child feels healthier compared to a year ago. Parents also reported significant improvements in the physical functioning and family cohesion domains of quality of life and general and total fatigue. The discrepancy between the parent's and child reports might be explained by a lack of power in the child forms (parent reports $n = 28$, child reports $n = 14$). When comparing classic infantile patients to childhood onset patients in terms of fatigue, classic infantile patients clearly benefited the most from the intervention as both children and parents showed large improvements in fatigue levels. This might be declared by the fact that classic infantile Pompe patients had the lowest fatigue scores at the start. Training studies in adults with late onset Pompe found mixed results ranging from an increase in the domains of general health and vitality after training in adult late onset Pompe patients to no changes in the quality of life after training.[11,31] Nevertheless, the latter study did report that patients experienced less fatigued after the intervention.[31] All in all, we think the intervention positively influenced physical functioning and fatigue.

4.3 | Nutritional status

4.3.1 | Body composition and energy balance

To the best of our knowledge, no other studies have investigated REE in patients with Pompe disease yet. When looking at REE, children had an increased REE compared to reference values (median 110% of predicted). However, children also consumed a median of 216 calories [−328–372.8] above their predicted TEE. After the 12 weeks intervention, median REE did not change compared to the control period. Due to the dietary advice children consumed less calories above their predicted TEE than before the intervention; however, daily consumption was still above their recommended intake. The amount of protein (grams) increased significantly after the intervention, both indicating that patients followed the dietary advice. These findings are in accordance with feedback from parents, as most stated that they were compliant with the dietary advice regarding protein intake, but still found it very difficult to adequately reduce caloric intake. Although protein intake increased and parents became more aware of the importance of protein in the diet of their children, it did

not reach the recommended 2 g/kg. Future studies should consider supplementing protein to make it easier for parents and children to reach the prescribed amount. The discrepancy between REE and intake is in accordance with the observation that at our center, we notice an increasing number of Pompe patients gain excessive weight, eventually resulting in obesity. No significant change was measured in body fat percentage after the intervention, this was the same as in other training studies in adult patients with late onset Pompe disease.[7,9] Possibly, body composition measuring techniques are not sensitive enough to measure subtle changes in body composition (as might be expected during a period of only 12 weeks), and sufficient power is lacking. DXA might be a more sensitive method to measure changes over a short period of time; however, in the study of berg et al., DXA also did not show any differences in body composition.

4.4 | Strengths and limitations

Our study has several strengths. This study is the first to prospectively investigate the effects of a tailored lifestyle intervention in pediatric Pompe patients on a broad spectrum of outcomes. For a rare disease like Pompe disease in children, our cohort is relatively large; however, in terms of statistical power, our cohort was small, especially the control period ($n = 6$). Although measured effects of the program were mainly positive, definite, and long-term conclusions regarding the effectiveness of the program are hard to draw, especially as each subgroup was very heterogeneous. Researchers (and of course also parents/children) in the study could not be blinded during measurements due to the content of the study. All training sessions were supervised by physical therapists, and adherence was high. Adherence to the tailored dietary advice, was hard to verify. Since we have combined the exercise training with high-protein diet advice, we are not able to distinguish the effects of these interventions separately. Future studies should investigate the added value of a high-protein diet to exercise in Pompe patients. Due to the COVID-19 lockdown, normal daily life activities could not continue, possibly negatively influencing variables such as exercise capacity, physical activity, and quality of life.

4.5 | Recommendations

Overall, the 12-week tailored lifestyle intervention was very well received, as reflected by the high training adherence, and as most children continued exercising after the intervention. Most children reported feeling stronger and less fatigued after the program, which was also confirmed by the results. Especially in the younger children, towards the end of the intervention, the training frequency of three times a week was high and the aerobic part of training boring. A lower training frequency, possibly including high-intensity interval training (as this form of training is more playful), might be more suitable to keep training fun for the long term. Pompe children with a stable disease trajectory showed the largest improvements on physical health, whereas patients that already show a rapidly progressive course of disease, appeared to benefit the least. We think exercise training as adjuvant therapy to ERT cannot change the progression of the disease, especially in classic infantile patients. Considering these results, we would recommend tailored made physical therapy including diet counseling in children that are clinically stable. In those with (classic infantile) Pompe disease that show a rapidly progressive course of disease, lower intensity and frequency training (including core stability) under close supervision of a physical therapist, should be encouraged to prevent scoliosis, contractures, and improve fatigue.

5 | CONCLUSION

The 12-week tailored lifestyle intervention showed improvements in muscle strength, core stability, muscle function, quality of life, and fatigue and was well received by patients and parents. Pompe patients with a stable disease trajectory benefited the most from the intervention. As the intervention seemed safe, children with Pompe disease should be encouraged to be physically active to optimize their physical and mental health.

ACKNOWLEDGMENTS

We would like to thank all patients and their parents for participating in the Exercise study. Also, all physical therapists, who trained the participants. We would like to thank Prof. Dr. Rizopoulos for his statistical advice. We would like to thank Prof. dr. K. F. M. Joosten for using the BODPOD. We would also like to thank W.M. Mouthaan and The Rotterdam Exercise Team: W.A. Helbing, M.W. Pijnenburg, J.C. Escher, J. Noske, A. van den Broek, J. Olieman.

FUNDING INFORMATION

This study was funded by the "Stichting Vrienden van Sophia" number B19-01 and "Stichting Prinses Beatrix Spierfonds" number: W.OK18 − 13. The authors confirm independence from the sponsors, the content of the article has not been influenced by the sponsors.

CONFLICT OF INTEREST STATEMENT

Prof. Dr. Ans T. van der Ploeg and dr. J. M.P. (Hannerieke) van den Hout participated in advisory boards and received consultancy fees and/or research grants of Sanofi/

Genzyme, Amicus, Denali, Spark Therapeutics, GSK, Biomarin, Takeda and others under agreements between these industries and Erasmus MC University Medical Center, Rotterdam, The Netherlands. Several of the authors of this publication are members of the European Pompe Consortium (EPOC) and the European Reference Networks for Hereditary Metabolic Disorders (Metab-ERN). All other authors, L.E. Scheffers, O.C. Somers, K. Dulfer, G.C. Dieleman, S. Walet, L.J. van der Giessen and L.E.M. van den Berg, have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

ETHICS STATEMENT

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (Ethics Committee of Erasmus MC Medical Centre, the Netherlands [NL.70912.078.19]) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients (from an age of 8 years old) and parents for being included in the study, and the study was registered at the International Clinical Trial Registry Platform of the World Health Organization https://trialsearch.who.int/Trial2.aspx?TrialID=NL8181 as Trial NL8181. The protocol of the Exercise study was published before.[1]

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Scheffers LE, Somers OC, Dulfer K, et al. Physical training and high-protein diet improved muscle strength, parent-reported fatigue, and physical quality of life in children with Pompe disease. *J Inherit Metab Dis*. 2023;46(4):605-617. doi:10.1002/jimd.12607