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Improvement of exercise capacity following neonatal respiratory failure: A randomized controlled trial

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Exercise capacity deteriorates in school-aged children born with major anatomical foregut anomalies and/or treated with extracorporeal membrane oxygenation. The aim of the present study was to evaluate whether exercise capacity can be improved in the short term and long term in children born with anatomical foregut anomalies and/or treated with extracorporeal membrane oxygenation. Therefore, we evaluated two different interventions in this single-blinded randomized controlled trial. Forty participants were randomly assigned to group A: standardized anaerobic high-intensity interval training plus online lifestyle coaching program, B: online lifestyle coaching program only, or C: standard of care. Inclusion criteria were as follows: score ≤ -1 standard deviation (SD) on the Bruce protocol. Exercise capacity was assessed at baseline (T0), after 3 months (T1), and after 12 months (T2). Exercise capacity improved over time: mean (SD) standard deviation score (SDS) endurance time: T0 −1.91 (0.73); T1 −1.35 (0.94); T2 −1.20 (1.03): both $P < .001$. No significant differences in maximal endurance time were found at T1 (group A-C: estimated mean difference (SDS): 0.06 $P = .802$; group B-C: −0.17 $P = .733$) or T2 (group A-C: −0.13 $P = .635$; group B-C: −0.18 $P = .587$). Exercise capacity improved significantly over time, irrespective of the study arm. Not only residual morbidities may be responsible for reduced exercise capacity. Parental awareness of reduced exercise capacity rather than specific interventions may have contributed. Monitoring of exercise tolerance and providing counseling on lifestyle factors that improve physical activity should be part of routine care, and aftercare should be offered on an individual basis.

KEYWORDS

clinical trial, exercise capacity, family factors, major anatomical foregut anomalies, neonatal extracorporeal membrane oxygenation, online coaching, physical activity, training program

1 | INTRODUCTION

Children born with major anatomical foregut anomalies, for example, congenital diaphragmatic hernia (CDH), esophageal atresia (EA), and congenital pulmonary airway malformation (CPAM), may require treatment with extracorporeal membrane oxygenation (ECMO) for cardiorespiratory failure. Also, neonates without congenital anatomical anomalies

(CAA) may require ECMO, for example, meconium aspiration syndrome or sepsis.[1,2]

We previously showed that children with CDH and EA are at risk for long-term persistent respiratory morbidity,[2,3] reduced exercise capacity,[4] and motor function problems.[5] Moreover, exercise capacity in neonatal ECMO survivors deteriorated between 5 and 12 years of age.[6] Reduced exercise capacity can lead to inactivity[7] and, in turn, to gross motor function problems. It may also lead to less participation in daily life activities, and consequently a greater risk for secondary disease.[8]

In general, early intervention might improve children's exercise capacity and therewith motor performance. In children with neonatal respiratory failure, intervention programs to improve exercise capacity are lacking. The question is whether persistent respiratory morbidity hampers improvement of exercise capacity. Training programs in children born with cardiac anomalies proved to be beneficial in increasing exercise capacity.[9,10] The few studies available on online coaching programs aiming to promote physical activity in children and in adults suggested that these programs may be beneficial.[11,12] We hypothesized that a short training program might be insufficient to achieve sustained improvement of exercise capacity in children with CAA and/or neonatal ECMO but that coaching aiming at influencing every day activities would render better effect.

We therefore conducted a randomized controlled trial (RCT) to answer the following questions.

1.1 | Primary research question

- Can exercise capacity be improved in these children?

1.2 | Secondary research questions

- Does intervention with either a standardized training program plus online lifestyle coaching or online lifestyle coaching only improve exercise capacity in the short term (3 months) and long term (12 months) and will intervention render greater effect than the standard of care?
- Does intervention with either a standardized training program plus online lifestyle coaching or online lifestyle coaching only improve motor performance, daily life activity, quality of life, and/or perceived motor competence (PMC)?
- Do family factors such as parental health status and their proactive coping influence the change in exercise capacity?
- Is change in exercise capacity diagnosis-dependent?

2 | PATIENTS AND METHODS

2.1 | Participants

From January 2013 till October 2015, subjects were recruited from the interdisciplinary follow-up program in our hospital.[4,6] Children fulfilling the inclusion criteria received written information after routine assessments at age 8 or 12 years. Eligible children not yet scheduled were contacted by mail. Inclusion criteria were as follows: age 7-12 years; diagnosis of CDH, EA, CPAM, and/or neonatal ECMO; and a score of at least 1 standard deviation (SD) below the norm on the maximal cardiopulmonary exercise test (CPET; Bruce protocol).[13] Exclusion criteria were as follows: delayed motor function (ie, percentile score < 6 on Movement Assessment Battery for Children second edition [MABC-2]) requiring intervention by a pediatric physical therapist (PPT); inability or contraindication to perform CPET; and insufficient command of Dutch language (child or parents). From March 2014 onwards, potentially eligible children treated in Radboud University MC-Amalia Children's Hospital (Nijmegen, the Netherlands) were recruited by mail as well.

Ethical approval was granted by the institutional review board (MEC-2011-475), and all parents and children up from 12 years provided written informed consent. Clinical Trial register: Netherlands Trial Registry: NTR3729.

2.2 | Design

In this RCT, participants were randomly assigned to a standardized training program for the child plus online lifestyle coaching for child and family (intervention group A), online lifestyle coaching as in group A (intervention group B), or standard of care (non-intervention group C). A note must be made about the standard of care. Our standardized follow-up program consists of assessments at the ages of 6, 12, and 24 months, and 5, 8, 12, 17 years, which implies that—at school age—the follow-up assessments take place at several years' intervals. In this RCT, the children in the non-intervention group received standard of care, but were invited for extra follow-up assessments 3 and 12 months after the baseline assessment ($T = 0$). Outcome measures were assessed at baseline (T0), after 3 months (T1), and after 12 months (T2) (Supporting Information). Assessments were performed by an experienced assessor blinded to group assignment. Outcomes were also analyzed blinded to group assignment. The setting was the outpatient clinic of our level III university hospital (Erasmus MC).

2.3 | Sample size calculation

Data of a previous study performed in school-aged neonatal ECMO survivors were used for the sample size calculation.[6] We hypothesized that improvement of the outcome of the Bruce protocol at T1 would be 1 standard deviation score (SDS) greater for participants in group A (compared with C) and 0.9 SDS greater for participants in group B (compared with C). We calculated that a sample size of 33 subjects per study arm would be required to obtain a power of 88% and 80% for groups A and B, respectively, with a two-sided significance level of 0.025 to adjust for the effects of multiple testing. We thus aimed to include 99 participants.

2.4 | Randomization

We used a random number generator to generate randomly ordered numbers from 1 to 99. A priori, it was established that numbers 1-33 would be allocated to group A, numbers 34-66 to group B, and numbers 67-99 to group C. These randomly ordered numbers were put into sequentially numbered (ie, 1, 2, 3 to 99), opaque, sealed envelopes by an employee who was not involved in this study. The first included participant received envelope 1, the second participant envelope 2, and so on.

2.5 | Intervention

The interventions are described in more detail in Supporting Information. This file includes a Table with detailed information on the anaerobic high-intensity interval training that was provided.

2.5.1 | Group A: standardized training program for the child plus online lifestyle coaching for child and family

The participants followed a standardized twice-weekly program of anaerobic high-intensity interval training for twelve consecutive weeks provided by a local community-based PPT. In the second half of the program, aerobic exercise training was extended.[14]

Besides, they took an online coaching program to increase physical activity, based on the Integrated Model for Change.[15]

2.5.2 | Group B: online lifestyle coaching for child and family

These participants only took the online coaching program as in group A.

2.5.3 | Group C: standard of care

Participants in the non-intervention group were routinely advised on doing physical activities and sports, supported with a hand-out.

2.6 | Measurements

All measurements are described in a short overview and in more detail in Supporting Information.

2.6.1 | Baseline data

The following baseline data were recorded: gender, age, diagnosis, gestational age, duration of artificial ventilation, and major cardiac anomalies. Furthermore, lung function[16-18] and growth[19] were assessed.

2.6.2 | Primary outcome

Exercise capacity

Exercise capacity was measured on a motor-driven treadmill, according to the Bruce protocol.[13]

2.6.3 | Secondary outcome

Motor performance

Motor performance was evaluated with the MABC-2.[20]

2.6.4 | Children's self-reports

Daily activity

Daily activity was evaluated with the daily activity questionnaire.[21]

Participation patterns, intensity, and preferences in leisure and recreation activities

The Children's Assessment of Participation and Enjoyment (CAPE) was used to identify participation patterns (diversity scores) and the intensity of leisure and recreation activities (intensity scores) from children's own perspectives. Preferences were assessed with the Preferences for Activities of Children (PAC).[22,23]

Quality of life

Perceived quality of life was measured with the Pediatric Quality of Life Inventory (PedsQL) 4.0.[24]

Perceived motor competence

PMC and importance of motor competence (IMC) were measured with the motor self-perception questionnaire.[25]

2.6.5 | Parental self-reports

Proactive coping competence

The various competencies involved in proactive coping were assessed with the Utrecht Proactive Coping Competence Inventory (UPCC).[26]

Health status

Parental health status was assessed with the Short Form-36 which contains two summary measures: physical health component summary (PCS) and mental health component summary (MCS).[27]

Online coaching program

The online coaching program recorded the number of days participants logged into this program.

2.7 | Statistical analysis

Differences in baseline characteristics between the study arms were evaluated with the Kruskal-Wallis test (continuous variables) and the chi-square test (categorical variables). The paired samples *t* test was used to test whether exercise capacity changed over time (T1-T0 and T2-T0). To test whether the secondary outcomes changed over time (T1-T0 and T2-T0), we used paired samples *t* tests or Wilcoxon signed-rank tests where appropriate. One-sample *t* tests were used to evaluate whether the normally distributed data of lung function, exercise capacity, motor performance, and health status differed from population norms (SDS = 0). We applied analysis of covariance (ANCOVA) to examine whether the study arm influenced continuous outcome variables with adjustment for the baseline measurements. This was also applied to examine whether the diagnosis influenced exercise capacity. A two-way interaction effect between the study arm and diagnosis group was added to the model if the interaction effect was statistically significant. ANCOVA was performed separately for T1 and T2. For categorical outcome variables, we used Fisher's exact tests to examine the effect of the study arm. We calculated the Pearson correlation between the change in exercise capacity and the change in motor performance or the change in number of days that participants walk or ride a bike for school-home transfers. Besides, we calculated the Pearson correlation between the change in exercise capacity and the proactive coping competence or health status of the parents. The Mann-Whitney test served to examine whether there is a difference between the intervention groups in number of days the participants logged into the online coaching program. There were some missing values in the outcomes of the statistical analyses, which were handled by performing complete case analyses. No missing values were obtained in the independent variables.

The analyses were performed with SPSS version 24. The level of significance was set to 0.05, but Bonferroni correction was applied in the ANCOVA models to adjust for multiple comparisons, resulting in an adjusted significance level of 0.025.

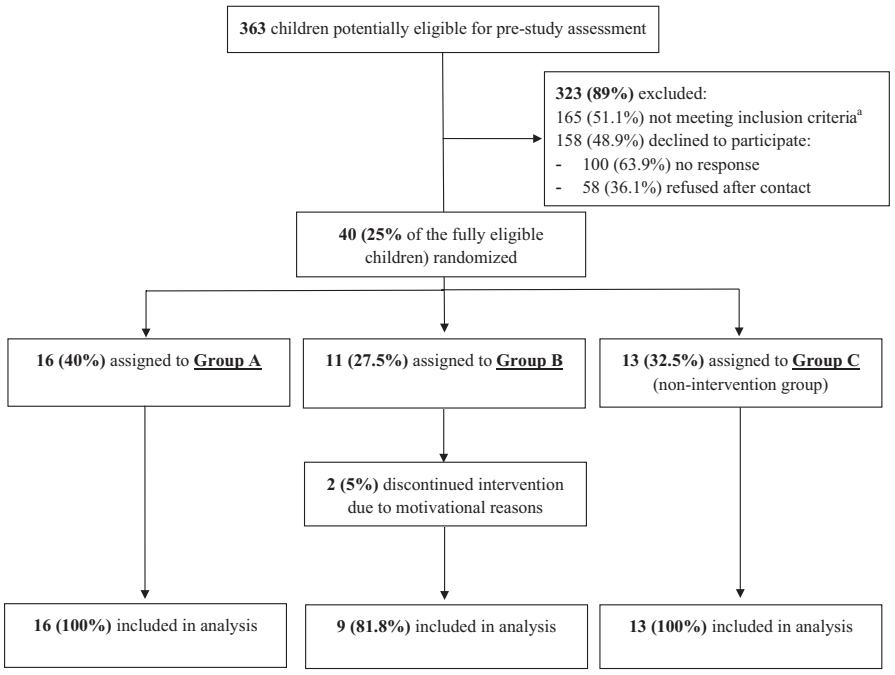

FIGURE 1 Inclusion flow diagram. [a]127 (77.0%) children had a normal exercise capacity (SDS endurance time>−1 on the Bruce protocol); 9 (5.5%) children had (severely) delayed motor function (percentile score < 6 at MABC-2) requiring intervention by an PPT; 29 (17.5%) children had inability or medical contraindication to perform the maximal cardiopulmonary exercise test.

3 | RESULTS

3.1 | Participants

We considered 363 children potentially eligible: 158 (48.9%) did not respond or refused participation after initial contact; 165 (51.1%) were evaluated but not included (Figure 1), mostly because the exercise capacity score was normal (in 77%). Eventually, 40 children participated (25% of the fully eligible children) and were randomly assigned to one of the three study arms. Only 2 (5%) participants, in group B, discontinued the intervention (Figure 1).

The PMC and IMC were filled in by all 40 participants at assessments; the other questionnaires by 38/40 at T0, 35/39 at T1, and 35/38 at T2.

Relevant baseline characteristics are listed in Table 1. Spirometry parameters were significantly below normal (all $P \leq .001$). Bronchodilation was not provided in nine participants with tracheomalacia or previous clinical deterioration after bronchodilation. Five participants (12.5%) had reversible airflow obstruction; the median (interquartile range [IQR]) relative change in forced expiratory volume in 1 second was 14 (13-16). The baseline characteristics between participants in the different study arms did not differ significantly (Table 1).

3.2 | Primary outcome

3.2.1 | Exercise capacity

Participants performed maximally on the exercise test at all assessments. Mean SDS (SD) endurance time improved significantly over time: T0 −1.91 (0.73); T1 −1.35 (0.94); T2 −1.20 (1.03): T0-T1 and T0-T2 $P < .001$. It was significantly below normal at all measurement points: all $P < .001$ and also for all study arms: $P < .05$ (Table 2).

TABLE 1 Baseline characteristics

	Total group n = 40	Group A n = 16	Group B n = 11	Group C n = 13	*P*-value[c]
Male, n (%)	22 (55.0)	12 (75.0)	5 (45.5)	5 (38.5)	0.116
Age in years	8.6 (8.2 to 11.8)	8.4 (8.1 to 10.9)	10.3 (8.3 to 12.0)	8.5 (8.2 to 11.0)	0.647
Gestational age	40.0 (37.6 to 40.9)	40.1 (39.1 to 41.2)	39.6 (36.9 to 41.0)	39.2 (36.4 to 40.2)	0.421
CAA, n (%)					
CDH without ECMO	9 (22.5)	3 (18.8)	2 (18.2)	4 (30.7)	
CDH with ECMO	3 (7.5)	2 (12.5)	1 (9.1)	—	
EA	15 (37.5)	3 (18.8)	6 (54.5)	6 (46.2)	
Resected CPAM without ECMO	1 (2.5)	1 (6.2)	—	—	
Resected CPAM with ECMO	1 (2.5)	1 (6.2)	—	—	
Tracheal stenosis with ECMO	1 (2.5)	1 (6.2)	—	—	
ECMO without CAA[a], n (%)	10 (25.0)	5 (31.3)	2 (18.2)	3 (23.1)	
Major cardiac anomaly[b], n (%)	1 (2.5)	1 (6.3)	—	—	
Duration of ventilation	7.2 (1.3 to 15.0)	9.0 (4.0 to 19.2)	2.5 (1.0 to 10.5)	11.0 (1.5 to 15.0)	0.235
Lung function before BD					
SDS FEV_1	−1.1 (−2.1 to − 0.2)[d]	−1.1 (−1.9 to − 0.6)[d]	−0.8 (−2.1 − 0.0)[d]	−1.4 (−3.0 to − 0.1)[d]	0.740
SDS FVC	−0.5 (−1.5 to − 0.1)[d]	−0.6 (−1.4 to 0.1)[d]	−0.4 (−1.5 to 0.1)[d]	−0.3 (2.1 − 0.3)[d]	0.829
SDS FEV_1/FVC	−1.0 (−1.8 to − 0.3)[d]	−1.2 (−2.2 to − 0.7)[d]	−0.5 (−1.1 to 0.3)[d]	−1.1 (−1.9 to 0.0)[d]	0.229
SDS FEF_{25-75}	−1.7 (−2.6 to − 0.5)[d]	−1.7 (−3.1 to − 1.3)[d]	−1.8 (−2.0 to − 0.4)[d]	−1.5 (−3.0 to − 0.2)[d]	0.419
SDS height	−0.1 (−0.8 to 0.4)	−0.2 (−0.8 to 0.2)	0.0 (−1.0 to 0.7)	−0.3 (−1.0 to 0.7)	0.853
SDS weight for height	0.6 (−0.6 to 1.7)	0.4 (−0.5 to 1.9)	0.7 (−0.6 to 1.2)	1.1 (−0.5 to 1.5)	0.732

Note: Data presented as median (interquartile range), unless otherwise stated. Group A = standardized training program for the child plus online lifestyle coaching for the child and its family; group B = online lifestyle coaching for the child and its family; group C = standard of care.

Abbreviations: BD, bronchodilation; CAA, congenital anatomical anomalies; CDH, congenital diaphragmatic hernia; EA, esophageal atresia; CPAM, congenital pulmonary airway malformation; ECMO, extracorporeal membrane oxygenation; FEV_1, forced expiratory volume in 1 second; FEF_{25-75}, forced expiratory flows between 25% and 75% of vital capacity; FVC, forced vital capacity; n, number of patients; SDS, standard deviation score.

[a]ECMO without CAA: meconium aspiration syndrome n = 6, persistent pulmonary hypertension of the newborn n = 2, sepsis n = 1, respiratory syncytial virus n = 1.

[b]Vitium cordis: double outlet right ventricle, open ductus Botalli with left-right shunt and atrial septal defect with surgical correction.

[c]Kruskal-Wallis test or chi-square test: difference between study arms.

[d]One-sample *t* test: significantly below normal: $P \leq .001$.

No significant differences in change in endurance time were found between the study arms (Table 3 and Figure 2). Table S3 shows the change in exercise capacity in the individual participants per study arm. The majority improved over time.

3.2.2 | Exercise capacity per diagnosis group: CAA vs neonatal ECMO without CAA

In participants with CAA (n = 30), exercise capacity improved over time: T0 −2.00 (0.79); T1 −1.44 (0.99); T2 −1.21 (1.11); T0-T1 and T0-T2 $P < .001$. The same was true for the neonatal ECMO-treated participants without CAA (n = 10): T0 −1.64 (0.48); T1 −1.11 (0.79); T2 −1.18 (0.82); T0-T1 $P = .029$ and T0-T2 $P = .030$. No significant differences in endurance time were found between the diagnosis groups at T1 (estimated mean difference SDS (95% CI): 0.18 (−0.42-0.66) $P = .660$) or T2 (0.37 (−0.16-0.91) $P = .164$). There was no significant interaction effect between the diagnosis and the study arm at T1 ($P = .286$) or T2 ($P = .305$).

3.3 | Secondary outcome

3.3.1 | Motor performance

Motor performance improved over time: mean (SD) SDS Total Impairment Score (TIS): T0 −0.25 (0.95); T2 0.14 (0.96): $P = .002$. The mean SDS TIS at T0 and T2 did not significantly differ from that in the reference population (see Table S4). We found no significant differences in motor performance between the study arms (see Table S5).

No significant correlation was found between the change (T0-T2) in mean SDS endurance time and change (T0-T2) in mean SDS TIS ($r = .104$, $P = .535$).

3.3.2 | Questionnaires

Self-reports

Daily activity. Scores on the daily activity questionnaire did not significantly change over time: T0-T1 $P = .714$; T0-T2 $P = .765$ (see Table S4). Still, at T1 and T2 more participants spent an average/or above-average amount of time (>1 h/wk) on sports (T0 44.8%, T1 57.2% and T2 65.7%). At the same time, more participants spent above-average time (>3.5 h/wk) on watching TV or playing video games (T0 23.7%, T1 34.4% and T2 34.4%). The scores were not significantly different between the study arms at all measurement points: T0 $P = .523$; T1 $P = .376$; T2 $P = .481$ (data not shown).

The change in number of days that participants walk or ride a bike for school-home transfers was significantly correlated with the change in endurance time ($r = .375$, $P = .045$).

Participation and preferences. The total diversity, total intensity, and total preferences scores had not significantly changed at T1 from T0, but had decreased significantly at T2 (see Table S4). The CAPE and the PAC results did not significantly differ between the study arms (see Table S5).

Quality of life. The scores of the physical, social, and total functioning scale increased significantly over time (see Table S4). No significant differences were found between the study arms (see Table S5).

Perceived motor competence. PMC did not significantly change over time: T0-T1 $P = .488$; T0-T2 $P = .431$ (Table S4). The study arm had no significant effect on PMC (see Table S5).

Also, IMC did not significantly change over time: T0-T1 $P = .475$; T0-T2 $P = .299$ (Table S4) and the study arm had no significant effect (see Table S5).

Parental self-reports

Proactive coping competence. The raw score (SD) on the UPCC was 2.97 (0.47) at T0, which indicates that parents considered themselves competent in proactive coping. Parental proactive coping did not influence the change in exercise capacity as this score did not significantly correlate with the change in mean SDS endurance time ($r = .044$, $P = .799$).

Scores on the UPCC did not significantly change over time (data not shown). No significant differences in the UPCC score were found between the study arms (see Table S5).

Health status. The mean (SD) SDS on the PCS was 0.40 (0.66) and on the MCS 0.08 (0.71) at T0. The mean SDS PCS was significantly higher than in the reference population at all measurement points, and the mean (SD) SDS MCS was normal at all points (data not shown). Parental health status did not influence the change in exercise capacity as parental health status and the change in mean SDS endurance time of the participants were not significantly correlated (PCS: $r = -.095$, $P = .580$; MCS: $r = .103$, $P = .551$).

Parental health status did not change significantly over time (data not shown). No significant differences were found between the study arms on the scores of the PCS and MCS (see Table S5).

Online coaching program. No significant difference was found between groups A and B in the number of days

TABLE 2 Primary outcome: SDS endurance time over time

	Total group	Group A	Group B	Group C
T0 Mean (SD) SDS	n = 40 −1.91 (0.73)[a]	n = 16 −1.84 (0.69)[a]	n = 11 −1.63 (0.46)[a]	n = 13 −2.23 (0.89)[a]
T1 Mean (SD) SDS	n = 39 −1.35 (0.94)[a]	n = 16 −1.23 (0.95)[a]	n = 10 −1.16 (1.06)[b]	n = 13 −1.66 (0.84)[a]
T2 Mean (SD) SDS	n = 38 −1.20 (1.03)[a]	n = 16 −1.17 (1.14)[a]	n = 9 −0.88 (1.17)	n = 13 −1.45 (0.77)[a]

Note: T0 baseline assessment; T1 assessment after 3 mo; T2 assessment after 12 mo. Group A = standardized training program for the child plus online lifestyle coaching for the child and its family; group B = online lifestyle coaching for the child and its family; group C = standard of care.

Abbreviations: SD, standard deviation; SDS, standard deviation score.

[a]significantly below the norm (compared with SDS = 0): $P \leq .001$ one-sample *t* test.

[b]significantly below the norm (compared with SDS = 0): $P < .05$ one-sample *t* test.

TABLE 3 Estimated mean differences SDS in change in endurance time between study arms

	Group A vs Group C	Group B vs Group C
T1-T0 Estimated mean difference SDS (95% CI)[a]	0.06 (−0.45 to 0.58) $P = .802$	−0.10 (−0.70 to 0.50) $P = .733$
T2-T0 Estimated mean difference SDS (95% CI)[a]	−0.13 (−0.68 to 0.42) $P = .635$	−0.18 (−0.84 to 0.48) $P = .587$

Note: T0 baseline assessment; T1 assessment after 3 mo; T2 assessment after 12 mo. Group A = standardized training program for the child plus online lifestyle coaching for the child and its family; Group B = online lifestyle coaching for the child and its family; Group C = standard of care.

Abbreviations: CI, confidence interval; SD, standard deviation; SDS, standard deviation score.

[a]Based on an analysis of covariance model adjusted for baseline measurement.

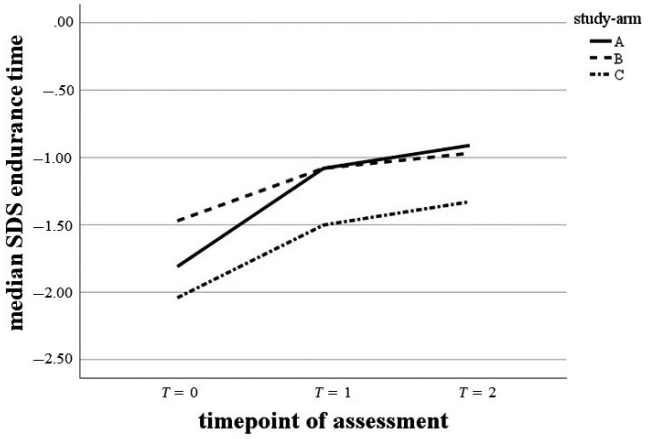

FIGURE 2 Median SDS endurance time over time of the study arms. Study arm A = standardized training program for the child plus online lifestyle coaching for the child and its family; study arm B = online lifestyle coaching for the child and its family; study arm C = standard of care. T0 baseline assessment; T1 assessment after 3 mo; T2 assessment after 12 mo. Abbreviation: SDS, standard deviation score

participants logged into the online coaching program (group A: median (IQR) number of days: 20 (10-45); B: 14 (9-24), $P = .256$).

Inclusion stop. The calculated sample size was not achieved (Figure 1). Active nationwide recruitment of participants with extension of the inclusion period had insufficient effect. From March 2014 onwards, potentially eligible children treated in Radboud University MC-Amalia Children's Hospital (Nijmegen, the Netherlands) were invited as well. Almost half of the patients and their parents (43/98 44%) responded, and thirty of them (31%) provided written informed consent. After this nationwide recruitment, twelve of the thirty patients (40%) who had provided written informed consent met the inclusion criterion of a score of at least 1 standard deviation (SD) below the norm on the maximal CPET and participated in the trial. As we did not expect a higher inclusion rate within the next years, the principal investigator stopped the inclusion after almost 3 years, in October 2015. This decision to stop was not influenced by preliminary results as we analyzed our data after the last included participant had finished the program.

4 | DISCUSSION

In this RCT, we showed that impaired exercise capacity improved in children with persistent respiratory morbidity following neonatal surgery for CAA and/or neonatal

ECMO. Improvement was not only seen in the intervention groups, but also occurred in the non-intervention group. Motor performance and self-reported physical and social functioning improved also in all three study arms.

The parents of our participants reported normal health status and normal competence in proactive coping. Their well-developed proactive coping competence may have contributed to change from a semi-active to an active lifestyle, including physically active school-home transfers, and hence to the improvement of exercise capacity in participants of all study arms.

Studies in children with other chronic conditions, such as cardiac anomalies, also found that training programs increased exercise tolerance.[9,10,28] However, these studies did not include controls. RCTs on improvement of exercise capacity in children are scarce: contradictory results have been reported for children with acute lymphatic leukemia.[29,30] Comparison with the present study is difficult due to differences in study population, intervention type, and primary outcome parameter. Interval training has been proven effective in ambulatory children with spina bifida.[31]

The CAPE scores in our study were in concordance with those of healthy Dutch children.[23,32] Therefore, it can be argued whether participation in our population would improve. Moreover, this questionnaire was developed in rehabilitation settings and might be more suitable for children with more severe physical disabilities, such as cerebral palsy.

Strengths of our study are the randomized controlled study design with only two dropouts from online coaching. The wide range in the use of the online coaching program suggests that not everyone adhered to this intervention. Future interventions should probably focus on a peer support system. The lack of peer support system use is a commonly reported problem in online interventions.[33]

The question is whether the lack of a positive effect of the interventions can be explained by study limitations. For one, the calculated sample size was not achieved despite nationwide recruitment, so that the group sample sizes were relatively small. Despite the low recruitment rate, the primary outcome exercise capacity improved significantly over time. The low recruitment rate increased the probability of not finding significant differences between the study arms. Besides, it is assumable that participation in this study created awareness of reduced exercise capacity and therewith lifestyle changes by the participants and their parents of the non-intervention group, a phenomenon known as the Hawthorne effect.[34] Also, the follow-up assessments after 3 and 12 months, which in our regular follow-up program are scheduled only after 4 to 5 years, probably contributed to this phenomenon. The positive significant correlation between the change in number of days that participants walk or ride a bike for school-home transfers and the change in endurance time, also in the non-intervention group, supports this effect. Secondly, the used questionnaires may not have been sensitive enough to evaluate changes in daily activities, especially if relatively young children have to recall events in the past week (daily activity questionnaire) or even in the past 4 months (CAPE). Moreover, children tend to overrate physical activities.[35] Therefore, our data do not allow concluding what factors contributed to improvement of exercise capacity. Thirdly, we refrained from using an activity tracker to measure daily activities. At the start of this study, the available equipment was not suitable to reliably record other physical activities than walking and running in children, as cycling and roller skating.[36] For future research, the use of activity trackers should be considered. Fourthly, it can be debated whether the interventions were optimal for our population. High-intensity training has been shown to be beneficial in RCTs with healthy or obese children,[37,38] and corresponds with the intensity of physical activities in the everyday life of school-aged children. As the use of the online coaching program was subject to variability, and we only had dropouts in group B, we assume that online individual coaching will only be beneficial for selected families.

5 | PERSPECTIVE

In previous studies, we showed that children born with major anatomical foregut anomalies and/or treated with ECMO are at risk for long-term respiratory morbidity,[2,3] reduced exercise capacity,[4] and even deterioration of exercise capacity.[6,39] In this RCT, we aimed to evaluate whether these children's exercise capacity can be improved. We showed that exercise capacity improved significantly over time, irrespective of the intervention. This implies that residual morbidities are not the only factor responsible for reduced exercise capacity. Enhanced awareness of impaired exercise tolerance might have resulted in improvement over time in all three study arms. Parental proactive coping competence can stimulate a more physically active lifestyle in their child. Our observations have implications for the counseling of children and their parents. We speculate that parents of children who survived neonatal critical illness consider their child more vulnerable than the parents of healthy children and may therefore be reluctant to encourage physical activities in childhood.[40] Close monitoring and counseling from an early stage onwards could improve physical activity and should be part of routine care.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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