EXERCISE IN PEDIATRIC MEDICINE

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EXERCISE IN PEDIATRIC MEDICINE

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EDITORIAL
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Editorial: Exercise in Pediatric Medicine

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Keywords: fitness, exercise is medicine, exercise testing, exercise training, sport, physical activity, health promotion

Editorial on the Research Topic

Exercise in Pediatric Medicine

Physical activity and exercise have a high potential in the treatment and prevention of many chronic medical conditions (CMC). Recent statistics from the Netherlands indicate that 1 in 10 children have a CMC, with a higher number in North America, where about 1 in 6 children are estimated to have a CMC. These children and their families often live complicated lives and are, in general, more frequent users of the healthcare system. Participation in organized and non-organized physical activities and sports is often more challenging for these children, as illustrated in the first ever Netherlands Physical Activity Report Card + for youth with a CMC (Burghard et al.).

Sufficient, age-appropriate levels and types of activities are important for healthy social, psychological, and physical development. The complicated relationship between physical activity and motor competence in pre-schoolers was also reported by Schmutz et al..

Alias et al. showed that the majority of children with Acute Lymphoblastic Leukemia (ALL) had low levels of daily physical activity after intensive chemotherapy. The authors recommend that physical activity should thus be promoted during and after cessation of ALL treatment to prevent long-term health risks and improve the overall quality of life (Alias et al.).

In subjects with clinically stable Cystic Fibrosis (CF), expiratory muscle strength might be a limiting factor for exercise performance. Sovtic et al. found an association between this factor and a decrease in exercise performance. They suggest that an increase in expiratory muscle strength might result in the improvement of exercise tolerance, a subject that needs further research (Sovtic et al.).

INTERVENTION PROGRAMS

There are several publications on this topic describing intervention studies. We have to be aware that performing intervention studies on a group of children with CMC is often challenging and very difficult. The authors of these studies are congratulated on their work. The inclusion of "real world" interventions and web-based interventions are also very welcome.

Lakes et al. described the effects of therapeutic ballet intervention in children with Cerebral Palsy. They observed increased physiological and cognitive functions in the children included in the study (Lakes et al.)

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Another report by Gitimoghaddam et al. described the effects of a pilot study investigating gymnastic-based movement therapy in children with neurodevelopmental disabilities. The study was undertaken in a natural environment and discusses the challenges faced by researchers investigating this kind of program (Gitimoghaddam et al.).

Zwinkels et al. reported that anaerobic performance and fat mass improved following a 6 month school-based sports program in children with CMC. These effects are promising for long-term fitness and health promotion because school-based interventions eliminate many barriers to the implementation of sports programs in this population (Zwinkels et al.).

Morales et al. performed a secondary analysis to identify factors that explain training effects in improvement in pediatric cancer patients and observed considerable individual variability. The biggest improvements were found in those with the lowest baseline fitness levels. This study is the first attempt to personalize exercise prescription in pediatric cancer patients (Morales et al.).

Lu et al. undertook a school-based exercise intervention program for children with asthma from a predominantly economically disadvantaged and minority population. They reported good feasibility and adherence to the program. Furthermore, the intervention was effective in improving aerobic fitness, body composition, asthma quality of life, and lipid outcomes. These data indicate the need for a larger multicenter trial designed to study "exercise in pediatric medicine" in this population (Lu et al.).

Another study by Atalla et al. presented real-world data on the intervention effects of physical activity and sedentary behavior among 3592 young people in a Brazilian city. Although there was no overall effect, physically inactive individuals had increased PA levels, and overweight participants with obesity experienced a reduction in BMI z-score. This finding reiterates the value of these types of interventions in increasing the health of a large group of children (Atalla et al.).

A novel way to deliver exercise interventions is by using a tele-exercise platform. Chen et al. reported on the use of an online platform to deliver supervised virtual group exercise in children with Cystic Fibrosis. They showed that the children had a positive experience with optimal participation and no risk for cross-infection: a very promising approach for delivering therapeutic exercise children with Cystic Fibrosis (Chen et al.).

Lastly, a contribution to this issue discusses the design of a study to investigate the effects of a web-based exercise intervention in children with congenital heart disease (Meyer et al.). This is also a promising approach to deliver therapeutic exercise to children who often have to travel a long distance to the hospital. Web-based interventions are more feasible in these populations than center-based interventions (Meyer et al.).

SPORTS

Several Studies Reported on Sport-Specific Topics

DiCesare et al. found that sport-specialized female athletes have biomechanical changes during puberty that are indicative of potentially compromised neuromuscular control that may increase their risk of injury. Consideration of maturation status may be an important factor in assessing the injury risk profiles of adolescent athletes who specialize in a sport (DiCesare et al.).

Lammers et al. investigated exercise-induced bronchoconstriction (EIB) in a pediatric population. They reported that predictions of EIB by pediatricians are sensitive but not specific and that the prediction of EIB severity was poor, with very important findings for awareness of disease management in children with EIB (Lammers et al.).

Other children with exercise-induced complaints are patients with exercise-induced laryngeal obstruction. Olin describes the preferred diagnostic and therapeutic approaches in a review article. As current diagnostic technology has considerably improved in recent years, more evidence-based approaches to treatment are needed (Olin).

Many pediatric patients with CMC are receiving suboptimal treatment in physical activity and fitness because many clinicians might not have adequate knowledge when it comes to physical activity counseling, testing, and training. With this Research Topic in Frontiers in Pediatrics, we hope that a part of this gap is filled.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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Effects of a School-Based Sports Program on Physical Fitness, Physical Activity, and Cardiometabolic Health in Youth With Physical Disabilities: Data From the Sport-2-Stay-Fit Study

Maremka Zwinkels[1,2], Olaf Verschuren[1], Astrid Balemans[1,3], Kristel Lankhorst[4], Saskia te Velde[4], Leendert van Gaalen[4], Janke de Groot[4,5,6], Anne Visser-Meily[1,7] and Tim Takken[6]*

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Objective: To investigate the effects of a school-based once-a-week sports program on physical fitness, physical activity, and cardiometabolic health in children and adolescents with a physical disability.

Methods: This controlled clinical trial included 71 children and adolescents from four schools for special education [mean age 13.7 (2.9) years, range 8–19, 55% boys]. Participants had various chronic health conditions including cerebral palsy (37%), other neuromuscular (44%), metabolic (8%), musculoskeletal (7%), and cardiovascular (4%) disorders. Before recruitment and based on the presence of school-based sports, schools were assigned as sport or control group. School-based sports were initiated and provided by motivated experienced physical educators. The sport group (n = 31) participated in a once-a-week school-based sports program for 6 months, which included team sports. The control group (n = 40) followed the regular curriculum. Anaerobic performance was assessed by the Muscle Power Sprint Test. Secondary outcome measures included aerobic performance, VO_2 peak, strength, physical activity, blood pressure, arterial stiffness, body composition, and the metabolic profile.

Results: A significant improvement of 16% in favor of the sport group was found for anaerobic performance (p = 0.003). In addition, the sport group lost 2.8% more fat mass compared to the control group (p = 0.007). No changes were found for aerobic performance, VO_2 peak, physical activity, blood pressure, arterial stiffness, and the metabolic profile.

Conclusion: Anaerobic performance and fat mass improved following a school-based sports program. These effects are promising for long-term fitness and health promotion, because sports sessions at school eliminate certain barriers for sports participation and adding a once-a-week sports session showed already positive effects for 6 months.

Clinical Trial Registration: This trial was registered with the Dutch Trial Registry (NTR4698).

Keywords: sports, physical fitness, physical activity, health promotion, children and adolescents, physical disability, chronic disease

INTRODUCTION

Daily physical activity is beneficial for all children and adolescents. For those with physical disabilities, similar physical activity recommendations account (1). In addition, exercise interventions have shown that youth with physical disabilities can improve physical fitness levels (2–7) and decrease cardiometabolic risk factors (4–7). Moreover, they have lower levels of physical fitness and participate less in competitive and recreational sports compared to peers who develop typically (3, 8). Since limited physical ability can interfere with being physically active in daily life and consequently affect their health later in life, maintaining sports participation and adequate performance-related fitness levels is especially important in this population (9, 10).

For youth with a physical disability, it seems more difficult to participate in sports and physical activities when compared to typically developing peers (11). In 2011, only 26% of Dutch children and adolescents with a physical disability from schools for special education participate in sports at least once a week compared to 71% in youth without physical disabilities (12). Reasons for this lower sports participation are being physically active is more challenging because of their disability, lack of trained support personnel, transportation problems, lack of acceptance, and no sports clubs in the neighborhood (13–15). Most of these barriers to be physical active can possibly be eliminated when a sports program is provided at school in the immediate after-school hours. This setting offers a familiar environment with supported trainers, acceptance, and no additional transportation except a postponed pickup from school.

In addition, a recent study has proposed the need for school-based initiatives, since their integrative approach is effective and even targets the least active children (16). Recent work in the typically developing population showed positive but inconsistent effects in increasing physical activity with after-school interventions (17, 18). Interventions that lasted more than 12 weeks and that focused solely on increasing physical activity by providing a sports program were most effective (18). According to the exercise principles, a training frequency of at least three sessions a week is recommended to improve cardiorespiratory fitness in youth who are typically developing (19, 20). By contrast, for children and adolescents with cerebral palsy (CP) who are very deconditioned, two sessions a week are also possible to induce or maintain effects (1). On the other hand, from a parents' perspective, they consider sports participation of once a week to be sufficient (21). Parents need to prioritize the frequency of sports participation with the demands of everyday life (22). In a recent qualitative research, all parents indicated that the intensity or frequency of a sports program to improve fitness levels was not of importance for them. They emphasized the importance of sports as "being active," having fun, and socialization (21).

For improving fitness levels, there is a discrepancy between exercise recommendations and feasibility in daily life for youth with disabilities and their parents. Providing a once-a-week school-based sports program can relatively easily be implemented and increase children's level of sports participation. However, it is unknown whether once a week is beneficial for fitness and health purposes in this population. The current study, denoted as the Sport-2-Stay-Fit study, will investigate the effects of a school-based once-a-week sports program on physical fitness, physical activity, and cardiometabolic health in children and adolescents with a physical disability.

METHODS

Design

The Sport-2-Stay-Fit study is a controlled clinical trial. The study was conducted at four schools for special education in The Netherlands between September 2014 and July 2016. In a previous publication, we described the study design extensively (23). The results of the school-based sports program will be published in two separate papers where this paper focuses on the fitness and health aspects. Both ethics approval and administrative site approvals were granted by the Medical Ethical Committee of UMC Utrecht in The Netherlands (#14-118). This trial was registered with the Dutch Trial Registry (NTR4698).

Participants

Children and adolescents with a physical disability were recruited *via* four schools for special education in The Netherlands. These schools, dedicated to youth with physical disabilities, have similar learning objectives as regular schools, but the children receive additional attention and support. Children and adolescents were screened by a physical therapist, a physical educator, or a physician for eligibility. Inclusion criteria were (1) a chronic disease or a physical disability; neuromuscular, musculoskeletal, metabolic, or cardiovascular disorder, (2) aged between 6 and 19 years, (3) participation in sports less than twice a week during leisure time in the preceding 3 months or advised to participate in sports by their physical therapist or a physician (4) understands simple instructions, and (5) were expected to be able to perform the physical fitness tests. Exclusion criteria were (1) having a progressive disease, (2) using a powered wheelchair for sport purposes, (3) participation in other research that could possibly influence current results. In addition, all parents and participants from 12 years of age provided informed consent prior to study initiation.

Procedure

Before recruitment, schools (n = 4) were assigned as sport or control site. This was directed by the current presence of school-based sports initiated by motivated physical educators. Schools that already provided (n = 1) or intended to provide (n = 1) school-based sports in addition to the regular curriculum were assigned sport sites. Otherwise, schools were assigned as control sites (n = 2). In case school-based sports had been provided before the start of the study, children and adolescents were only included if they had not participated during the preceding 3 months. Regardless of the group enrolled, all participants followed a high-intensity interval training (HIT) for 8 weeks as an initial start-up for their fitness level and to get familiarized with exercise (23). In this way, all participants knew in what group they would be enrolled: HIT and school-based sports (i.e., sport group) or HIT and control (i.e., control group). The focus of the current study is the school-based sports program, results of the HIT are described elsewhere (24). Outcome measures were assessed at baseline (T0), after 8 weeks of HIT (T1), and at completion of 6-months intervention (T2). Similar outcome measures were evaluated at T1 and T2 except for physical activity. Because no short-term effect was expected on physical activity following HIT (T1) (25, 26), the baseline physical activity (T0) was used to analyze the effectiveness. All outcome measures across all schools were assessed by the same trained researcher together with research assistants. The assessors were not blinded for group allocation.

Intervention

All participants performed HIT for 8 weeks, twice a week for 30 min, containing 8–12 series of 30-s all-out exercises. Detailed information about the training schedule is described elsewhere (23). After 8 weeks, the sport group commenced with the school-based sports program. The program was provided once a week for 45 min by an experienced physical educator at school in addition to the regular physical education schedule. In contrast to the regular physical education where half of the time is spent on skill practice, cooperation, and management (27), sport is about moving more intensively. No instructions were given on exercise intensities, but children and adolescents were encouraged to be physically active, play the game, and have fun (21). The content of the lesson was adapted by the physical educator based on the children's skills and cognitive level. The sports program included, but was not restricted to, soccer, (wheelchair) basketball, (wheelchair) hockey, and/or easy administered games like playing tag. The presence of the participants was documented every session.

Outcome Measures

Since intermittent bouts of intense exercise reflect children's daily activity pattern, the primary outcome was anaerobic performance (28). Outcome measures were tested during school hours, except from physical activity, and were subdivided into four different occasions within 2 weeks: (a) height, weight, anaerobic fitness, and strength, (b) aerobic fitness, (c) blood pressure, arterial stiffness, and body composition, and (d) metabolic profile.

PHYSICAL FITNESS

Anaerobic Fitness

Anaerobic performance was measured with the Muscle Power Sprint Test either while running, walking, or propelling a manual wheelchair as described previously (29, 30). This is an intermittent sprint test consisting of three or six 15-m sprints with a standardized rest of 10 s between sprints. Participants who were ambulatory had to complete six 15-m runs, while wheelchair users completed three 15-m sprints at a maximal pace. Both peak power (PP) and mean power (MP) were calculated from the results of the sprints. To assess agility, time was recorded during a 10 × 5-m sprint test where children or adolescents had to sprint 10 times as fast as possible between two lines of 5 m apart without rest (29).

Aerobic Fitness

For aerobic fitness, both performance (achieved shuttles) and VO_2 peak were measured during a 10-m shuttle run/ride test (SRT) (31, 32). The SRT is an incremental exercise test where participants had to adjust their running, walking, or wheelchair propulsion pace to the beep signals until they failed to reach the line twice within one level. The test protocol was selected based on their level of mobility as described previously (23). During the SRT, a calibrated mixing chamber Cortex Metamax 3X (Samcon bvba, Melle, Belgium) was used to measure VO_2 peak. Metabolic stress test software (Metasoft Studio) was used to measure oxygen uptake (VO_2), carbon dioxide production (VCO_2), peak heart rate (HR), and respiratory exchange ratio (RER) = (VCO_2/VO_2). Each test lasted until exhaustion. To determine whether a subject reached their maximal effort, two out of the following three criteria had to be achieved: HR $\geq$ 180 bpm, RER $\geq$ 1.00 at peak exercise, or subjective signs of intense effort, such as sweating, facial flushing, or a clear unwillingness to continue.

Strength

Grip strength was measured using a hand-held dynamometer (CITEC, CIT Technics, Haren, The Netherlands). The mean grip strength was calculated out of three attempts with the preferred hand. To assess the explosive strength, either the standing-broad jump or the one-stroke push was performed in those who were ambulatory and propelling a wheelchair, respectively (33). The standing-broad jump referred to the distance jumped with two legs together, while the one-stroke push referred to the distance covered in their wheelchair by one push.

PHYSICAL ACTIVITY

The total physical activity was measured objectively using the Activ8 activity monitor (2M Engineering, Valkenswaard, The Netherlands). The system measures acceleration in three planes and is valid to detect six types of activities in persons who are ambulatory: lying, sitting, standing, walking, cycling, and running (34). Participants wore the Activ8 for 7 consecutive days. The device was fixed with Tegaderm™ waterproof skin tape on the ventral side of the upper leg allowing participants to take a shower or a swim. At least two school days with a minimum of 600 min wear time was needed for a representative weekday. For weekend days, at least 1 day of 600 min wear time was required (35). The time spent lying and sitting (sedentary time) and the time spent standing, walking, cycling, and running (active time) were calculated in minutes. Children and adolescents who were manual wheelchair-using ($n = 9$) wore the device as well. However, we omitted the data from the analyses since this device has not yet been validated for wheelchair users.

CARDIOMETABOLIC HEALTH

Cardiovascular

Both resting blood pressure and arterial stiffness were noninvasively measured with the Arteriograph (Litra BV, Amsterdam, The Netherlands). The measurement was performed in a supine position using an inflatable cuff on the right upper arm. Participants rested supine for 10 min prior to the recording, and they were asked not to move or talk during the test. Arterial stiffness contained two independent values: pulse wave velocity (PWV) and the augmentation index (AIx). The PWV was measured as the speed at which an aortic pulse travels; increased speed indicates stiffer arteries. The AIx provides information on the peripheral resistance of the endothelial vessels; increased index indicates a higher peripheral resistance. To control for differences in sex and age, *Z*-scores of AIx were calculated according to reference values of Hidvégi et al. (36).

Metabolic

Height and weight were measured to determine body mass index (BMI). A detailed description has been described previously (23). To control for differences in age, *Z*-scores of BMI were calculated according to Dutch reference values (37). For waist and hip circumference, a horizontal measure was taken at the umbilicus and trochanter major, respectively. Fat mass was measured in a supine position with bioelectrical impedance analysis, using the Bodystat Quadscan 4000 (Euromedix, Leuven, Belgium). To determine the metabolic profile, a finger puncture was performed. This was an optional measurement, and consent was asked separately to parents and participants from 12 years of age. During this procedure, blood was drawn through a finger puncture from which the total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), fasting glucose, and triglyceride were analyzed. The analyses were performed using a Cholestech LDX analyzer (Mediphos Medical Supplies BV, Renkum, The Netherlands). All participants were instructed not to eat or drink for 3 h prior to this procedure. Before the finger puncture, participants were asked about the fasting period, and if possible, the measurement was postponed. Otherwise, only total cholesterol, LDL, HDL, and triglyceride data were used for analysis (38).

DATA ANALYSIS

A sample size calculation showed that 32 participants per subgroup were needed to detect a 20% difference between groups in anaerobic performance (23). Statistical analysis was performed using SPSS for Windows (version 21.0, SPSS Inc., Chicago, IL, USA) with a statistical significance level of $p = 0.01$ to correct for testing multiple hypotheses. Descriptive statistics were presented as means and standard deviation. To determine the intervention effect, linear regression analyses were performed according to the intention to treat principle. In the linear regression analyses, the outcome measures at $T2$ were the dependent variables, with group allocation and the measured outcome at $T1$ as independent variables. Since participants were not randomly allocated, the outcome measures at $T1$ were included in the analyses to correct for potential baseline differences between groups. In addition, baseline differences in subject characteristics were checked. Subgroup response patterns on age, sex, and mobility level were analyzed and included as confounders in the analyses when they changed the intervention effect. Besides, response patterns of the different schools were analyzed and included as a cluster variable if they changed the intervention effect. Data were graphically checked for normal distribution using residual plots. Variables with non-normally distributed residuals were logarithmically transformed prior to linear regression, after which the results were transformed back, providing a between-group regression coefficient which has to be interpreted as a ratio. The residuals of all variables were normally distributed after logarithmic transformation. Since the dataset was expected to contain incomplete data for some variables, we used multiple imputations to create and analyze 10 imputed datasets. The imputation model included the outcome measures and sex, height, age, weight, and mobility level in the regression model. Regression coefficients (β) and the 95% confidence interval were reported for the regression model. For clinical purposes, the estimated marginal means of both groups, the mean difference, and relative effect (%) were calculated. Linear regression analyses were both performed on the original data and multiple imputation data. Since both models resulted in similar effects, only the multiple imputation models are shown here.

RESULTS

A total of 138 participants were invited to participate between September 2014 and November 2015 of whom 78 decided to participate. Seventy-one children and adolescents participated in the current study (**Table 1**). Due to practical reasons, one participant of the sport group was not able to attend the sports program and was therefore assigned to the control group. Prior to the start of the study, sports participation at $T0$ did not differ between the sport [1.1 (1.1) times a week] and control group [0.8 (0.8) times a week] ($p = 0.285$), whereas at $T2$ sports participation differed significantly between the sport [2.1 (1.0) times a week] and control group [0.9 (0.8) times a week] ($p < 0.001$).

Following the school-based sports program, three participants dropped out and some participants did not complete all assessments as illustrated in **Figure 1**. According to the finger puncture, 74% and 85% of the participants provided consent for the sport and control group, respectively. All measured data at *T*1 and *T*2 are shown for physical fitness and physical activity in **Table 2** and for cardiometabolic health in **Table 3**.

Adherence to the sports program was on average 86%, with children and adolescents attending on average 14.4 (4.1) with a range of 5–20 sport sessions. To illustrate, five adolescents attended less than 75% of the program, due to surgery ($n = 1$), other priorities ($n = 1$), and truancy ($n = 3$). No adverse events related to the sports program were reported. Time between measurements was 6.6 (1.3) months with a range of 4.6–10.6 months. The sport group was measured within 2 weeks after finishing the sports program. The huge range between measurements is due to participants of the control group who left school during the study period and agreed to return to finish the assessments on a different occasion.

TABLE 1 | Characteristics of participants.

	Sport (n = 31)	Control (n = 40)
Age (years), mean (SD)	13.4 (3.0)	14.0 (2.8)
Sex, *n* male (%)	23 (74)	16 (40)
Height (cm), mean (SD)	156.4 (17.5)	157.1 (10.4)
Weight (kg), mean (SD)	54.4 (20.8)	56.9 (18.6)
Level of mobility, *n* (%)		
Able to run	22 (71)	15 (38)
Able to walk	6 (19)	19 (47)
Wheelchair user	3 (10)	6 (15)
Diagnoses, *n* (%)		
Neuromuscular	22 (71)	35 (87)
– *Cerebral palsy*	10 (32)	16 (40)
– *Spina bifida*	–	5 (12)
– *Psychomotor retardation*	4 (13)	5 (12)
– *Acquired brain injury*	2 (97)	1 (3)
– *Other*	6 (19)	8 (20)
Cardiovascular	2 (6)	1 (3)
Metabolic	4 (13)	2 (5)
Musculoskeletal	3 (10)	2 (5)

EFFECT OF INTERVENTION

Physical Fitness

As shown in **Figure 2A** and **Table 4**, a significant effect in favor of the sport group was found for anaerobic performance on MP ($\beta = 1.16$, IC = 1.05–1.28[1]) and PP [$\beta = 1.15$, IC = 1.04–1.27 (see text footnote 1)]. The between-group difference was 23 W (16%) and 25 W (15%) for MP and PP, respectively. No significant effect was observed for agility (**Table 4**). In addition, no intervention effect was demonstrated for aerobic performance (**Figure 2B**), VO_2 peak, and strength (**Table 4**).

Physical Activity

At baseline, no seasonal differences were found among participants measured in the autumn, winter, and spring. Sports participation was increased during the school-based sports program in the sport group with 1.2 (0.9) times a week compared to 0.1 (0.9) times a week in the control group ($p < 0.001$). Between-group differences showed no intervention effect on physical activity.

[1]Regression coefficients should be interpreted as a ratio as it was logarithmically transformed.

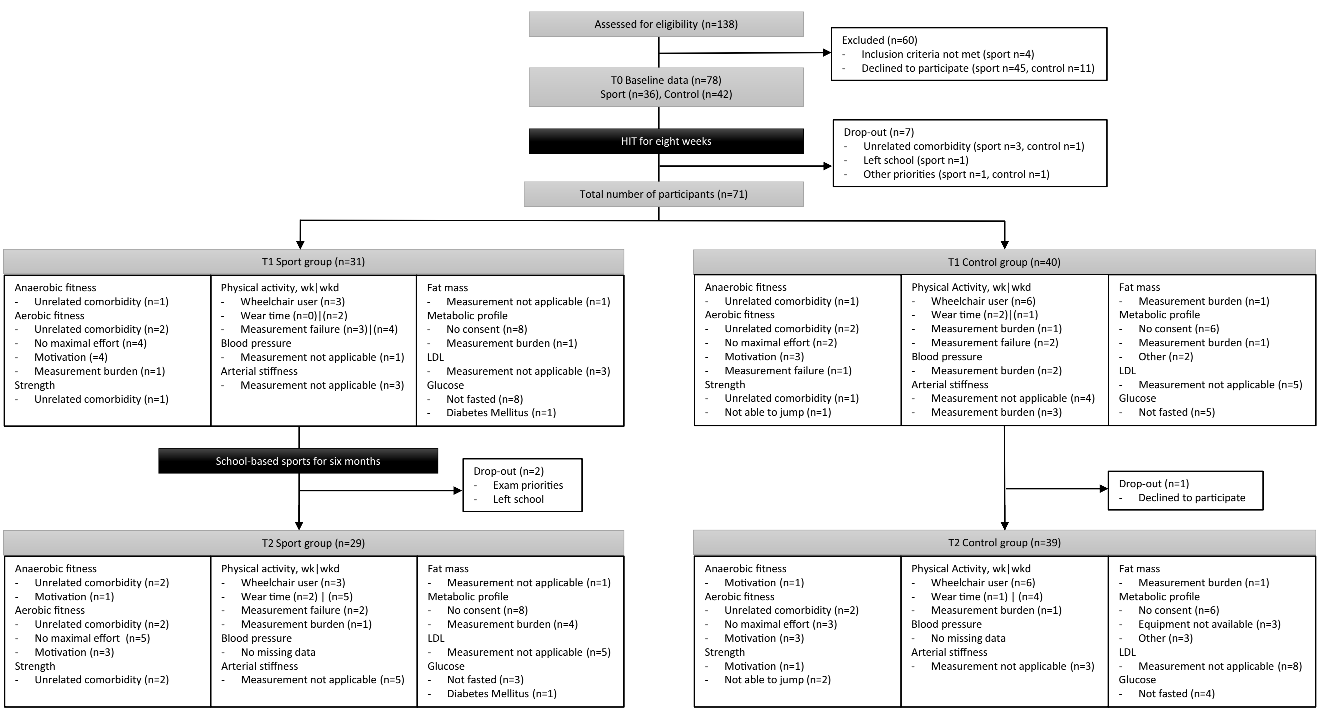

FIGURE 1 | A flowchart from initial inclusion to intervention and reasons for missing data per outcome measure.

TABLE 2 | Mean (SD) of physical fitness and physical activity before (*T*1) and after (*T*2) the school-based sports program.

		*T*1				*T*2			
		n	**Sport Mean (SD)**	***n***	**Control Mean (SD)**	***n***	**Sport Mean (SD)**	***n***	**Control Mean (SD)**
Anaerobic fitness	Anaerobic performance—MP (W)	30	247.9 (188.7)	39	144.0 (107.2)	26	279.2 (208.7)	38	146.3 (109.5)
	Anaerobic performance—PP (W)	30	300.0 (226.5)	39	167.3 (128.3)	26	326.7 (227.3)	38	168.7 (124.7)
	Agility (s)	30	24.6 (6.9)	39	28.4 (7.0)	26	25.2 (8.4)	38	28.2 (6.9)
Aerobic fitness[a]	Aerobic performance (shuttles)	21	13.5 (3.7)	33	14.0 (4.2)	19	12.6 (3.4)	31	13.6 (4.6)
	VO_2 peak (ml/kg/min)	20	42.6 (8.8)	32	34.6 (7.0)	19	37.9 (7.2)	31	34.3 (8.0)
	VO_2 peak (ml/fat free mass/min)	20	58.2 (9.7)	32	49.9 (9.4)	19	51.9 (6.1)	31	50.0 (9.9)
	HR peak (bpm)	20	194 (11)	32	184 (16)	19	192 (11)	31	185 (14)
	RER	20	1.11 (0.11)	32	1.10 (0.09)	19	1.11 (0.07)	31	1.11 (0.10)
	VE peak (l/min)	20	79.6 (35.6)	32	69.5 (28.0)	19	72.9 (33.7)	31	70.2 (27.2)
Strength	Grip strength (*n*)	30	153.1 (88)	38	144.7 (57.6)	27	147.8 (84.8)	38	149.2 (56.2)
	Standing-broad jump (cm)[b]	27	110.9 (40.6)	31	71.9 (28.5)	24	110.0 (40.3)	30	75.8 (23.5)
	One-stroke push (m)[c]	3	7.65 (0.83)	6	6.78 (2.50)	3	6.00 (0.97)	6	6.21 (2.09)
Physical activity[b]	Sedentary time—week (min)	25	588.8 (90.4)	29	554.1 (101.9)	21	551.1 (79.2)	31	562.0 (85.1)
	Sedentary time—weekend (min)	22	518.3 (112.0)	28	540.1 (85.1)	18	494.9 (151.8)	28	544.5 (106.1)
	Active time—week (min)	25	271.7 (63.3)	29	259.2 (104.4)	21	302.1 (69.8)	31	282.1 (83.6)
	Active time—weekend (min)	22	281.7 (86.3)	28	229.1 (80.9)	18	301.7 (117.1)	28	245.9 (90.3)

MP, mean power; PP, peak power; VO_2, oxygen uptake; HR, heart rate; RER, respiratory exchange ratio; VE, ventilation.
[a]*Included only participants who reached maximal effort.*
[b]*Included only participants who were ambulatory.*
[c]*Included only wheelchair users.*

TABLE 3 | Mean (SD) of cardiometabolic health before (*T*1) and after (*T*2) the school-based sports program.

			*T*1				*T*2			
		Ref[a]	***n***	**Sport Mean (SD)**	***n***	**Control Mean (SD)**	***n***	**Sport Mean (SD)**	***n***	**Control Mean (SD)**
Cardiovascular	Systolic blood pressure (mmHg)	<130	30	119.6 (15.3)	38	121.9 (11.4)	29	120.8 (14.6)	39	123.7 (1323)
	Diastolic blood pressure (mmHg)	<80	30	64.1 (8.4)	38	67.1 (8.4)	29	65.8 (11.3)	39	71.0 (10.3)
	AIx (%)	<15	28	9.82 (9.93)	33	9.58 (8.45)	24	9.50 (10.1)	36	12.0 (8.34)
	AIx (*Z*-score)	NA	28	0.06 (1.25)	33	0.03 (1.22)	24	0.01 (1.16)	36	0.49 (1.15)
	PWV (m/s)	<7	28	5.74 (0.89)	33	6.02 (0.94)	25	5.95 (0.94)	36	6.03 (0.81)
Metabolic	BMI (kg/m²)	<23	31	21.7 (5.4)	40	23.2 (5.2)	29	22.2 (6.1)	39	23.5 (5.1)
	BMI (*Z*-score)	NA	31	1.15 (1.54)	40	1.45 (1.33)	29	1.16 (1.64)	39	1.39 (1.39)
	Waist circumference (cm)	<85	31	77.3 (14.8)	39	82.4 (15.3)	29	78.4 (16.4)	39	84.3 (16.1)
	Waist–hip ratio	<0.95	31	0.96 (0.05)	39	0.95 (0.08)	29	0.97 (0.06)	39	0.99 (0.07)
	Fat mass (%)	<25	30	26.7 (9.8)	39	32.4 (10.0)	28	25.9 (9.5)	38	32.7 (8.93)
	Total cholesterol (mmol/l)	3.0–5.0	22	3.88 (0.84)	31	3.85 (0.57)	17	3.78 (0.80)	27	3.99 (0.58)
	HDL (mmol/l)	>1.0	22	1.37 (0.48)	31	1.18 (0.29)	17	1.31 (0.46)	27	1.23 (0.30)
	LDL (mmol/l)	<3.2	19	1.93 (0.55)	26	2.32 (0.46)	12	2.07 (0.50)	19	2.28 (0.52)
	Total cholesterol/HDL	<5.0	22	3.07 (1.00)	31	3.43 (0.87)	17	3.14 (1.07)	27	3.43 (0.96)
	Triglyceride (mmol/l)	0.6–2.2	22	1.56 (1.00)	31	0.96 (0.52)	17	1.10 (0.72)	27	1.28 (0.94)
	Glucose (mmol/l)[b]	3.5–5.6	13	5.05 (0.70)	26	4.70 (0.46)	13	4.80 (0.62)	23	5.00 (0.55)

AIx, augmentation index; PWV, pulse wave velocity; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density protein.
[a]*Cutoff reference values of Hidvégi et al. (36), Talma et al. (37), Bodystat Quadscan 4000, and Cholestech LDX software.*
[b]*Included only participants who were fasted.*

Sedentary and active time during both week and weekend days showed no between-group difference following the school-based sports program (**Table 4**; **Figure 2C**).

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No effects were found for blood pressure and arterial stiffness (**Table 5**). Although not statistically significant, a change of 0.53 *Z*-score on AIx might be clinically relevant (**Figure 2D**). A significant effect in favor of the sport group was demonstrated for fat mass (β = −2.78, IC = −4.78 to −0.78). The sport group lost 2.8% more fat mass compared to the control group (**Figure 2E**). No effects were observed for BMI, waist–hip ratio, and metabolic profile. For triglyceride, a small but nonsignificant effect was found [β = 0.64, IC = 0.43–0.94 (see text footnote 1)] with a between-group change ratio of −0.44 mmol/l in favor of the sport group (**Figure 2F**).

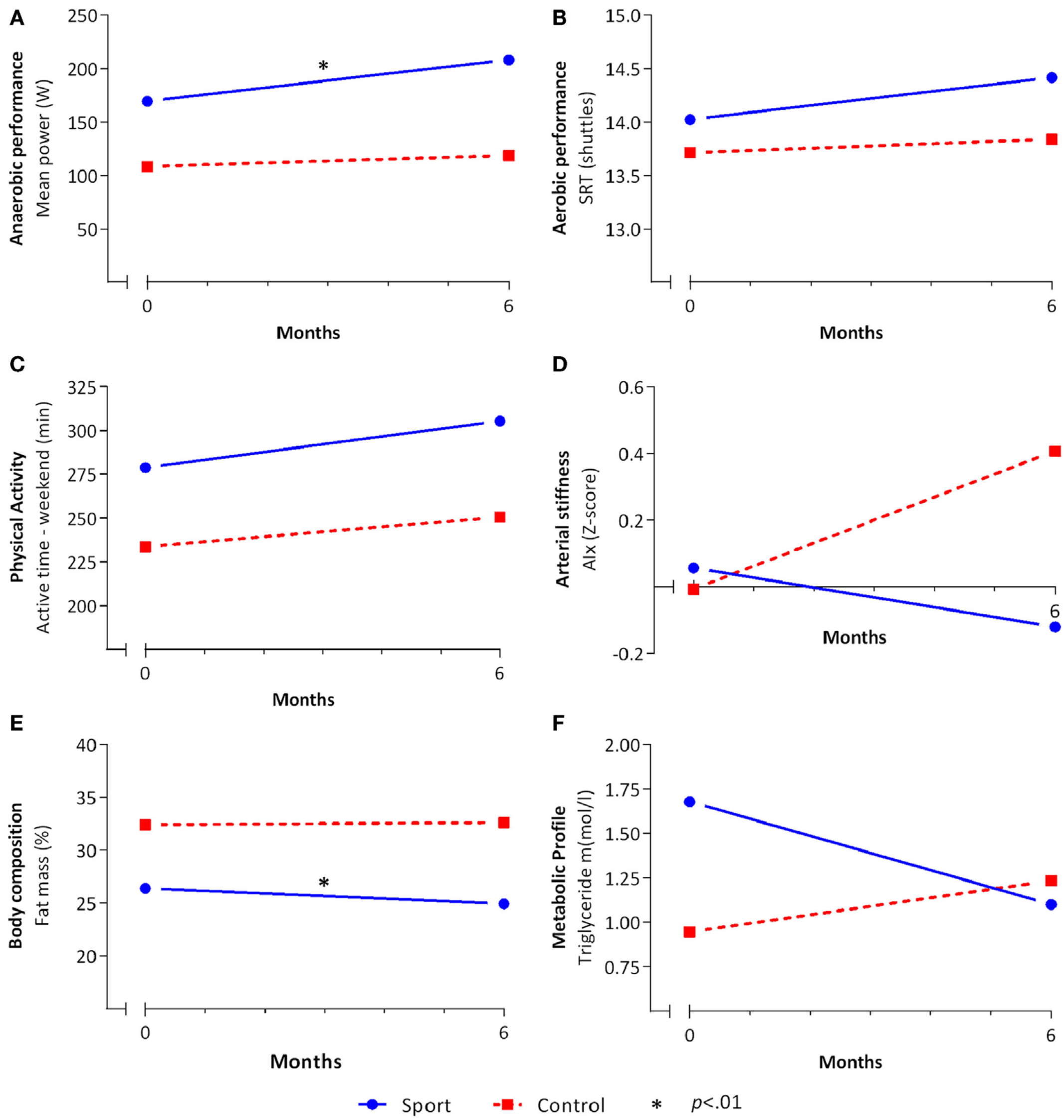

FIGURE 2 | Effects of the school-based once-a-week sports program. The mean values for the sport (solid blue line) and control (dashed red line) group before (*T*1) and after (*T*2) the school-based sports program of **(A)** anaerobic performance, **(B)** aerobic performance, **(C)** physical activity, **(D)** arterial stiffness, **(E)** body composition, and **(F)** metabolic profile on the multiple-imputed model. Linear regression analyses were done on the multiple-imputed model adjusted for *T*1. *Significant ($p < 0.01$) effect in favor of the sport group.

DISCUSSION

The aim of this study was to evaluate the effects of a school-based once-a-week sports program on physical fitness, physical activity, and cardiometabolic health in youth with physical disabilities. For all participants, both able to walk/run or propel a manual wheelchair, a school-based sports program is feasible and can be performed safely. Despite the heterogeneity of the group, increasing the level of sports participation once a week for 45 min showed already positive effects after 6 months. We found effects in favor of the sport group in both anaerobic performance and fat mass.

The school-based sports program resulted in a positive within-group difference of 23 W (16%) in anaerobic performance. This absolute increase is comparable with the 20 W (38%) improvement after 8 months of exercise training in children and adolescents with CP (39). The higher relative difference, 16% in the current study versus 38%, can be explained by the lower baseline values in the study by Verschuren et al. (39) Moreover, 8 weeks of HIT prior to the school-based sports program resulted already in an increase in anaerobic performance in both sport and control groups of 11% (24). Hence, independent of baseline values, once-a-week sports participation improves anaerobic performance even further. Another remarkable finding is that the control group maintained its gains on anaerobic performance following the regular curriculum of 6 months. It is unknown which factors contribute to this sustainability, but probably youth with physical disabilities are more active in daily

TABLE 4 | Results from the linear regression analyses assessing the intervention effect on physical fitness and physical activity.

		Linear regression[a]		Estimated marginal means Differences between groups			
		β	95% CI	Sport	Control	MD	%
Anaerobic fitness	Anaerobic performance—MP (W)[b]	1.16	1.05–1.28*	164.8	142.2	22.6	16
	Anaerobic performance—PP (W)[b]	1.15	1.04–1.27*	192.3	167.1	25.2	15
	Agility (s)[b]	1.02	0.96–1.07	25.8	25.4	0.41	1.6
Aerobic fitness	Aerobic performance (shuttles)	0.31	−1.19–1.81	14.3	14.0	0.31	2.2
	VO_2peak (ml/kg/min)	−1.55	−4.66–1.56	35.5	37.0	−1.55	−4.2
	VO_2peak (ml/fat free mass/min)	−3.00	−7.92–1.92	49.5	52.5	−3.00	−5.7
Functional strength	Grip strength (*n*)	−7.72	−17.97–2.53	147.6	155.3	−7.72	−5.0
	Standing-broad jump (cm)[c]	−0.12	−7.31–7.07	96.8	94.0	−0.12	−0.1
	One-stroke push (m)[d]	−0.80	−2.86–1.25	5.61	6.41	−0.80	−13
Physical activity[c]	Sedentary time—week (min)	−26.7	−66.8–13.4	544.8	571.6	−26.7	−4.7
	Sedentary time—weekend (min)	−40.6	−119.0–37.8	497.8	538.4	−40.6	−7.5
	Active time—week (min)	8.0	−31.4–47.4	294.7	286.6	8.0	2.8
	Active time—weekend (min)	33.7	−40.1–107.4	291.5	257.8	33.7	13

*$p < 0.01$.
CI, confidence interval; MD, mean difference; MP, mean power; PP, peak power; VO_2, oxygen uptake.
[a]*Multiple imputation models adjusted for baseline values. The intervention effect was not substantially confounded by age, sex, level of mobility, or school.*
[b]*Regression coefficients should be interpreted as a ratio as it was logarithmically transformed.*
[c]*Included only participants who are ambulatory.*
[d]*Included only wheelchair users.*

TABLE 5 | Results from the linear regression analyses assessing the intervention effect on cardiometabolic health.

		Linear regression[a]		Estimated marginal means Differences between groups			
		β	95% CI	Sport	Control	MD	%
Cardiovascular	Systolic blood pressure (mmHg)	−0.46	−5.50–4.59	122.5	123.0	−0.46	−0.4
	Diastolic blood pressure (mmHg)	−2.57	−7.24–2.10	67.2	70.0	−2.57	−3.7
	AIx (%)	−3.02	−7.35–1.31	8.93	11.95	−3.02	−25
	AIx (*Z*-score)	−0.53	−1.10–0.04	−0.08	0.45	−0.53	−117
	PWV (m/s)	0.20	−0.15–0.54	6.18	5.98	0.20	3.3
Metabolic	BMI (kg/m²)	0.05	−0.64–0.90	22.8	22.8	−0.05	−0.2
	BMI (*Z*-score)	−0.06	−0.25–0.14	1.23	1.28	−0.06	−4.3
	Waist circumference (cm)	−1.13	−3.41–1.15	80.8	82.0	−1.13	−1.4
	Waist–hip ratio	−0.02	−0.04–0.00	0.97	0.99	−0.02	−1.9
	Fat mass (%)	−2.78	−4.78 to −0.78*	27.7	30.5	−2.78	−9.1
	Total cholesterol (mmol/l)	−0.35	−0.80–0.10	3.67	4.02	−0.35	−8.8
	HDL (mmol/l)	−0.07	−0.29–0.15	1.21	1.28	−0.07	−5.6
	LDL (mmol/l)	−0.05	−0.37–0.28	2.08	2.13	−0.05	−2.2
	Total cholesterol/HDL	0.02	−0.44–0.47	3.31	3.29	0.02	0.5
	Triglyceride (mmol/l)[b]	0.64	0.43–0.94	0.78	1.21	−0.44	−36
	Glucose (mmol/l)[c]	−0.31	−0.68–0.07	4.80	5.11	−0.31	−6.0

*$p < 0.01$.
CI, confidence interval; MD, mean difference; AIx, augmentation index; PWV, pulse wave velocity; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density protein.
[a]*Multiple imputation models adjusted for baseline values. The intervention effect was not substantially confounded by age, sex, level of mobility, or school.*
[b]*Regression coefficients should be interpreted as a ratio as it was logarithmically transformed.*
[c]*Included only participants who were fasted.*

life compared to several years ago. A recent cross-sectional study showed that anaerobic performance increased in youth with CP between 2004 and 2014 (40). What we can conclude thought is that children and adolescents with physical disabilities improve anaerobic performance with an extra sports session a week, even after a training period.

The sports program resulted in a positive effect on fat mass, but found no differences in BMI, while other studies reported positive effects on BMI after a school-based intervention program (41, 42). Both fat mass and BMI are generally known to identify adiposity, although BMI fails to distinguish between lean and fat mass and lacks in sensitivity (43, 44). This might explain why BMI remained unchanged in the current study. Possibly, a small shift from fat to lean mass has occurred in the sport group, while weight and consequently BMI remained unchanged. Besides BMI, also no changes were found in waist circumference and waist-to-hip ratio, while other studies showed significant changes in adolescents with CP following an exercise program (4, 6). Possibly, if participants continue with sports participation, or exercise more frequently, in the longer term, these nonsignificant differences in health will diverge positively compared to individuals who do not exercise regularly (45, 46).

The current school-based sports program was performed once a week. Possibly, the frequency of once a week could explain why we found no significant effects on most of the outcome measures. However, once a week reflects daily life, since there is a discrepancy between the requirements from exercise physiology perspectives and the feasibility or the priority of sports participation. Although participants did not train following exercise guidelines, increasing sports participation with once a week improved anaerobic performance and fat mass. Consequently, being active is always better than being inactive (47) and is the starting point for an active and healthy adulthood (48). The current study demonstrated that sports participation of only once a week already shows positive effects after 6 months and tend to induce more effect over a prolonged period. Beside sports participation, daily physical activity also consists of playing outside and active transportation. Compared to typically developing peers, the current population is also less active in these domains of physical activity (12). Families of youth with a physical disability should therefore be encouraged to perform an additional activity in the week or weekends to optimally profit from the benefits of physical activity.

The current study examined the effects of group exercise on various outcome measures. Although we were interested in the group effects, reasons for participation may vary across individuals (21). For example, children and adolescents want to keep up with friends in playing soccer, lose weight, make friends, or just have fun. In the current study, we did not measure these reasons. To establish greater and clinical relevant effects, future research should tailor outcome measures on individual needs. For example, school-based physical activity program targeted at overweight children reduces BMI and blood pressure to a greater extent compared to the general population (41, 42). Moreover, the current school-based sports program did not lead to significant changes in daily physical activity. This probably needs an intervention with a behavioral component, which we did not include. However, earlier research with a behavioral component showed also no effects on physical activity in youth with CP (25, 26). A recent review showed that both parental involvement by education or homework tasks and the inclusion of activities conducted after school time induce greater effects on physical activity and body composition (41).

Several limitations should be taken into account. Firstly, the current study is not controlled by a randomly assigned group. This resulted in very dissimilar groups. Although we corrected for group differences at *T*1, it is difficult to attribute the improvement of anaerobic performance to the sports program only. A second limitation of this study is the composition of the study population comprising a large age range and a variety of diagnoses. More boys and youth who are able to run were included in the sport group compared to the control group. For this reason, the results should be interpreted more carefully. Thirdly, our results cover only the Dutch population of youth with physical disabilities. In The Netherlands, these children with special needs are often assigned to schools for special education, while in other countries, these children follow inclusive education. Therefore, the practical implication of school-based sports programs at schools for special education may be different in other countries.

In conclusion, a school-based once-a-week sports program improved anaerobic performance and fat mass after 6 months in youth with physical disabilities. No intervention effects were found for aerobic performance, VO_2 peak, strength, physical activity, blood pressure, arterial stiffness, and the metabolic profile. These effects are promising for long-term fitness and health promotion, because in the current study, barriers for sports participation were eliminated by providing sports at school, and only a training volume of once a week was added. Future research on school-based sports programs in this population should tailor outcome measures on individual needs and involve parents to induce greater and clinical relevant effects.

ETHICS STATEMENT

This study was carried out in children and adolescents with a chronic disease or a physical disability in accordance with the recommendations of Good Clinical Practice with written informed consent from all subjects. All parents and participants from 12 years of age gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Medical Ethical Committee of UMC Utrecht in The Netherlands (#14-118).

AUTHOR CONTRIBUTIONS

MZ and KL contributed to the design of the study and collection of data. MZ, AB, SV, and LG helped to analyze the data. OV, JG, AV, and TT conceived of the study, participated in its design and coordination. MZ wrote the manuscript with input from all authors, who read and approved the final manuscript.

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2017 Dutch Report Card^{+}: Results From the First Physical Activity Report Card Plus for Dutch Youth With a Chronic Disease or Disability

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Background: The Dutch Active Healthy Kids (AHK) Report Card^{+} (RC^{+}) consolidates and translates research and assesses how the Netherlands is being responsible in providing physical activity (PA) opportunities for youth (<18 years) with a chronic disease or disability. The aim of this article is to summarize the results of the Dutch RC^{+}.

Methods: Nine indicators were graded using the AHK Global Alliance RC development process, which includes a synthesis of best available research, surveillance, policy and practice findings, and expert consensus. Two additional indicators were included: weight status and sleep.

Results: Grades assigned were: Overall Physical Activity, *D*; Organized Sports Participation, *B*–; Active Play, *C*–; Active Transportation, *A*–; Sedentary Behavior, *C*; Sleep *C*; For Weight Status, Family and Peers, School, Community and Built Environment, Government Strategies, and Investments all *INC*.

Conclusions: The youth with disabilities spend a large part of the day sedentary, since only 26% of them met the PA norm for healthy physical activity. Potential avenues to improve overall physical activity are changing behaviors regarding sitting, screen time, and active play. The Netherlands is on track regarding PA opportunities for youth with disabilities, however they are currently not able to participate unlimited in sports and exercise.

Keywords: children, youth, chronic disease, disability, health, exercise

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INTRODUCTION

According to the World Health Organization (WHO) physical inactivity is the fourth leading risk factor for mortality. Regular physical activity (PA) reduces the risk of many diseases including cardiovascular disease, diabetes, breast and colon cancer, and depression (1). Noting that the more physically active the child the greater the health benefit, specific research showed that PA has positive effects on musculoskeletal health, cardiovascular health, and mental health (2). It has been indicated as well that the earlier in life one starts engaging in sports and exercise, the longer one benefits from it (3). Therefore, PA is important. However, according to the Global Matrix 2.0, in which Report Cards from 38 countries, including the first Dutch Physical Activity Report Card, were compared regarding PA behavior, norms were often not met by typically developing youth (4). The Report Card is an annual update or "state of the nation" that assesses how a country is doing as a nation at promoting and facilitating PA opportunities for children and youth and grades outcomes using an academic letter grade approach (i.e., A, B, C, D, F). Data to grade the outcomes are drawn from several sources, including the research literature, governmental agencies, and non-governmental organizations[1] (5).

Next to typically developing children, also many children with disabilities are not physically active (6). Even though it might be especially important for this group of children to engage in sports and exercise, because of the positive health effects in the physical, mental, and social domain (4, 7–10). Because of multiple barriers, this group should perhaps be more stimulated and encouraged to engage in an active lifestyle in a broad sense: from PA during sports and play activities and reducing sedentary behavior, to behavior related to sleep, and weight/nutrition (11).

Over the past few years, changes have occurred to facilitate the sports and exercise behaviors of people with disabilities in the Netherlands. Many organizations, foundations, and governmental bodies developed or funded projects that focus on improving PA and sports participation among people with disabilities. However, it is not yet clear what the overall effects of these projects were and where the gaps are. Do people with disabilities feel less restricted in the opportunities they have to participate in sports?

In the Netherlands, there was no overview yet of the actual status of PA behavior, sleeping behavior and weight status for youth with disabilities. Regarding the proven and potential positive effects of exercise for a good health, it was considered useful to fulfill this gap, by Active Healthy Kids the Netherlands, which consists of a group of researchers in the field of PA in children and youth, with a mission to inspire the nation to engage all children and youth in PA by providing expertise and direction to policy makers and public on how to increase, and effectively allocate resources and attention toward PA for Dutch children and youth. This is also the first Report Card in the world that was specifically developed for this group of children.

With this Report Card+, we want to gain more insight in the PA levels and patterns of the Dutch youth with a chronic disease or disability and answer the question "*how (un)limited are the possibilities for the Dutch youth with disabilities to be physical active?*" (**Figure 1**).

In line with this, another aim was to compare the results of the Report Card for Dutch typically developing youth with the Report Card+ for Dutch youth with disabilities.

FIGURE 1 | Front cover of the 2017 Dutch Physical Activity Report Card+.

METHODS

For the developmental process, guidelines of the Active Healthy Kids Canada framework were followed (5). Eleven indicators were graded in this Report Card. Nine of the indicators were part of this standard international framework. It was decided to add sleep behavior and weight status as additional indicators. The indicators were divided over three categories, except weight status, which did not fit in any of the categories (**Figure 2**). The grades were based on the percentage that met the single or multiple benchmarks.

The principal investigator and project manager formed a research work group (RWG) together with seven researchers of the University Medical Centre Utrecht, Utrecht University, Utrecht University of Applied Sciences and Center of Excellence in Rehabilitation Medicine Utrecht.

An expert group was formed with the involvement of National Institute for Public Health and Environment (RIVM), Mulier Institute, Dutch Olympic Committee*Dutch Sports Federation (NOC*NSF), Windesheim University of Applied Sciences, Knowledge Centre for Sports Netherlands (KCS), Hanze University of Applied Sciences Groningen, Amsterdam University of Applied Sciences, Institute for Health and Care Research, Netherlands Institute for health service research

[1] For a more detailed description about the Report Card, see Colley et al. (5)

Abbreviations: BMI, Body mass index; CBS, Statistics Netherlands; INC, Incomplete; KSC, Knowledge Centre for Sports Netherlands; MET, Metabolic equivalent; NHS, National Health Survey; NIVEL, Netherlands Institute for health service research; NNGB, Dutch Physical Activity Guideline; NOC*NSF, Dutch Olympic Committee*Dutch Sports Federation; PA, Physical activity; PE, Physical Education; RIVM, National Institute for Public Health and Environment; RWG, Research work group; SCP, the Netherlands Institute for Social Research; WHO, World Health Organization.

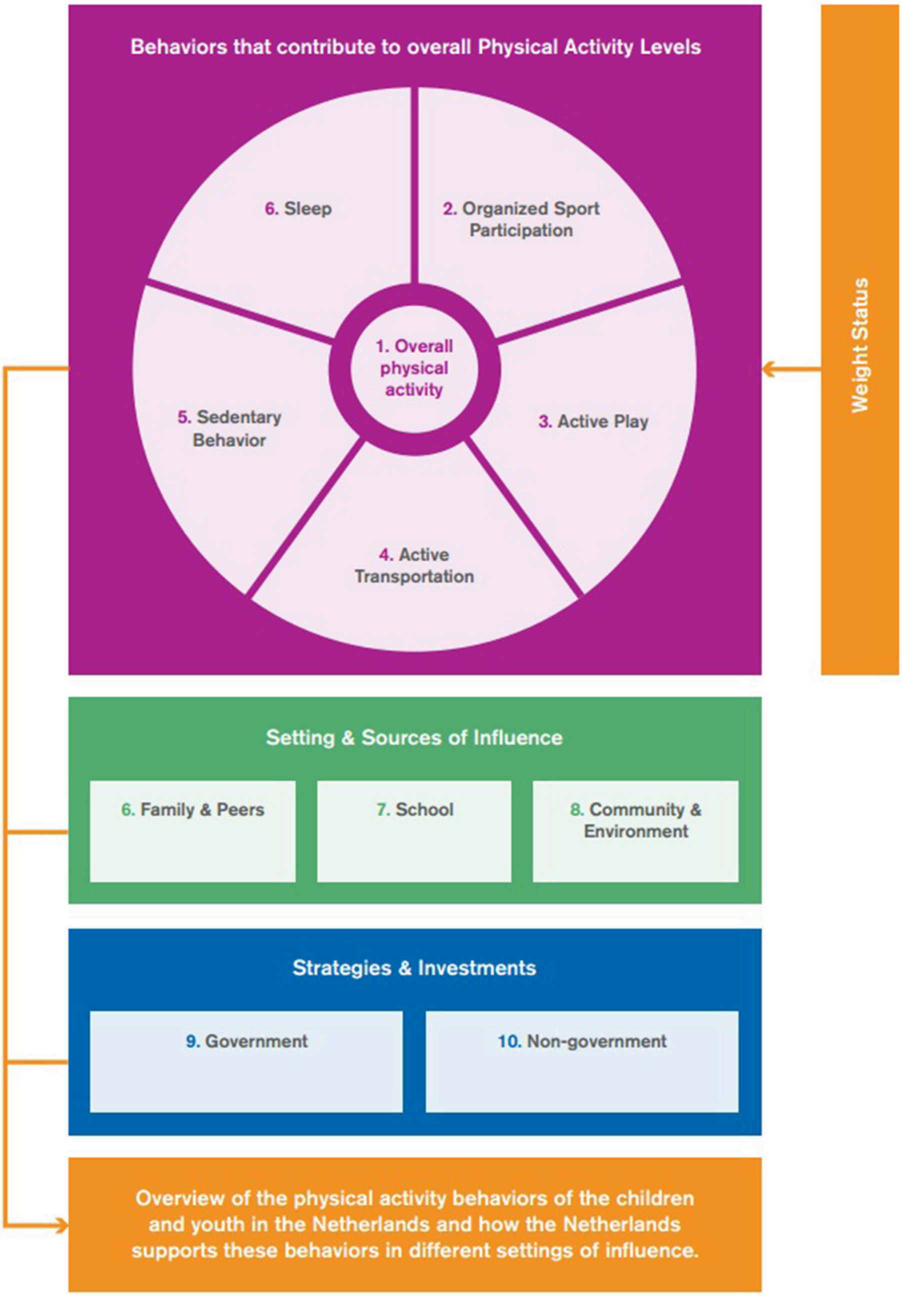

FIGURE 2 | Overview categories and related indicators.

(NIVEL), and an advisory role for the Primary Education Board [PO-Raad].

Both the RWG and the expert group were responsible for the interpretation and evaluation of the data sources and evidence and had to decide about definitions and benchmarks of the indicators for the grading and were responsible for the final grading.

For the evaluation of the indicators, data of the period 2011 up to 2015 have been included. When available, we used data gathered by Statistics Netherlands (CBS) and the RIVM as the primary source. These organizations annually collect data about several lifestyle themes, the Lifestyle Monitor, part of which is the National Health Survey (NHS) (12). Most of the grading was based on this survey. The Lifestyle Monitor divides youth in two age groups: 4–11 years and 12–17 years. As a consequence of this, both age groups were assessed for each indicator. Unfortunately, the sample sizes for the years 2011 up to 2014 were too small for a subgroup analysis. For 2015, 142 children were included for the age range 4–11 years and 232 children were included for the age range 12–17 years. For the youngest age category (4–11 years), the answers were parent reported. For the older age group (12–17 years) the NHS was a self-report questionnaire. If the required data to grade an indicator could not be provided by the primary sources, other governmental and non-governmental sources were used.

Children with disabilities in the Netherlands could attend regular education or special education at special schools. The situation of scholars attending special education was described when reports were available (13). The grades of the indicators were based on the data about youth with disabilities in general from the NHS.

As this Report Card+ was developed following a standard framework that was also used for the first Dutch Physical Activity Report Card for typically developing children, the results of both Report Cards could be compared.

Benchmarks

The first six indicators are Overall Physical Activity, which is also the first category, and the behaviors that contribute to that: Organized Sports Participation, Active Play, Active Transportation, Sedentary Behavior, and Sleep. For all of these indicators the grading was based on data from the NHS for children with disabilities in general and, when available, data from the Mulier Institute were used to describe the situation of children attending special education (13).

For the first indicator, Overall Physical Activity, the grading was based on the percentage of children who met the Dutch Physical Activity Guideline [NNGB: Dutch Guidelines Healthy Physical Activity; to be at least moderate active (at least 5 MET) for at least 60 min every day]. For this indicator data on children attending special education were available.

The RWG and expert group reached consensus to use data regarding engaging sports on a weekly basis, thus the grading of Organized Sports Participation was based on the percentage of children and youth who participated in organized sports and/or PA programs weekly.

For children attending special education, it was known how many children were a member of a sports club and how many played non-school based sports at least once a week. Regarding Active Play, the grading was determined by the percentage of children who played outside for at least 60 min after school, for 7 days a week. The NHS does not include questions about active play behavior in 12–17 year old youth, therefore the grade was based only on 4–11 year old children. For the scholars attending special education the percentages of children who played outside 5–7 times a week were reported.

Active Transportation was assessed by the percentage of children who use active transportation (walking and cycling) to get to and from places (school and/or work) for at least 3 days a week. Of children attending special education, only the amount of children who used active transport was known and not the weekly frequencies.

For Sedentary Behavior only the amount of time spent in front of a screen (screen time) was surveyed, so the grading was based only on this criteria even though this does not cover all sedentary time. The number of children who watch television or sit in front of the computer less than 2 h a day outside school hours determined the grade for this indicator. No numbers where available on sedentary time of scholars attending special education. The indicator Sleep was assessed by the amount of children meeting the sleep duration recommendation for their age group. The sleep duration recommendations used are described in the study of Hirshkowitz et al. (14). These recommendations are for healthy individuals with normal sleep. The appropriate sleep duration for school-aged children is considered between 9–11 h each night and for adolescents this is 8–10 h (14).

For the additional indicator Weight Status, the grade was based on the percentage of children with a normal body weight (BMI between 18.5 and 25 kg/m^2 was classified as normal weight) (15). Data for this indicator were taken from the NHS for the children with disabilities in general. Data of scholars attending special education were used from reports from the Mulier Institute (13).

The next category, Settings and Sources of Influence, consists of the indicators Family and Peers, School and Community and Environment. No data of the NHS regarding these indicators were present. Thus, no general information was present. Other sources were used for assessment of the indicators in this category.

The criteria of Family were: "percentage of parents who facilitate PA and sports opportunities for their children (e.g., volunteering, coaching, driving, paying for membership fees, and equipment)," "percentage of parents who meet the PA guidelines for adults" and "percentage of parents who are physically active with their kids." For Peers the criteria were: "percentage of children and youth with disabilities with friends and peers who encourage and support them to be physically active" and "percentage of children and youth who encourage and support their friends and peers to be physically active." However, as there was no consistent data for children with disabilities in general nor for children attending special education (not all clusters[2]), the RWG and experts decided that this indicator could not be graded. The available numbers of some of the clusters in special education from the Mulier Institute and other sources were used to get some insight in this indicator.

For School the following criteria were set: "the percentage of schools with an active school policy (e.g., offering sports- and exercise activities next to physical education (PE) or activities during recess, collaboration with communities and/or sports clubs, presence of annual planning)," "percentage of schools with a PE specialist," "the percentage of schools were the students have at least 90 min of PE per week," and lastly "the percentage of students who have at least 45 min of outside play time

[2]**Cluster I:** Schools for visual impaired children or children with multiple disabilities who are visually impaired or blind. **Cluster II:** Schools for deaf children and hearing impaired children, children with speech or language difficulties and children with communicative problems, as with some forms of autism. **Cluster III**: Schools for children with motor and/or mental disabilities, chronically ill children and children with epilepsy. **Cluster IV**: Schools for children with psychiatric disorders or severe behavioral problems and schools that are related to pedagogical institutes.

during school for 5 days per week." Again, however, it was decided to grade this indicator as Incomplete. Data was present about regular education and special education. However, as a consequence of the regulation "Appropriate Education" [Wet Passend Onderwijs][3], some children with disabilities attended regular schools and participate in regular PE. The specific situation for these children was unknown.

The last indicator of this category, Community and Environment, also had several criteria: "the percentage of children and parents who perceive their community/municipality is doing a good job at promoting PA (e.g., variety, location, cost quality)," "the percentage of communities/municipalities that report they have policies promoting PA," "the percentage of communities/municipalities that report they have infrastructure (e.g. sidewalks, trails, paths, bike lanes) specifically geared toward promoting PA," "the percentage of children or parents who report having facilities, programs, parks, and playgrounds available to them in their community," "the percentage of children or parents who report living in a safe neighborhood where they can be physically active," "the percentage of children who report having well-maintained facilities, parks and playgrounds in their community that are safe to use" and finally, "the percentage of children and parents who report that in organizations like sports clubs, they (their child) are socially accepted and that social accessibility is present." Also for this indicator it was decided to mark it as an Incomplete. In the Report Card for typically developing children, data of the Leisure time Omnibus [Vrijetijdsomnibus] of the CBS and the Netherlands Institute for Social Research (SCP) was used to grade this indicator. Unfortunately, the sample size of children with disabilities was too low for both 2012 and 2014 to use the results.

The last category, Strategies and Investments was divided in the indicators Government and Non-Government. The criteria that were set were: "evidence of leadership and commitment in providing PA opportunities for all children and youth," "allocation of funds and resources for the implementation of PA promotion strategies and initiatives for all children and youth" and "demonstrated progress through the key stages of public policy making (i.e., policy agenda, policy formation, policy implementation, policy evaluation, and decisions about the future)." No clear numbers were available to state that policy is efficient or how much financing is acceptable. Therefore, the decision was made to grade this indicator with an Incomplete. Multiple governmental documents were studied and reports of the Mulier Institute on different policies and programs were evaluated. For Non-Government, annual reports and websites of several national and regional foundations and organizations were considered.

The RWG and experts evaluated the evidence for each of the indicators and discussed the proposed grading. The grades were based on the percentages of youth meeting the defined benchmark. Some indicators are stand-alone, while others are comprised of several components. A was 81 to 100%, B was 61 to 80%, C was 41 to 60%, D was 21 to 40%, F was 0 to 20%. INC was incomplete data or not enough available evidence to assign a grade to the indicator or absence of clear well-established criteria. This grading system is in accordance to the Canadian Report Card framework (5).

When the data about scholars attending special education showed that the situation for that particular indicator was considerably better or worse for these children, the grade was given a plus or minus respectively.

[3]In 2014, the regulation "Appropriate Education" [Wet Passend Onderwijs] was introduced, which aims that every student should attend a school that provides education suited to their talents and capabilities. Schools should adapt their teaching to the individual child's development and offer extra assistance. This applies to the school where the child is currently registered, another mainstream school or a school providing special education (16).

RESULTS

The 2017 Dutch Report Card+ is the first ever assessment of PA behaviors, settings, and sources of influence and government strategies and investments for children with a chronic disease or disability. The grades are summarized in **Table 1**.

Overall Physical Activity Levels: D

The grade for Overall Physical Activity levels was a *D*. In 2015, 26% of both children and youth (4–17 year olds) met the Dutch PA guideline of Healthy Physical Activity (NNGB). Scholars of cluster II schools were the most physically active compared to the other clusters. Of the scholars attending cluster II schools 35% exercised 8 or more hours per week (excluding sports) (13). For the cluster I and III scholars this was 21% and in cluster IV 27% (13).

Organized Sports Participation: B–

Of the 4–11 year olds 69% and of the 12–17 year olds 73% was considered a weekly athlete (12) Among scholars attending special schools, the sports participation was lower. Cluster IV scholars had the highest sports participation, namely 45 vs. 25, 37, 26% for cluster I, II, III, respectively (13).

Active Play: C–

Of the 4–11 year old children with disabilities 53% played outside for at least 60 min after school, on all days of the week (12).

TABLE 1 | Overview of indicators and corresponding grades.

Indicator	Grades
Overall physical activity	D
Organized sports participation	B–
Active play	C–
Active transportation	A–
Sedentary behavior	C
Sleep	C
Weight status	INC
Family and peers	INC
School	INC
Community and the built environment	INC
Government strategies and investments	INC

Scholars of cluster II schools, most often played 5–7 times per week outside (45%), compared to cluster I (31%), III (30%), and IV (33%) scholars. The average amount of minutes of active playtime outside school hours was 529 min per week for the 4–11 year old children with disabilities (13).

Active Transportation: A–

Of the children in the age of 4–11 years 39% cycled 3 or more days to or from school or work and this was 38% for walking 3 or more days per week.

Of the 12–17 year olds 71.8% cycled 3 or more days to or from school or work and this was 15.8% for walking 3 or more days per week (12).

Only 4% of the children in cluster I schools used active transportation to get to their school (13). This was 18% in cluster II, 13% in cluster III, and 30% in cluster IV schools (7, 13).

Sedentary Behavior: C

Of the 4–11 year old children 45.5% sat in front of the computer or watched TV, less than 2 h a day (average day of the week), outside school. This was only 23.2% for 12–17 year old children (12). No data concerning sedentary behavior was available for scholars in special schools.

The 4–11 year olds sat/lay on average 7.9 h per day on a school day, compared to 11.1 h for the 12–17 year olds. On a day off from school, the younger age group sat/lay on average 6.5 h, compared to 9.2 h in the older age group (12).

Sleep: C

Of the 4–11 year old children with disabilities 26% met the sleep recommendations. This was 63% in the 12–17 year old age group (12). No data was present about sleep behavior of scholars attending special schools.

Weight Status: INC

The sample size of the NHS was unfortunately too small, to grade this indicator. These data showed however, that the mean BMI of the 4–11 year olds was 16.5 and 20.8 kg/m^2 in the 12–17 year old age group (12).

When evaluating the scholars who attended special schools (all clusters together), 68% of the children had a normal weight, 11% was underweight, 17% was overweight, and 4% obese. When comparing the different clusters, the highest percentage of overweight and obese children (combined) was found in cluster III schools (25%) (13).

Family and Peers: INC

No data of the NHS regarding "Family & Peers" were present. Thus, no general information was present to grade this indicator. Data was only available on parents of children in cluster III or IV schools. No information about the parental behavior in the other two clusters was present, consequently an Incomplete was graded. Of the parents of cluster IV scholars 59% considered it important that their child engages in sports or exercise frequently. Of the parents 72% encouraged their child to play sports or exercise frequently (8). A smaller study showed that parents of whom the child joins a sports club, stimulate their children significantly more ($p = 0.05$) to sports and exercise, than parents whose child is not a sports club member (9).

School: INC

Data was present about regular education and special education. However, as a consequence of the regulation "Appropriate Education" [Wet Passend Onderwijs][3], some children with disabilities attend regular schools and participate in regular PE. The specific situation for these children was unknown and consequently an Incomplete was graded. Key findings about the situation in special schools will be given.

Concerning active school policies, 71% of the special schools offered their students other sports and exercise activities, next to PE (10). All cluster I and II schools, had a PE specialist, and 84.2 and 94% of the cluster III and IV schools had a PE specialist respectively. All cluster schools offered twice a week PE (7, 8, 13) The number of average minutes PE per week varied between 63 min per week in cluster III to 103 min in cluster IV (7, 8).

Regarding playtime during school recess, 50% of the 4–11 year old students played at least 45 min outside during school time for 5 days per week and the average active play time at school was 284 min per week for this age group (12).

Community and the Built Environment: INC

As mentioned in the methods, the sample size of children with disabilities in the Leisure time Omnibus [Vrijetijdsomnibus] of the CBS and SCP was unfortunately too low to grade this indicator. A smaller study showed that 12% of the parents of children with disabilities reported that play sets/grounds are not nearby enough. Only 2% of these parents reported that the play sets/equipment are not safe and/or badly maintained and only 1% considered them not safe (for younger children). Only 9% of these parents reported that it was not safe for their children to play in the neighborhood, due to traffic safety (16).

Government Strategies and Investments: INC

This indicator about the current policy of the government could not be judged. There have been several initiatives that have to resulted in a more physically active youth. Unfortunately, no clear criteria and monitors were present to evaluate the effectiveness of these initiatives and policies.

With regard to foundations, we saw that proportionally more foundations were founded to help or facilitate children with disabilities in their possibilities to play sports or exercise compared to foundations for typically developing children.

DISCUSSION

The primary aim of this Report Card+ was to provide an overview of the methods and results of the first Dutch Report Card+ for youth with disabilities. The results showed that about a quarter of the Dutch youth with disabilities met the PA norm.

In 2016 the results of the first Dutch Physical Activity Report Card were published (17). These results were compared with the Report Card+ results (**Figure 3**). A notable finding was that the percentages of children that met the Dutch

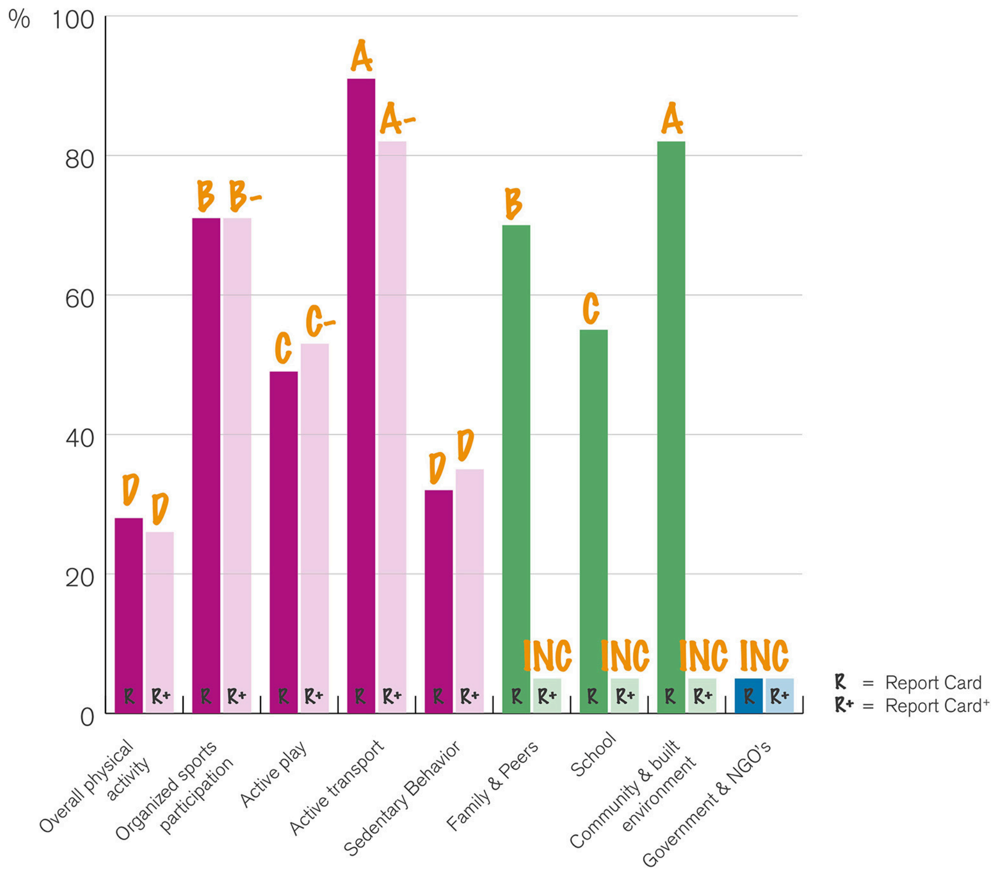

FIGURE 3 | Comparison of the results of the Report Card and the Report Card+.

Physical Activity Guidelines was the same for children with and without disabilities (26%). Assessing the different indicators that contribute to Overall Physical Activity (Organized Sports, Active Play, Active Transport, and Sedentary Behavior), it was clear that the youth with disabilities used active transport less often than their typically developing peers. Regarding youth attending special education, norms were less often met than in youth attending normal education. The differences between healthy children and children attending special education may be caused by the (social) accessibility and by the diversity of disorders/disabilities. Noteworthy, was that in the Report Card+, only six of the 11 indicators could be graded and five were graded an Incomplete, thus we stated that the national monitoring in youth with disabilities is unfortunately lacking. Therefore, it was difficult to make powerful statements about possible causes (17).

Other indicators for which improvement is warranted are sedentary behavior and active play. The Dutch youth with disabilities spent a large part of the day sitting or lying and/or behind a screen, especially during school times. Though, around half of the children with disabilities engaged in daily active play for at least 60 min, the other half did not. Thus, changing the behaviors regarding, sitting (at school), screen time, and active play, seems most likely to improve overall activity levels.

Fortunate, a large part of the youth with disabilities engaged in sports weekly and chose an active mode of transportation for their way to school. It is important that the conditions for these indicators will remain this high in the future. Solutions should be developed to make it possible for more scholars in special schools to travel to school (partly) using active transportation. Furthermore, sports clubs need to educate their staff and volunteers more properly so children and their parents experience less barriers to join a sports club.

The role of the parents and family is of high importance as well in this group of children. Even though no grade could be assigned to this indicator, results demonstrated that parents should be more informed about their large influence as a role model for all behaviors and that their home rules are of high relevance as well. Stimulating parents to engage in sports and exercise activities with their whole family should be more promoted. In addition, strategies that promote sports opportunities for children with disabilities, such as sports and play activities in the neighborhood and foundations who can help families with less financial back up, should be improved. Currently, too many children and parents are not familiar with these possibilities and sports opportunities.

As the indicator sedentary behavior showed, the youth with disabilities sat the most during school hours. Strategies to interrupt the long sitting duration should be developed and implemented, for example physically active academic lessons. As school is the place where all children can be reached, strategies, and financial resources are needed to enlarge the duration of PE lessons and to realize higher intensities during these lessons.

Further, collaborations between all sectors should be stimulated. Problems in the accommodation and offer of sports and other active activities will benefit from this. Furthermore, it is important to involve parents, PE specialists and teachers in realizing and improving the sports opportunities for children with disabilities. Both parents and teachers know the child and his/her possibilities and disabilities the best and can search together with the sports clubs for the most appropriate sports activity.

Strengths and Limitations

This is the first ever developed Physical Activity Report Card+ for children and youth with a chronic disease or disability. This Report Card provides a comprehensive overview about how the Netherlands is doing, regarding PA opportunities, overall PA levels and the role of sources of influence for children with disabilities.

Strength of this Report Card+ is the participation of many experts and organizations in this area, which made that many important data sources were identified and included. Unfortunately, not all indicators were integrated in national surveys yet (e.g., family and peers) and in the national surveys no clear demarcation was present for children with disabilities. No subcategories could be made and the size of the researched population is small. Furthermore, only the data of 2015 from the NHS could be used because the sample sizes in the years 2011-2014 were too small to analyze. With this in mind, one can question whether these results actually represented the current situation for people with disabilities and youth in particular. Making appropriate policies based on the results of this monitoring should therefore be questioned.

CONCLUSION

Based on the results of this Physical Activity Report Card+, only 26% of the Dutch youth with a chronic disease or disability met the current national PA guidelines. The most important behaviors to change that will most likely result in improvement of overall PA levels seem to be sitting (at school), screen time, and active play. In the past few years, many initiatives, possibilities, and policies were developed and the Netherlands is on track, but currently, the Dutch youth with disabilities is not yet able to participate completely unlimited in sports and exercise.

ADDITIONAL INFORMATION

The long form Report Card+, with more background information about the developmental process, methods, indicators, and recommendations, is available online: http://www.super-lab.nl/reportcarddownloads/.

AUTHOR CONTRIBUTIONS

TT was the principal investigator and MB was the project manager according to the international Report Card framework. NdJ and SV supported TT and MB in their work in the Report Card developmental process (for example, literature search, analyzing the results, writing of final Report Card, and the manuscript).

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Web-Based Motor Intervention to Increase Health-Related Physical Fitness in Children With Congenital Heart Disease: A Study Protocol

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Objective: Exercise interventions are underutilized in children with congenital heart disease (CHD) especially when the primary outcome is not peak oxygen uptake. Most of the studies are restricted to a low sample size and proximity of the patients to the study centers. Now eHealth approaches bear a promising but also challenging opportunity to transmit such intervention programs to participants, and check progress and compliance from remote. This study will aim to improve health-related physical fitness (HRPF) with a 24 weeks web-based exercise intervention.

Methods and Design: The current study is planned as a randomized control trial (RCT) with a crossover design and the aim to improve functional outcome measures. It also estimates adherence and feasibility in patients with CHD in this web-based exercise/motor intervention over 24 weeks. Primary outcome will be the improvement of HRPF. Secondary outcomes are, functional and structural arterial stiffness measures and health-related quality of life. Thus, 70 children from 10 to 18 years with CHD of moderate and complex severity will be recruited and allocated randomly 1:1 in two study arms after baseline testing for their HRPF, arterial stiffness measures and health-related quality of life. For 24 weeks, participants in the intervention arm will receive three weekly exercise video clips of 20 min each. Every video clip comprises 20 child-oriented exercises which have to be executed for 30 s followed by a recovery period of 30 s. Each session will start with 3–4 warming-up exercises, followed by 10–12 strength and flexibility exercises, and ending with 3–4 min of cool down or stretching tasks. Continuous video clips will be streamed from a web-based e-Learning platform. The participant simply has to imitate the execution and follow some short advices. After each session, a brief online survey will be conducted to assess perceived exertion and feasibility.

Discussion: The study will help to determine the efficacy and applicability of a web-based exercise intervention in children with CHD in regard to functional outcome measures. In addition, it will outline the effectiveness of remote monitoring, which provides a cost effective approach to reach patients with CHD that are low in prevalence and often do not live in close proximity to their tertiary center.

Trial Registration: https://ClinicalTrials.gov Identifier: NCT03488797.

Keywords: web-based, intervention, eHealth, exercise, congenital heart disease, children

BACKGROUND

Children with congenital heart disease (CHD) show reduced motor competence or motor ability (1–4) as well as limitations in fine and gross motor skills (5–7). These skill-based limitations from early infancy are tracked into adulthood with further negative effect on health-related physical fitness (HRPF) and muscle strength (8–11). That those limitations still exist in the vast majority of children with CHD outline recent projects on health-related physical fitness (HRPF) and cardiovascular health (12–17).

These circumstances should in general be a reason to worry and a starting signal for exercise promotions and interventions to overcome such deficits to facilitate normal social integration and school sport participation as early as possible. Unfortunately, a review from 2013 outlines that exercise interventions are still underutilized, because of the relatively low prevalence of single types of CHD and the proximity to the study centers (18). One drawback is that the primary outcome of those studies always refers to improvements in peak oxygen uptake, while any forms of motor-related competences are of minor interest. This is probably the case, because motor-related competences do not represent a hard clinical endpoint like parameters derived from cardiopulmonary exercise testing (19–21). Another drawback refers to the willingness and availability of the parents to escort their children to the study centers.

Within the last years, digitalization has also shaped the field of medicine and many studies on eHealth and communication technology–based interventions for promoting physical activity (PA) show remarkable results (22). The new appealing possibility to transmit, conduct and control interventions from remote is also promising for studies in the field of patients with CHD. It is now possible to involve children with long distance to the study center to realize studies that otherwise would fail due to sample size. Currently children and adolescents grow up to be "digital natives" which are even more familiar in handling and executing app-based tasks, than dealing with paperwork. In addition, communication via social media platforms becomes more and more appropriate to monitor the study progress and maintain study compliance, instead of classic phone calls.

Abbreviations: CHD, congenital heart disease; cIMT, Carotid Intima-media Thickness; HRPF, heat-related physical fitness; HRQoL, Health related Quality of Life; PWV, pulse wave velocity; RCT, randomized controlled trial.

In patients with CHD, eHealth is largely unexplored with only one published study on physical exercise on aerobic fitness so far (23, 24). Therefore, we have launched a randomized controlled trial (RCT) that aims to improve functional outcome measures, primarily HRPF, in children and adolescents with CHD via a tailored web-based exercise/motor intervention over 24 weeks. That article describes the study protocol in detail.

METHODS

Design and Participants

The current study is planned as a randomized control trial (RCT) with a crossover design and the purpose to improve functional outcome measures in patients with CHD via a web-based exercise/motor intervention over 24 weeks. The treatment scheme and data collection is presented in **Figure 1**. According to the inclusion and exclusion criteria outlined in **Table 1**, 70 children will be recruited and allocated randomly 1:1 in the two study arms after baseline testing. After 24 weeks, there will be a re-assessment of the clinical measurements.

The accordance of the Declaration of Helsinki (revision 2008) and the Good Clinical Practice Guidelines is the basis of this upcoming study. The study protocol is already approved by the ethical board of the Technical University of Munich (project number: 130/17S). All children and their guardians will provide written informed consent. The trial is already registered at https://ClinicalTrials.gov (NCT03488797).

Intervention

The motto of the exercise/motor intervention is "One Hour a Week, Brings Mobility, Power and Speed" which refers to the weekly training volume of 60 min. These 60 min are separated into 3 weekly sessions of 20 min each. The intervention is set up for 24 weeks (~6 month), resulting in a total of 72 exercise sessions (3 sessions per week over 24 weeks) for each participant.

Each session comprises 20 child-oriented exercises with the focus to increase strength and flexibility. Exercises are executed for 30 s followed by a recovery period of 30 s. Each session starts with 3–4 warming-up exercises, followed by 10–12 strength and flexibility exercises, and ending with 3–4 cool down or stretching tasks.

All exercise sessions are continuous video clips transmitted to the participants via the web-based e-Learning platform Einstein (https://einstein.costner.is). The participant simply has to imitate the execution and follow some short advices. For a better

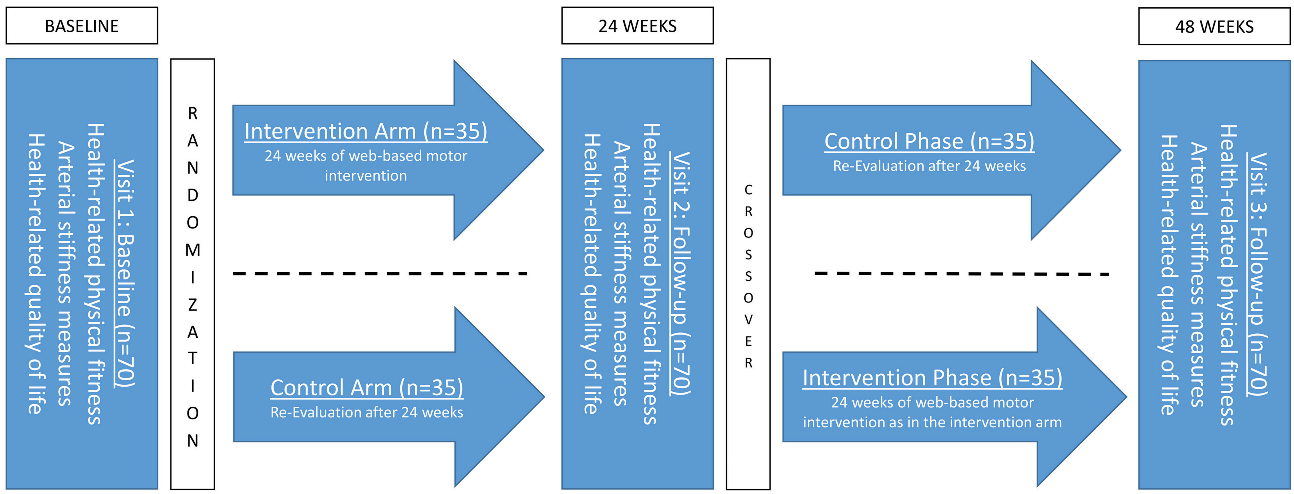

FIGURE 1 | Study design and intervention scheme.

TABLE 1 | Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Age 10–18 years old	Severe arrhythmias
CHD with moderate to complex severity according to the ACC criteria*	Severe left heart failure
Health-related physical fitness <50th percentile (healthy reference)	Chromosomal anomalies and/or genetic syndromes
German speaking	Severe physical and/or sensory impairments (hearing, visual, or psychomotor)
Internet availability and an internet-capable device to use the intervention app	Elective cardiac intervention within the next 6 months following enrollment
Informed consent of parent/guardian as well as of the child	

*According to Warnes et al. (25).

orientation, a timer in the upper right corner displays the duration of exercise and the time of recovery. Beep signals indicate the last 3 s of the exercise and recovery period.

After each session, the screen will jump to a short online survey. Participant will give a quick report on perceived exertion (Borg scale) and feasibility of the actual session. The investigator can thereby monitor adherence rate and, in case of lacking compliance, intervene via email or telephone calls. The three video clips will be available for 1 week (Monday to Sunday) and the participant is free to choose when to train. At the end of a week all sessions will be erased from the account and replaced by new 3 sessions. That procedure will be repeated over the target 24 weeks.

Clinical Measurements

All of the clinical measurements at baseline, short term (after 24 weeks of intervention and control group) and long-term (48 weeks after baseline) follow-up (**Figure 1**) will be conducted in the outpatient clinic of the German heart center in Munich.

Health Related Physical Fitness (HRPF)

HRPF will be tested by five different tests of the FITNESSGRAM®(26) test battery in standardized order. The tests will be supervised by an experienced sports exercise physiologist.

- **Curl-Up**: Abdominal strength and muscular endurance
  Execution: Supine position, flexed knees with an angle of around 140° and feet placed on the ground. Arms stretched out beside the body. The upper body moves slowly toward the knees and afterwards back to the ground.
  Assessment: Score of valid curls-ups.
- **Push-Ups**: Upper body strength and muscular endurance
  Execution: Prone position, with stretched back and legs. Arms straight under the shoulders pushing the body up and down.
  Assessment: Score of valid push-ups.
- **Shoulder Stretch**: Upper arm and shoulder girdle flexibility
  Execution: Hands clenched to fists. Bring fists together as close as possible behind the back. Avoid hollow back.
  Assessment: Distance of the knuckles of the forefingers. Both sides.
- **Sit and Reach**: Hamstring flexibility
  Execution: Siting position, one leg stretched against a box, toes stretched upright. Other leg flexed. Reaching to the toes or further with straight arms.
  Assessment: Negative or positive values in cm depending on the zero line of the box/toes. Both sides.
- **Trunk Lift**: Trunk extensor strength and flexibility
  Execution: Lying outstretched in prone position. Arms tight to the body and hands under the thighs. Lifting upper body without bouncing while looking toward the ground.
  Assessment: Distance chin to ground in cm. Best of two trials.

Detailed information of the exercises and the test execution can be accessed from the online supplement of our recently published study in children with total cavopulmonary connection (13, 17).

Measures of Arterial Stiffness

Functional: pulse wave velocity (pwv) and central systolic blood pressure (CSBP)

Measures of arterial stiffness involve pulse wave velocity (PWV) and central systolic blood pressure. Functional measures of arterial stiffness play a significant role in the development of cardiovascular disease and associations to physical activity have been outlined in adult and pediatric cohorts as well (27, 28).

Therefore, the automated, oscillometric Mobil-o-Graph (I.E.M GmbH, Stolberg, Germany) is used. The measurement will be performed at the left upper arm after resting in supine position for 5 min. Cuff size is adjusted for individual arm circumference. The inbuilt ARCSolver algorithm of the device uses a transfer function to calculate PWV and central systolic blood pressure based on the peripheral wave form (29). The device has shown good validity and applicability in several studies, even in patients with CHD (12, 30, 31).

Structural: carotid intima-media thickness (cIMT)

Carotid intima-media thickness (cIMT) is a marker for structural changes of the vessels and for early atherosclerosis. It is shown that physical activity in general is associated with favorable IMT outcomes in children and adolescents (32, 33).

cIMT will be measured using B-Mode ultrasound. To minimize inter- and intra-observer variability the guidelines of the Cardiovascular Prevention Working Group of the Association for European Paediatric Cardiology are followed (34).

The semi-automated GM-72P00A Cardiohealth Station from Panasonic (Yokohama, Japan) is used together with a linear probe of 9 MHz to assess cIMT at the arteria carotis communis. The measurements are conducted in supine position with patients head turned 45 degrees to the opposite of the examined side and the neck slightly tilted backwards. In the first step, the neck vessels were scanned for plaques in a cross-section, afterwards the common carotid artery was displayed in the longitudinal view.

Pictures are then taken of the cIMT on the far-wall, in the end-diastolic phase, ∼1 cm proximal to the bifurcation in two angles on the left (210° and 240° degrees) and two angles on the right side (120° and 150° degrees).

Health Related Quality of Life (HRQoL)

The KINDL-R questionnaire is handed out to assess Health related Quality of Life (HRQoL). It is a common, international and well standardized questionnaire for evaluating children's HRQoL from a subjective perspective (35–38). It exists in three versions according to the different age groups. In this study, the KidKINDL for children aged 7–13 years and the KiddoKINDL for chidlren aged 14–17 years is used.

The questionnaire consists of 24 items that refer to the past week and is answered on a 5-point Likert scale (never, seldom, sometimes, often, and always). The scored items are then transferred to a total HRQoL score and to six subscales (physical, emotional, self-esteem, family, friends, everyday functioning). All subscales are graded on a scale from 0 to 100, whereby higher values reflect better HRQoL.

Enrollment

The participants will perform the five motor tasks initially. Based on the test results of a reference cohort, LMS values were calculated according to Cole (39) using R-Studio (version 0.99.879, R-Studio Inc.) with the module extensions *gamlss* (version 3.4-8) and AGD (version 0.34). Children with CHD will be classified according to those established LMS values and z-scores displayed for every of the five tasks and HRPF z-score as the mean of the five tasks.

Participants are consecutive randomized and, when admitted to the intervention arm, start directly the week after screening for baseline characteristics with the exercise program. Every participant receives an anonymous account where 3 sessions will appear every week.

Endpoints

Primary Endpoint

The primary endpoint criterion refers to an improvement of health-related physical fitness, assessed as the mean z-score of the five tests, 24 weeks (∼6 month) after intervention.

Secondary Endpoints

Secondary endpoints are as followed:

- Compliance (adherence) with the supervised web- and home-based intervention measured as participation rate in the training sessions (%).
- Improvement of Central/peripheral blood pressure after 24 weeks (∼6 month) after intervention.
- Improvement of Intima-media thickness after 24 weeks (∼6 month) after intervention.
- Improvement of health-related quality of life 24 weeks (∼6 month) after intervention.
- Improvement of pulse wave velocity 24 weeks (∼6 month) after intervention.

Sample Size Calculation

Sample size was calculated with G* (http://www.gpower.hhu.de) according to the primary endpoint criterion. According to our preceding cross-sectional study (12, 13, 40) a HRPF z-score of about -0.64 ± 0.9 (27th percentile) was averaged in the CHD children in comparison to the healthy reference. The study aims to improve HRPF to a value of 0.0 ± 1.0 (50th percentile) at the end of the intervention. With a power of 85% on a one-sided level of significance of 0.05 a sample size of 31 per group is necessary. Assuming a slight drop out of about 10% in total 70 children will be recruited and allocated randomly 1:1 in the two study arms.

Statistical Methods

Difference of the HRPF z-score for each participant will be compared between both study groups using an independent two-sample *t*-test (if normal distributed) or Mann–Whitney U-Test (if skewed). To calculate gender specific and group specific differences over time, repeated ANOVA measures (if normal distributed) or Friedman-test (if skewed) will be performed. In terms of drop-out an intention to threat analysis will be performed. Two-sided level of significance of 5% will be considered for this primary endpoint.

DISCUSSION

The objective of this RCT is to determine the effect on HRPF and other functional outcome measures, as well as the compliance of a web-based exercise intervention in children with CHD.

Several studies in CHD have shown that participation in a physical exercise-training program is safe and improves fitness (18, 41). Unfortunately, those exercise interventions are underutilized in children with CHD and fitness, as the primary endpoint, is mostly just determined as an improvement in peak oxygen uptake while interest in other functional measures is rare. Indeed, peak oxygen uptake may be the most important prognostic parameter for survival in patients with CHD (19–21) but it is controversial whether that importance already exists in children with CHD. The idea behind is the changing landscape of older patients with CHD that will develop acquired cardiovascular disease, such as hypertension and hyperlipidemia (42, 43). From the perspective of primary prevention, it is therefore more important to shape PA behavior early in life that yield health benefits later in life. Motor skill development across the childhood has proven to influence children's PA behavior beneficially later in life in many ways (44, 45). Therefore, the objective of this study refers to HRPF and other functional outcomes instead of solely peak oxygen uptake.

Several studies already have investigated the feasibility and effectiveness of a home-based exercise intervention for young and adult people with CHD (14, 18). The utility of exercise interventions for this target group is unchallenged, but in 21 studies only 621 subjects, 30 per study, were included (18). Those small sample sizes very often lead to missing results and weak generalizability. Moreover, supervised training interventions are difficult to schedule and to conduct because of the low prevalence of patients with CHD.

To overcome those problems this study uses a web-based solution for two reasons. First, to include more patients in particular from remote areas and second, to deliver and monitor the intervention more effectively. The proposed training stimulus of 3 session of 20 min per week result in a relatively low real training volume of 30 min per week because the other 30 min are recovery time. Most of the studies mentioned in the comprehensive review (18) had longer durations for one training session and an overall higher workload per week but were conducted for only 12 weeks. Since this study takes twice as long we decided not to occupy the patient with intensive training. Instead it is assumed that less workload throughout the week leads to a better long-term compliance. That is also the reason why the patient is free in performing its 3 sessions per week instead of sticking to a fixed schedule.

The biggest challenge is the monitoring of the home-base intervention. Indeed 10 of the 21 studies did not report participation rate. Commonly in home-based intervention that is done by training logs and/or regular phone calls—a method that is inappropriate and especially uneconomical these days because they are not manageable outside a clinical study. With the electronic reporting and the possibility of tracking when training session were streamed it is much easier to follow compliance. In addition, automated messages can be sent to the patients to remind him/her of the execution and vice versa the supervisor when a training progress is missing. Nevertheless, it cannot entirely ruled out that the patients cheat in reporting. Consumer friendly wearable technology is a promising prospect in dealing with that issue but currently applications that are easy to use and connected to a central server are missing (46).

Web-based or eHealth PA interventions in patients with CHD are virtually not existent. Only the PReVaiL (23, 24) trial tried to assess benefits and harms of a tailored eHealth intervention with education and individual counseling in adolescents with CHD. Unfortunately, no change in oxygen uptake, PA and health-related quality of life occurred 52 weeks after the educational and motivational intervention. However, the most frustrating point was the low compliance to the intervention, which clearly outlined the vulnerability of those web-based approaches. Therefor our web-based intervention will contain exercise videos for a maximum of 24 weeks to minimize the number of drop-out. Further each exercise session consists of 20 different exercises that won't take more than 20 min. This means the amount of exercise is right at a level where changes in HRPF still can be expected but former inactive people aren't overstrained with an excessive exercise amount. Nevertheless, eHealth provides easy and wide reachability by low cost. Strategies have to be developed and evaluated to use this technique to maintain and improve the clinical care in this growing cohort of patients with CHD. This study aims to understand feasibility and compliance of those web-based studies.

AUTHOR CONTRIBUTIONS

MM, A-LH, LB, RO, PE, and JM were all involved in development of the study protocol. JM prepared the initial draft of the manuscript. MM and AH set up the database infrastructure for the intervention. All authors read, contributed to editing, and approved the final manuscript.

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Respiratory Muscle Strength and Exercise Performance in Cystic Fibrosis–A Cross Sectional Study

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Introduction: Decreased respiratory muscle strength in patients with cystic fibrosis (CF) may cause progressive exercise intolerance during cardiopulmonary exercise testing (CPET), and may contribute to the development of chronic respiratory insufficiency. The aim of this study is to evaluate exercise tolerance during CPET of children and adults with clinically stable CF who exhibit different respiratory muscle strength.

Methods: Sixty-nine clinically stable CF subjects aged 8–33 years underwent spirometry, body plethysmography, CPET, and respiratory muscle strength measurement. Respiratory muscle strength was measured using maximal inspiratory pressures (Pi_{max}) and maximal expiratory pressures (Pe_{max}). Participants were stratified into three groups according to Pi_{max} values:below normal ($\leq$80% predicted), normal (81–100% predicted), and above normal (>100% predicted). A similar stratification of participants was made according to Pe_{max} values. The oxygen consumption on peak load (VO_{2peak}) was expressed relative to BM (VO_{2peak}/kg), relative to BM raised by the exponent of 0.67 ($VO_{2peak}/kg^{0.67}$) and as log-linear adjustment of VO_{2peak} ($VO_{2peak/kg-alo}$).

Results: Participants with low Pe_{max} values had a lower mean maximum load per kilogram/predicted (W_{max}; $p = 0.001$) VO_{2peak}/kg ($p = 0.006$), $VO_{2peak}/kg^{0.67}$ ($p = 0.038$) and $VO_{2peak/kg-alo}$ ($p = 0.001$). There were no significant differences in exercise tolerance parameters with regard to Pi_{max} values. Stepwise multiple linear regressions confirmed that Pe_{max} ($B = 24.88$, $\beta = 0.48$, $p < 0.001$) was the most powerful predictor of W_{max}. There were no statistically significant differences in age, lung function parameters, exacerbation score, or respiratory muscle strength according to gender.

Conclusions: In subjects with clinically stable CF, expiratory muscle strength is associated with a decrease in exercise performance during CPET and can predict exercise intolerance. Increase in expiratory muscle strength by patient specific rehabilitation protocols would result in improvement of exercise tolerance.

Keywords: cystic fibrosis, exercise testing, spirometry, whole body plethysmography, respiratory muscle strength

INTRODUCTION

Lung hyperinflation, decreased lung function, and malnutrition are leading causes of progressive exercise intolerance in patients with cystic fibrosis (CF) (1). Respiratory muscle weakness may also contribute to the development of chronic respiratory insufficiency (2). However, previous studies have not successfully confirmed a significant relationship between respiratory muscle strength, nutritional status, lung function, and exercise tolerance (3).

Measurement of maximal respiratory pressures serves to determine whether respiratory muscle weakness exists and to quantify its severity. It is cheap and simple way to evaluate respiratory muscle force. The results of studies published to date regarding muscle strength in CF patients are contradictory (2–5). Some studies evaluating maximum static respiratory pressures have indicated preserved respiratory muscle strength in CF patients, although there are opposing opinions (2, 3, 6, 7). The preserved strength was attributed to respiratory muscles being exercised through chronic coughing and an increased ventilatory load. Opposite findings were presumably not related to metabolic reasons or lower serum androgen concentrations (8, 9). Patients with mild CF exhibit significantly diminished maximal inspiratory pressure (Pi_{max}) and maximal expiratory pressure (Pe_{max}) compared with healthy controls (7). The relationship between respiratory muscle strength and the results of modified shuttle tests has already been investigated (10), but the relationship between respiratory muscle strength and the results of cardiopulmonary exercise testing (CPET) had not been investigated until now.

The aim of this study is to evaluate exercise tolerance during CPET of children and adults with clinically stable CF who exhibit different respiratory muscle strength. We hypothesized that the patients with more severe lung disease would have decreased respiratory muscle strength, which may have a negative influence on exercise tolerance.

METHODS

Study Design

This was a cross sectional study of respiratory muscle strength and exercise tolerance, conducted from August 2016 to August 2017 in Mother and Child Health Institute of Serbia, the national CF center. Patients and their legal guardians signed informed consent documents before participating in the study. The protocol was approved by the Ethics Committee of the Mother and Child Health Institute of Serbia (number 82/16). All subjects and their legal guardians gave written informed consent in accordance with the Declaration of Helsinki.

Subjects

For this study, 71 subjects with mild to moderate CF lung disease aged 8–33 years were screened. Although this represents a relatively inhomogeneous age group, all subjects had previous experience with measurements as defined by the protocol of the study. All participants were clinically stable, without symptoms of pulmonary exacerbation, defined as systemic antibiotic use for at least 6 weeks prior to the start of the study. Although previous studies had not shown that pulmonary exacerbation has a negative impact on muscle strength, these studies showed it has a negative influence on lung function and exercise tolerance (11–13). Height and body mass (BM) were recorded. Adiposity was expressed as Z-score of body mass index (BMI). Body mass was also raised to the 0.67.

Measurements of lung function and respiratory muscle strength were taken, and exercise testing was performed in consecutive order, at the same time of the day on each occasion, after a half-hour pause between each procedure. Treatment with bronchodilators was allowed as routine therapy, as well as a regular course of physiotherapy at home prior to the study.

Lung Function and Cardiopulmonary Exercise Testing

Spirometry and whole-body plethysmography were performed on a pneumotach system using a volume-constant method (MasterLab, Jaeger, Würzburg, Germany). The reference equations used for pulmonary function testing were those of Zapletal et al. (14) Participants performed progressive CPET on an electrically braked cycle ergometer (MasterScreen CPX; Jaeger, Würzburg, Germany), following the modified Godfrey protocol to maximum effort. Work increments were planned individually to reach the maximal exercise level by approximately 8–10 min. The determination of maximal effort was based on objective criteria: peak heart rate (HR) >95% HR predicted (210 – age) or respiratory exchange ratio (RER) >1.1. Two patients who did not achieve at least one of these criteria were excluded from the study. Patients breathed through a tightly sealed mask with electronically compensated dead space. Mask was connected to a TripleV sensor. Expired gas passed to an attached metabolic cart (Oxycon pro, Carefusion) with oxygen and carbon dioxide analyzers. Oxygen saturation (SaO_2) was measured continuously with sensors placed on participants' fingertips (Model 3011; Nonin Medical, *Minneapolis MN,* USA). A computer calculated breath-by-breath tidal volume, respiratory rate and minute ventilation, oxygen consumption (VO_2), carbon dioxide production (VCO_2), and RER as well. The oxygen consumption on peak load (VO_{2peak}) was expressed in absolute values ($L{\cdot}min^{-1}$), relative to BM (VO_{2peak}/kg) and relative to BM raised by the exponent of 0.67 ($VO_{2peak}/kg^{0.67}$). In addition, log-linear adjustment of VO_{2peak} ($VO_{2peak/kg-alo}$) was done as it was proposed by Welsman et al. (15). Ventilation relative to VO_2 and VCO_2 was expressed as ventilatory equivalents for O_2 and CO_2 (V_E/VO_2 and V_E/VCO_2). The reference values of peak exercise capacity (W_{max}) were those of Wasserman et al. (16) The anaerobic threshold (AT) was determined using the V-slope method (17). Participants were asked to score their sense of breathlessness at W_{max} using a ten-point Borg scale immediately after exercise. Study participants were familiar with CPET, performed on regular annual check-ups, according to Statement of European Cystic Fibrosis Exercise Working Group (18).

TABLE 1 | Demographic data.

Mean ± SD	Total	Male	Female	Children	Adults
Age (years)	16.8 ± 6.5	17.7 ± 6.5	15.8 ± 6.5	12.3 ± 3.1	23.4 ± 4.1†
Exacerbation score (1/year)	1.6 ± 0.7	1.4 ± 0.7	1.7 ± 0.7	1.5 ± 0.7	1.5 ± 0.7
BMI	18.4 ± 3.3	19.2 ± 3.4	17.6 ± 2.9*	17.3 ± 3.3	20.3 ± 2.5†
FEV_1 (%)	76.5 ± 27.1	76.7 ± 28.3	76.4 ± 26.2	84.3 ± 25.8	65.1 ± 25.1†
FVC (%)	83.0 ± 23.3	83.8 ± 24.9	82.2 ± 21.8	86.5 ± 23.4	77.8 ± 22.6
RV/TLC (%)	167.8 ± 53.3	166.3 ± 57.8	169.4 ± 48.7	158.1 ± 48.4	182 ± 0, 57.7†
VO_{2peak}/kg	33.2 ± 7.5	35.1 ± 7.8	31.2 ± 6.6*	35.6 ± 6.7	29.8 ± 7,3†
$VO_{2peak}/kg^{-0.67}$	115.3 ± 28.8	127.2 ± 27.5	102.2 ± 24.4†	116.2 ± 27.3	113.9 ± 31.3
VO_{2peak}/kg_{alo}	4.2 ± 0.3	4.3 ± 0.3	4.1 ± 0.3†	4.4 ± 0.3	4.2 ± 0.2†
W_{max} (%)	85.1 ± 17.6	83.2 ± 19.4	87.2 ± 15.5	82.7 ± 16.1	88.5 ± 19.5
Pi_{max} (%)	108.1 ± 34.6	102.1 ± 39.3	114.6 ± 27.7	112.1 ± 37.0	102.1 ± 30.3
Pe_{max} (%)	104.3 ± 34.4	100.2 ± 33.6	108.8 ± 35.3	102.9 ± 32.9	106.4 ± 37.1
VE/VCO_2 W_{max}	32.4 ± 4.2	31.4 ± 4.3	33.5 ± 3.7*	32.8 ± 3.8	31.9 ± 4.6
BRI W_{max}	0.8 ± 0.3	0.9 ± 0.3	0.8 ± 0.2	0.8 ± 0.2	0.9 ± 0.3
SpO_2 rest (%)	96.7 ± 2.0	96.9 ± 1.8	96.5 ± 2.2	96.9 ± 1.9	96.3 ± 2.2
SpO_2 W_{max} (%)	91.7 ± 5.4	91.7 ± 4.9	91.7 ± 5.9	93.1 ± 4.4	89.7 ± 6.1†

*RV/TLC, residual volume/total lung capacity; W_{max}, maximal load; VO_2peak/kg, maximal oxygen consumption/kg; BRI, breathing reserve index; Pi_{max}, maximal inspiratory pressure; Pe_{max}, maximal expiratory pressure; V_E/VCO_2, ventilatory equivalent for carbon dioxide. *$p < 0.05$, †$p < 0.01$.*

TABLE 2 | Exercise testing and respiratory muscle strength.

		N	W_{max} (%)	VO_{2peak} ml/kg	VO_{2peak} ml/kg$^{0.67}$	VO_{2peak} ml/kg-alo	Dyspnea score
Pe_{max} (% pred)	≤80%	15	72.7 ± 17.2	27.9 ± 6.5	98.9 ± 36.6	4.1 ± 0.4	7.3 ± 1.9
	81–100%	22	83.1 ± 16.5	34.6 ± 6.9	121.8 ± 25.7	4.3 ± 0.3	6.6 ± 1.5
	>100	32	92.3 ± 15.3	34.8 ± 7.4	118.4 ± 24.4	4.2 ± 0.3	6.5 ± 1.5
	Total	69	85.1 ± 17.6†	33.3 ± 7.5†	115.3 ± 28.8*	4.2 ± 0.3†	6.7 ± 1.6
Pi_{max} (% pred)	≤80%	14	75.4 ± 20.9	32.8 ± 9.48	117.2 ± 32.3	4.3 ± 0.3	7.5 ± 1.9
	81–100%	15	88.2 ± 16.6	32.1 ± 9.4	120.4 ± 34.0	4.3 ± 0.3	6.8 ± 1.4
	>100	40	87.3 ± 15.9	33.8 ± 5.9	112.7 ± 25.7	4.2 ± 0.3	6.4 ± 1.5
	Total	69	85.1 ± 17.6	33.3 ± 7.5	115.3 ± 28.8	4.2 ± 0.3	6.7 ± 1.6

*W_{max}, maximal load; VO_2peak/kg, maximal oxygen consumption/kg; VO_{2peak}, expressed relative to BM raised by the exponent of 0.67 ($VO_{2peak}/kg^{0.67}$); log-linear adjustment of VO_{2peak} ($VO_{2peak/kgalo}$); Pi_{max}, maximal inspiratory pressure; Pe_{max}, maximal expiratory pressure. *$p < 0.05$. †$p < 0.01$.*

Respiratory Muscles Strength Measurement

Respiratory muscle strength was measured using a handheld mouth pressure meter (MicroRPM, CareFusion Ltd., San Diego, CA, USA) connected to a computer (Puma® software). All procedures were performed with the subjects seated comfortably, and maximum respiratory pressures were expressed as Pi_{max} (maximal inspiratory pressures) and Pe_{max} (maximal expiratory pressures) (19). A maximal static expiratory maneuver was measured from total lung capacity (TLC), and a maximal static inspiratory maneuver from residual volume (RV). Pressure was maintained for at least 1.5 s so that the maximum pressure sustained for 1 s could be calculated. Participants were encouraged to give their best effort during the procedure. Five or more measurements, separated by 2 min of rest, were taken until two reproducible maximal values were obtained. The results were expressed as percentage predicted for age and gender using reference values of Wilson et al. (20).

In order to evaluate differences in lung function and exercise tolerance, participants were stratified into three groups based on Pi_{max} values: group 1 (≤80% predicted), group 2 (81 to 100% predicted), and group 3 (>100% predicted). A similar 3-group stratification was made based on Pe_{max} values.

Statistical Analysis

Statistical analyses were performed at the Institute for Medical Statistics, School of Medicine, Belgrade. Differences between groups were analyzed using one-way analysis of variance (ANOVA). Student's *t*-test was used to examine differences between males and females. Simple linear regression was used to predict W_{max} as the dependent variable. Multiple and stepwise linear regressions were used when several predictors that might explain the model of one dependent variable were present. *P*-values < 0.05 indicated statistical significance. Sample size estimation was performed according to data obtained after evaluation of the results from the first 15 subjects. The power of the one-way ANOVA procedure was 0.920. Data were analyzed using SPSS 21 for Windows and expressed as mean ± SD.

RESULTS

Data collected from 69 participants with CF (36 males, 33 females) were included in this analysis. The mean participant age was 16.8 ± 6.5 years (range, 8–33 years). Mean values of Pi_{max} and Pe_{max} were within the normal range.

Children and adolescents had significantly higher FEV_1 ($p < 0.001$), VO_{2peak}/kg ($p = 0.001$) $VO_{2peak/kg-alo}$ ($p < 0.001$), than adults. There were no significant differences with regard to participant's age comparing W_{max}, $VO_{2peak/}kg^{0.67}$, Pi_{max}, and Pe_{max} (**Table 1**).

Participants with decreased Pe_{max} had significantly lower lung function values: lower mean FEV_1 ($p < 0.001$), and higher mean RV/TLC ($p = 0.002$). Differences were not proved to be statistically significant between Pi_{max} groups.

CPET measurements showed that subjects with low Pe_{max} had lower mean W_{max} ($p = 0.001$), VO_{2peak}/kg ($p = 0.006$), $VO_{2peak}/kg^{0.67}$ ($p = 0.038$) and $VO_{2peak-alo}$ ($p < 0.001$) values. There were no significant differences in exercise tolerance with regard to Pi_{max}. There were no significant differences between groups with regard to oxygen saturation rate SpO_2 at W_{max} or dyspnea score (**Table 2**).

There were no statistically significant differences in age, lung function parameters, exacerbation score or respiratory muscle strength according to gender. Males had better BMI, VO_{2peak}/kg, $VO_{2peak}/kg^{-0.67}$, $VO_{2peak-alo}$ and ventilatory equivalent for CO_2 (V_E/VCO_2; **Table 1**).

Simple linear regression showed that Pe_{max}, FEV_1 (%) and RV/TLC (%) were independent statistically significant predictors of W_{max} (**Table 3**).

Stepwise multiple linear regressions confirmed the value of Pe_{max} ($B = 24.883$, $\beta = 0.483$, $p < 0.001$) as the best predictor of W_{max}, instead of parameters that were excluded from the analysis (RV/TLC, BMI, Pi_{max}, FEV_1; **Figure 1**).

TABLE 3 | Linear regression with W_{max} as a dependent variable.

Independent variable	Simple linear regression			Multiple regression models		
	B	SE	*p*	*B*	SE	*p*
Pi_{max}	11.9	6.1	0.05	−4.5	6.40	0.49
Pe_{max}	24.9	5.5	<0.001	20.6	6.75	0.003
FEV_1 (%)	0.30	0.07	<0.001	0.14	0.22	0.26
RV/TLC (%)	−0.15	0.04	<0.001	−0.04	0.06	0.48

RV/TLC, residual volume/total lung capacity; Pi_{max}, maximal inspiratory pressure; Pe_{max}, maximal expiratory pressure.

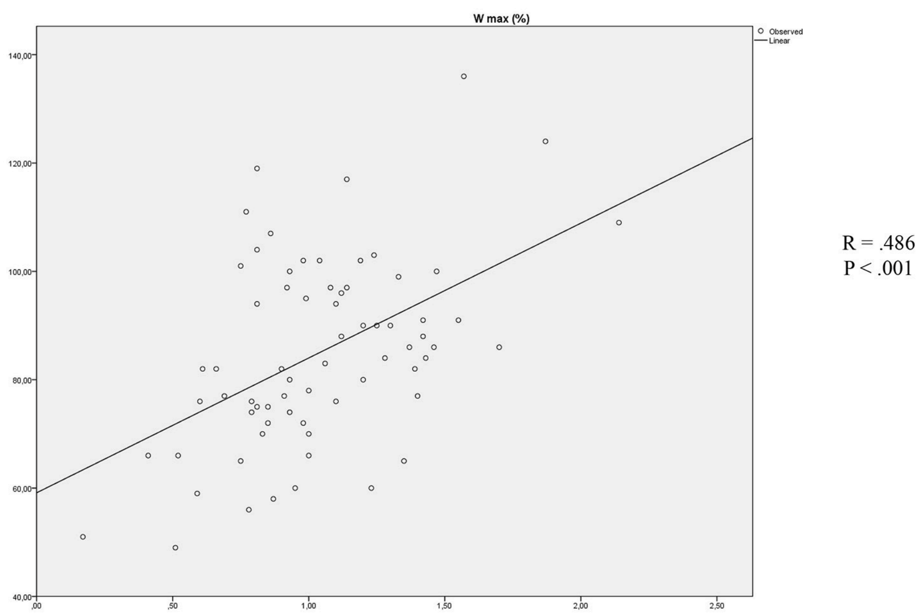

FIGURE 1 | Association between Pe_{max} and W_{max}.

DISCUSSION

Our study showed that CF subjects with decreased expiratory muscles strength had diminished lung function and exercise tolerance. Lower values of lung function and exercise intolerance were not shown to be related to inspiratory muscle strength.

Peripheral muscle dysfunction (both strength and endurance) in patients with CF is probably multifactorial. Divangahi et al. (21) showed in animal models that lack of the cystic fibrosis transmembrane conductance regulator (CFTR) in skeletal myotubules, including the diaphragm, lead to dysregulation of calcium homeostasis, augmentation of inflammatory gene expression, and increased muscle weakness. Although this is an interesting finding, diminished sarcolemmal excitability due to dysfunctional CFTR is only one of several possible causes of reduced muscle strength in patients with CF (22). Probably the most prominent is physical inactivity, which leads to plain myopathy. Myopathy is generally the result of a sedentary lifestyle, and can be improved with physical exercise. Other factors (e.g., systemic inflammation, oxidative stress, frequent exacerbation, use of systemic corticosteroids, malnutrition) also contribute to skeletal muscle atrophy and weakness in CF patients (23).

Although frequent use of systemic corticosteroids in some CF patients may have a negative influence on skeletal muscle strength, the leading factors used to explain the associated respiratory muscle weakness were pulmonary hyperinflation and malnutrition (24–26). Using near-infrared spectroscopy and *P* magnetic resonance spectroscopy with a relatively small group of CF patients displaying preserved lung function, Werkman et al. (27) did not find that intrinsic metabolic abnormalities in oxygenation and muscle oxidative metabolisms contributed to exercise intolerance. Static hyperinflation has also been shown to be an important cause of ventilatory limitation during progressive CPET (28). We have shown a significant negative correlation between Pe_{max} and hyperinflation, which was not the case with Pi_{max}. Dassios et al. (7) showed that CF patients with mild lung disease exhibit impaired respiratory muscle function in comparison to healthy controls. Our results, from a smaller group of patients comparable in age, also showed the lowest values of static respiratory pressures in patients with decreased lung function. However, the only difference that proved to be significant was a reduction in expiratory muscle strength. Furthermore, we showed that, during CPET, Pe_{max} was a useful predictor of W_{max}, which is a "gold standard" for the estimation of exercise tolerance. In both healthy individuals and in CF patients with mild lung disease, expiratory muscles (mostly abdominal and rib cage muscles) are active only in the case of an increased workload. With this in mind, we think that the primary dysfunction of these muscle groups is caused by rib cage deformity, which leads to secondary muscular inefficacy. Interesting data showing a negative correlation between respiratory pressures and the upper arm muscle area confirmed the importance of complementary estimation of nutritional status as well as BMI calculation (29). In addition, static respiratory pressures correlate with skeletal muscle strength (10). This correlation leads to one of the limitations of our study: it lacked the particular estimation of abdominal and rib cage muscles strength.

We showed a significant positive correlation between FEV_1 and Pi_{max}, a finding that is in accordance with recently publish data on adults with CF (30). However, we found an insignificant correlation between inspiratory muscle strength and exercise capacity during CPET. This finding is in opposition with some previous studies that estimated exercise tolerance using a modified shuttle test (10). Field tests, although being useful in clinical practice are often submaximal and its usefulness may be limited. Leroy (31) indirectly confirmed our results in their research, showing no significant correlation between inspiratory muscle endurance calculated from Pi_{max} and exercise capacity.

Regardless of disease severity, regular physical activity improves exercise tolerance and respiratory muscle strength (32). Exercise programs improve muscle endurance, which influences the sensation of dyspnea during exercise (6, 22). This is of particular importance, knowing that CF patients are at increased risk of respiratory muscle fatigue (29).

Dunnink et al. accentuated decreased respiratory muscle strength in females among CF patients with a mean age of 26 years (10). We did not show such a difference. In fact, females exhibited better mean Pe_{max} and Pi_{max} in our study. This is probably because the lung function results of the younger cohort in our study were not significantly different between males and females, which was the case in the above-mentioned research. Increased VO_2/kg in males can be explained by gender-dependent skeletal muscle composition.

Normalizing the data using allometric scaling has been proposed as an efficient method when large body mass differences are present (15). We showed that younger participants with milder lung disease had higher values of $VO_{2peak-alo}$ that can be explained by muscle wasting in more severe disease. Nevertheless, age difference was not proved to be significant factor comparing respiratory muscle strength.

We think regular measurement of respiratory muscle strength should be a usual clinical practice for patients with CF, especially because it can be accurately measured with portable mouth pressure manometers. The practice may help in recognizing those patients in need of intensive rehabilitation programs and observed exercise training to improve habitual physical activity and respiratory muscle strength.

AUTHOR CONTRIBUTIONS

AS contributed for literature search, data collection, study design, analysis of data, manuscript preparation, and review of manuscript. PM contributed for data collection, study design, analysis of data, manuscript preparation, and review of manuscript. GM-S contributed for literature search, study design, analysis of data, manuscript preparation, and review of manuscript. GT contributed for study design, analysis of data, manuscript preparation, and review of manuscript.

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Tele-Exercise as a Promising Tool to Promote Exercise in Children With Cystic Fibrosis

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Introduction: Cross-infection risk from contact exposure limits exercise opportunities in children with cystic fibrosis (CF). The purpose of this study is to evaluate the feasibility of a new live-streamed platform which delivered supervised and interactive group exercise sessions to CF children via digital devices while avoiding contact exposure.

Methods: Ten CF children participated in a 6-week tele-exercise program. The program consisted of three 30-min sessions per week for a total of 18 sessions and included aerobic, resistance, and flexibility exercises. Sessions were streamed via a HIPAA compliant VSee telemedicine platform. Instructors and participants were able to interact in real-time online. Heart rate (HR) monitors were used to evaluate exercise intensity with a goal of moderate-vigorous physical activity ≥10 min, 70% of the sessions. System usability scale (SUS) and qualitative questionnaires were used to gauge participants' satisfaction and feedback.

Results: On average participants attended 85% of the sessions. For the overall sessions participants exercise 21.1 ± 6.9 min at moderate-vigorous physical activity. Nine out of 10 participants used the exercise platform without parental guidance. Qualitative questionnaire and System Usability Scale (SUS) indicated that all participants enjoyed the tele-exercise program and highly rated the exercise platform 90.8 out of 100 (passing > 68).

Conclusions: Tele-exercise platform is a promising new approach to promote exercise in children with CF. The online platform allows supervised virtual group exercise experience with optimal participation and no risk for cross-infection. This approach might prove to be useful in enhancing the use of exercise as therapy in children with CF.

Keywords: exercise training, fitness, exercise medicine, pediatrics, physical activity

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INTRODUCTION

Fitness in patients with cystic fibrosis (CF) is associated with increased survivability (1) but only 60% of CF centers follow the recommendation for annual fitness tests (2). Promoting exercise at home has yet to be adopted as an integral component of CF care. Summer residence exercise programs for children with CF, in which the exercise regimens and social milieu can be geared to the needs of these patients with CF, lead to significant improvement in exercise parameters and well-being (3). However, concerns regarding the cross-infection risk have almost completely eliminated such group activities preventing CF patients from receiving the benefit of peer interactions which can promote physical activity in youth (4).

There is an emerging body of literature suggesting that telemedicine has been proved useful in providing home rehabilitation for chronic diseases (5, 6). Tele-exercise has the promise to provide a supervised group exercise experience while mitigating the potential problem of cross-infectivity. No studies have been done to assess the feasibility of tele-exercise in CF. Our pilot study was the first to examine the implementation of an interactive tele-exercise program with real-time wearable device data collection in pediatric CF patients. Our goal was to evaluate the feasibility of a streaming software program and remote monitoring as a convenient and accessible method for pediatric CF patients in order to maintain desired level of physical activity.

MATERIALS AND METHODS

Participants

Ten children and adolescents with CF 8–20 years of age participated in this study. **Table 1** illustrates the anthropometric, physiological and genetic characteristics of the participants. Those who had severe pulmonary disease (FEV1 < 40%), recent pulmonary exacerbation within the last month, or unable to perform exercise as determined by their physician were excluded from the study. **Figure 1** depicts an overview of study design. The study was approved by the Institutional Review Board at Memorial Care Health System, and written informed assent and consent was obtained from all participants and their parents upon enrollment.

Anthropomorphic Assessment

Standard calibrated scales and stadiometers were used to determine height and body mass. Body mass index [BMI = wt/ht^2 (kg/m^2)] percentile was calculated using the published standards from the Centers for Disease Control, National Center for Health Statistics (7).

Fitness Assessment

Each participant performed a ramp-type progressive cycle ergometer cardiopulmonary exercise test (CPET) using the Medgraphics Ultima™ CardiO2® gas exchange analysis system before and after the 6-week tele-exercise program. Following 1 min of unloaded pedaling, the work rate (WR) was increased at 10–15 watts/min increments to the limit of the subject's tolerance. Gas exchange was measured breath-by-breath and peak VO_2 was calculated using standard methods (8, 9). There is currently no validated, universally-accepted respiratory exchange ratio (RER) cutoff in children for the determination of peak VO_2. We used RER > 1.0, a criterion used by Rowland and coworkers (10). Percent predicted peak VO_2 was calculated based on Medgraphics pediatric norms. Pulmonary function testing was done prior to the fitness test to measure maximal expiratory flow rates (FEV1).

Software Setup

Each participant was instructed how to download and setup VSee, a HIPAA compliant and encrypted telemedicine program. A member of the research team was available to visit the participant's homes to help set up or for troubleshooting. Before starting the exercise program, a test run was performed on VSee with research staff and the participant to ensure that lighting and internet connection was optimal.

Exercise Program

The exercise program consisted of three 30-min session per week over 6 weeks for a total of 18 sessions. One participant wanted to volunteer but, for personal reasons, did not want to exercise with other children even virtually. The remaining nine participants were divided into three groups. Each session was streamed in real-time using VSee and allowed live interaction among the instructors and participants. Sessions consisted of 3–4 min of warmup, 20–25 min of aerobic and plyometric exercises, ending with 3–4 min of stretching and huff coughing.

Exercise intensity during the sessions was assessed using Polar heart rate (HR) monitors. Moderate physical activity (PA) was defined as 60–75% of estimated maximum HR of 200 bpm. Vigorous PA was defined as >75% of estimated maximum HR. The number of minutes participants exercised at moderate-intensity (120–150 bpm), vigorous intensity (150–180 bpm) and >180 bpm was recorded. The aim was to have at least 10 min out of the 30-mi exercise session at moderate-vigorous exercise intensity in at least 70% of the exercise sessions. Data is presented as means ± SD.

Questionnaires

Following the tele-exercise program, participants completed a system usability scale (SUS) to evaluate the user's satisfaction and the technological effectiveness of the software. SUS scores range from 0 to 100 with a passing score > 68 (11). The SUS is a widely used assessment tool to rate the perceived usability of computing products such as telemedicine platforms (12). Participants also answered a qualitative questionnaire regarding their thoughts about the program:

What was your most/least favorite part of the program and why?
What were the most/least favorite exercises and why?
Would you participate in a similar program again?
What type of changes have you seen because of the program, if any?
How has the program helped you?

RESULTS

Participants attended on average 15 (85%) of the sessions with nine participants attending 13 (75%) or more of the 18 exercise sessions (**Table 1**). One participant attended 5 (28%) of the sessions due to scheduling conflicts with school and extracurricular activities. Each session lasted about 30 min. 9 out of the 10 participants achieved the target HR goal and participants overall spent 21.1 ± 6.9 min on moderate-vigorous PA. Participants exercised 15.3 ± 3.4 min at moderate

TABLE 1 | Participants anthropometric, physiological, and genetic characteristics.

Subject ID	Age range	Genetics	Baseline BMI % ile	Baseline Peak VO_2 (mL/kg/min) (%predicted)	Post-training peak VO_2 (mL/kg/min) (%predicted)	Baseline FEV1 (L)	Post-training FEV1	Sessions attended (Total = 18)
1	11–15	F508, p.R1066H, P.L1324P	63	27.4 (76)	28.8 (79)	86	88	17
2	11–15	F508, F508	33	33.9 (80)	35.2 (89)	94	98	5
3	16–20	C.2988 + IG > A, N1303K	74	28.4 (83)	27.3 (77)	91	83	17
4	11–15	F508, 1717-IG->A	17	43.8 (97)	36.5 (83)	74	76	14
5	6–10	F508, C948delT (1078delT)	61	40.1 (102)	41.7 (99)	88	85	16
6	16–20	3,120 + G7A/3876delA	76	23.9 (70)	25.7 (75)	65	52	13
7	16–20	F508, F508	17	28.7 (81)	29.2 (83)	75	72	17
8	11–15	F508, F508	81	32.3 (88)	33.6 (92)	110	110	14
9	11–15	W1282x/2183 delAA>G	72	44.1 (98)	46.2 (103)	86	88	15
10	16–20	F508, F508	17	27.9 (71)	23.1 (58)	81	63	18

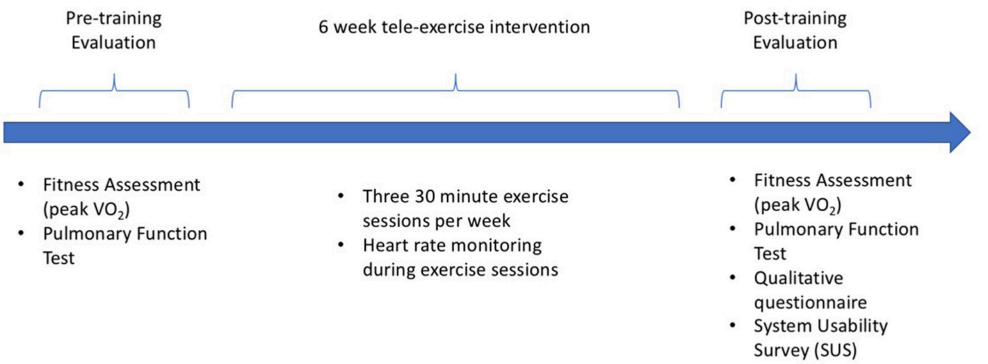

FIGURE 1 | Overview of study design.

intensity (120–150 bpm), 5.8 ± 4.6 min at vigorous intensity (150–180 bpm) and achieved maximum HR of 159.5 ± 10.4 bpm. Baseline peak VO_2 was on average 84.6 ± 11.3% predicted and did not change following the 6-week exercise intervention. No significant differences beyond normal short-term variability were observed between pre- and post-exercise program in pulmonary function test (PFT) (13). The participant who had the largest relative reduction in FEV1 and peak VO_2 at post-training also had respiratory illnesses on the day of the test (**Table 1**).

Using the System Usability Scale, the exercise program on the VSee platform was highly rated by the participants with a score of 90.8, suggesting that the software platform and exercise program was easy to use without requiring outside guidance or intervention. Qualitative questionnaire indicated that all participants liked the tele-exercise program and wanted to continue with the exercise sessions. Participants enjoyed having the motivation to exercise, the opportunity to be led by an instructor, and most of them cited the social benefits of a group setting as their favorite parts of the program:

"Love chatting with everyone."

"Talking to people because it made the sessions more fun."

"Seeing friends and the instructor."

"I love working out with everyone even though I'm exhausted, I have fun, it makes me not hate working out."

"I like socializing with everyone."

"All of [it] because it is exercise [I] would not have otherwise gotten."

Only one participant had a technological critique because her "screen kept freezing." Participants provided statements on how the program had helped them:

"Helped me exercise instead of watching TV."

"It made me 'exercisable' and got to see the doctor."

"It helped me because I'm always lazy to work out or do it myself.

"Strengthened muscle around my knees so [they] had more stability, drastically decreasing my knee pain. Also noticed that the exercises got easier as the program went by."

"Great shape and it was fun."

"Less coughing, less lung issues [that] negatively impact [my] daily life. . . , more positive, better sleep."

DISCUSSION

The aim of this study was to evaluate feasibility of an online interactive platform as a way to deliver and promote exercise in children with CF. Nine out of 10 participants attended most of the exercise sessions, suggesting that streaming tele-exercise sessions is a viable and convenient method to encourage physical activity without subjecting them to the cross-infection risks associated with in-person group activity. The tele-exercise platform allows for flexible scheduling and is accessible from home, bypassing transportation barriers. From most of the participants' observations, the appeal of the tele-exercise program seemed to be centered on the group supervised training.

Incorporating remote monitoring was essential for instructors to adjust the exercise prescription based on the participant's performance. During the exercise session, instructors would pause periodically to ask participants for their HR readings. In this study, nine participants achieved target HR goal, while one was just below (9.4 ± 5.3 bpm) the target HR goal. An improvement to the next iteration of the tele-exercise program would be the addition of another platform that displays an overview of all participants' HR in real-time.

In contrast to traditional tele-rehabilitation studies using phone calls or video recording interventions, our study relied on the participants ability to use the VSee streaming platform as well as their home webcams. We found that regardless of age, participants had little trouble with signing on or using the platform and in fact, were overall very satisfied with their experience with the software. One participant reported difficulties with periodically having their screen frozen, which was attributed to the internet and could be avoided by checking the home's internet bandwidth prior to implementing the program to ensure that the VSee program could run with adequate resolution.

People with CF often feel isolated as they cannot interact face to face with their peers due to the high risk of cross contamination (14). There is evidence to support the idea that accountability is an important factor in exercise program adherence. Participants were motivated to log in because they had friends who share the same chronic disease to exercise with.

This study highlights the need for evaluating tele-exercise programs for children with CF. To improve aerobic fitness, the current program should be modified to include exercises at a higher target HR for longer duration. A larger study is needed to evaluate participants' retention in a longer program and evaluate additional physiological and psychological variables, such as muscle strength, agility, balance and cognitive function in different tele-exercise programs.

SUMMARY

Tele-exercise program is an innovative and promising approach to promote physical activity in children with CF through live interaction of streamed exercise sessions. Most participants felt they were part of a virtual exercise group. This platform is user-friendly and can be easily deployed for pediatric CF patients to provide supervised training, monitoring HR response and shortness of breath, while mitigating cross-infection risk. This approach may prove to be useful in enhancing the use of exercise as therapy in children with CF.

AUTHOR CONTRIBUTIONS

JC, DC, AS, and SR-A: conception and design of study. JC and AS: data collection. JC, DC, FH, AS and SR-A: data analysis and interpretation. JC, DC, AS, and SR-A: drafting the article. JC, DC, AS, EN, and SR-A: critical revision of the article. JC, DC, FH, AS, EN, and SR-A: final approval of the version to be published.

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Tackling Youth Inactivity and Sedentary Behavior in an Entire Latin America City

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Real-world interventions are fundamental to bridge the research-practice gap in healthy lifestyle promotion. This study aimed to assess the impact of a 7-month, intensive, city-wide intervention ("Life of Health") on tackling youth inactivity and sedentary behavior in an entire Latin-American city (Jaguariuna, Brazil). For youth, a program focused on tackling inactivity/sedentary behavior was delivered at every school ($n = 18$). Plausibility assessments (pre-to-post design) were performed with 3,592 youth (out of 8,300 individuals at school age in the city) to test the effectiveness of the intervention. Primary outcomes were physical activity and sedentary behavior. Secondary outcome was BMI *z*-score. Physical activity did not change (0; 95%CI:-2.7–2.8 min/day; $p = 0.976$), although physically inactive sub-group increased physical activity levels (11.2; 95%CI:8.8–13.6 min/day; $p < 0.001$). Weekday television and videogame time decreased, whereas computer time increased. Participants with overweight and obesity decreased BMI *z*-score (-0.08; 95%CI:-0.11−0.05; p <0.001; −0.15; 95%CI:-0.19−0.11; $p < 0.001$). This intervention was not able to change the proportion of physical inactivity and sedentary behavior in youth at a city level. Nonetheless, physically inactive individuals increased PA levels and participants with overweight and obesity experienced a reduction in BMI *z*-score, evidencing the relevance of the intervention. Education-based lifestyle programs should be supplemented with environmental changes to better tackle inactivity/sedentary behavior in the real-world.

Keywords: physical activity, sedentarism, healthy lifestyle, school-based intervention, obesity

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INTRODUCTION

Physical inactivity (i.e., the inability to achieve the minimum recommended levels of physical activity [PA]) and sedentary behavior (i.e., any waking behavior in a sitting/laying position with low energy expenditure) are important risks factors associated with childhood obesity and related health problems in most Western countries (1, 2). PA among children and adolescents is believed to be insufficient (3) and low levels of PA seem to continue into adulthood (4). Thus, combating physical inactivity and sedentary behavior during childhood is a key strategy for preventing future health risks (5, 6).

However, a systematic review concluded that a lack of high-quality large-scale studies precluded conclusions on the effectiveness of efforts to promote PA in youth (7). Moreover, community-based interventions tackling sedentary behavior, which has been associated with obesity in youth, independently of physical inactivity (8), are scant.

The "Life of Health" was a real-word, multi-faceted intervention aimed to promote lifestyle changes in an entire Latin-American city with over 50,000 inhabitants. Specifically for youth (approximately 8,300 people), the intervention mainly focused on tackling physical inactivity and sedentary lifestyle concomitantly through a 5-goal program delivered at every city school ($n = 18$). Using plausibility assessments (evaluations that are aimed at making causal statements of effectiveness using observational designs), we aimed to report on the impact of this intervention in the city's youth.

METHODS

The aims, basis and description of all activities/policies pertaining to the "Life of Health" intervention are found in **File S1**, whereas details about the city where the intervention took place are described in **Table S1**. Health professionals and researchers, with the financial and operational support of a private company and the local government (i.e., Education and Health Secretaries), jointly designed this program. In the case of youth, the "Life of Health" intervention was focused on increasing PA levels and reducing sedentary behavior. To achieve this, school directors and pedagogy coordinators from every school of Jaguariuna (Sao Paulo, Brazil) were personally trained by PA promotion specialists to disseminate a 5-goal program to all teachers from the city's educational system, which was implemented through group meetings at each school. Teachers were encouraged to accomplish all the goals and adapt them according to their possibilities (e.g., availability of materials and infrastructure). The 5-goal program comprised the following recommendations:

i. To reduce, at least, 5 min of sedentary behavior per hourly class, encouraging standing up during roll call, seminars, work groups, etc.
ii. To spread campaign posters across the school environment, containing positive messages, such as "While chatting, stand up!"; "Sit down only when you're tired!"; "Go to the playground!"; "How about doing sports?"; "Reduce TV time!."
iii. To enrich the school environment encouraging physical activity during recreation and/or lunch breaks, providing the students with full access to exercise equipment and devices (e.g., balls, ropes, hula-hoops, etc.).
iv. To open the school's games fields, sports halls and playground to the local community. [This was particularly relevant in low-income neighborhoods where the school was the only safe environment for engaging in physical activities.]
v. To advise parents on the relevance of increasing physical activity and reducing sedentary of their children. In brief, parents were personally counseled to (a) constrain children's time watching TV or playing videogames; (b) advise their children to break up sedentary time during periods of prolonged sitting; (c) spend leisure time with family and/or friends outdoor (e.g., parks, community clubs); (d) register children in sports clubs and/or wellness centers; and (e) provide children with rewards, incentives and/or positive feedback for engaging in physical activities and/or reducing sedentary time.

Throughout the program, members of the intervention team visited every school at least once and maintained weekly telephone contact with the schools' representatives to ensure the implementation of the program, as well as to stimulate teachers to adhere to it.

Primary outcomes were PA level and sedentary behavior, assessed through a validated questionnaire (9). In brief, this tool obtains information about (a) participation in up to 3 types of structured and/or unstructured physical activities and/or sports according to weekly frequency and daily duration, with the sum of the three activities resulting in a final score for PA; and (b) time spent in sedentary activities (i.e., TV watching, playing videogame, and using computer). Because this questionnaire was only validated for children ≥10 years old, it was not applied to participants aged <10 years ($n = 1{,}442$). Participants were classified as sufficiently physically active if they performed a minimum of 60 min/day of structured and/or unstructured PA during leisure-time (10), and engaging in excessive sedentary time if they spent more than 2 h/day in screen-based behavior (11, 12). Secondary outcome was BMI z-score, calculated using the WHO AnthroPlus® software (13).

Children and adolescents from every school were invited to participate in the study through an explanatory document about the intervention sent to parents or legal guardian(s). All individuals who brought the signed informed consent to school prior to assessments were included. Data collection was performed between April and December of 2016. This study was approved by the ethical committee.

Plausibility assessments with a pre-to-post design were performed using generalized estimating equations (GEEs), with the assumption of a linear distribution, id link function, and an exchangeable working correlation for repeated outcomes over time for the participants. The models were adjusted for age, sex, and BMI. Sub-analyses were also conducted accounting for stratus of age [6-12 [or 10-12 for PA/sedentary behavior variables], and 13-17 years], sex, BMI, physical inactivity, and sedentary lifestyle. Data analyses were performed using a statistical package (SPSS, version 17.0). Significance level was set at $p \leq 0.05$. Data are presented as mean ± SD, absolute numbers, percentages, delta scores, and/or 95%CI.

RESULTS

This study enrolled 3,592 participants (∼43% of all school-aged youth from the city) and 378 were lost to follow up (**Figure S1**). Participants' demographic characteristics are presented in **Table S2**.

TABLE 1 | Physical activity and sedentary behavior before and after the intervention ($n = 2{,}036$).

Variable	Pre	Post	Delta change	95% CI	p
Physical activity, min/day	37.2 ± 52.2	37.4 ± 55.9	0.0	−2.7 to 2.8	0.976
SEDENTARY BEHAVIOR, MIN/DAY					
Television time during weekdays	128.9 ± 105.2	121.7 ± 105.2	−8.5	−12.7 to −4.3	<0.001
Television time during weekend days	79.6 ± 79.4	78.2 ± 83.8	0.0	−3.7 to 3.8	0.980
Time spent playing video games	57.4 ± 101.3	37.8 ± 81.1	−20.9	−25.0 to −16.8	<0.001
Time spent on computer	93.3 ± 139.3	149.0 ± 176.6	63.7	56.5 to 71.0	<0.001

Data are expressed as mean ± standard deviation, delta change (Post – Pre), and 95% CI of the difference. P-value was adjusted by age, sex, and BMI.

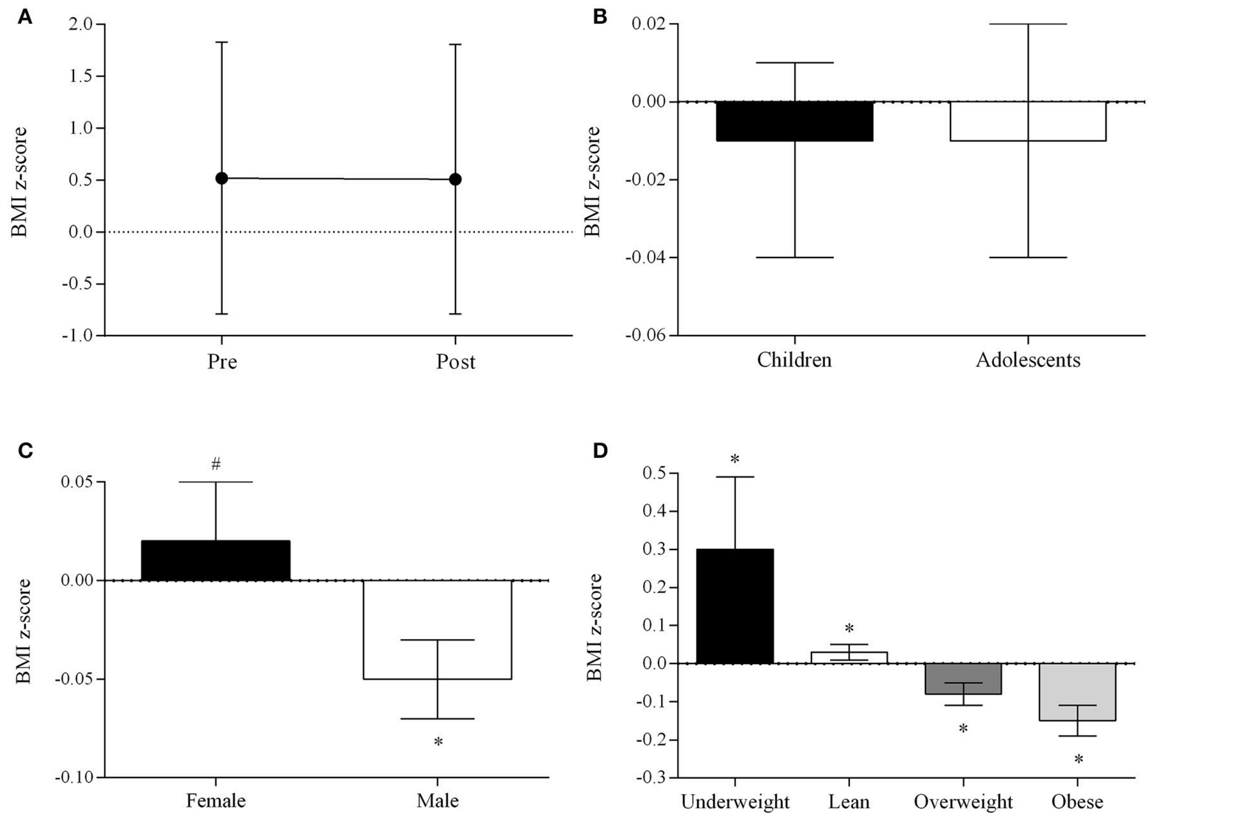

FIGURE 1 | BMI *z*-score before and after the intervention **(A)**, and changes in BMI *z*-score stratified by age **(B)**, sex **(C)**, and BMI **(D)**. Data are expressed as mean ± standard deviation, and delta change (Post - Pre) and 95% CI of the difference. $^*p < 0.05$, $^{\#}\ p < 0.10$; adjusted by age, sex, and BMI.

Overall, PA did not change following the intervention (Pre: 37.2 ± 52.2, Post: 37.4 ± 55.9; difference: 0.2; 95%CI:−2.7 to 2.8 min/day; $p = 0.976$; **Table 1**). The proportion of physically active participants did not change (−1%; 95%CI: − 9% to 9%; $p = 0.664$; **Figure S2**). Children decreased PA (Pre: 39.8 ± 54.6, Post: 34.6 ± 53.7; difference: − 5.2; 95%CI: − 9.9 to − 0.4 min/day; $p = 0.033$, **Table S3**), whereas adolescents tended to increase it (Pre: 35.8 ± 50.8, Post: 39.2 ± 57.2; difference: 3.3; 95%CI: − 0.1 to 6.7 min/day; $p = 0.057$, **Table S5**). However, physically inactive participants increased PA (Pre: 15.8 ± 17.0, Post: 26.4 ± 43.4; difference: 11.2; 95%CI: 8.8 to 13.6 min/day; $p < 0.001$; **Table S11**). Sex, BMI, and sedentary lifestyle did not affect the results (**Figure S2**, **Tables S5–S10**, **S12**).

Overall, television time during weekdays reduced (Pre: 128.9 ± 105.2, Post: 121.7 ± 105.2; difference: −8.5; 95%CI: −12.7 to −4.3 min/day; $p < 0.001$) whereas television time during weekend days did not change (Pre: 79.6 ± 79.4, Post: 78.2 ± 83.8; difference: 0; 95%CI: − 3.7 to 3.8 min/day; $p = 0.980$; **Table 1**). Time spent playing videogames decreased (Pre: 57.4 ± 101.3, Post: 37.8 ± 81.1; difference: −20.9; 95%CI: −25.0 to −16.8 min/day; $p < 0.001$) while time spent on computer increased (Pre: 93.3 ± 139.3, Post: 149.0 ± 176.6; difference: 63.7; 95%CI: 56.5 to 71.0 min/day; $p < 0.001$; **Table 1**). The frequency of sedentary participants did not change (2%; 95%CI: −2% to 5%; $p = 0.097$; **Figure S3**). When participants were sub-divided according to age, sex, BMI, sedentary lifestyle, and physical inactivity, the results followed a similar pattern to the overall sample (**Tables S3–S12**). The exception was the absence of changes in television time during weekdays for males and underweight participants.

Overall, BMI *z*-score did not change (Pre: 0.52 ± 1.31, Post: 0.51 ± 1.30; mean difference: −0.01; 95%CI: −0.03 to 0.01; $p = 0.192$; **Figure 1A**) and age did not influence the results (**Figure 1B**). Females tended to increase BMI *z*-score whereas males reduced it (**Figure 1C**). Underweight and lean participants showed increased BMI *z*-score; in contrast, participants with overweight and obesity experienced reductions in BMI *z*-score (Pre: 1.45 ± 0.30, Post: 1.38 ± 0.51; difference: −0.08; 95%CI: −0.11 to −0.05; $p < 0.001$; and Pre: 2.65 ± 0.51, Post: 2.50 ± 0.60; difference: −0.15; 95%CI: −0.19 to −0.11; $p < 0.001$; **Figure 1D**).

DISCUSSION

This intensive, intersectoral intervention did not change the prevalence of physically inactive or sedentary youth at a city level. However, the intervention improved PA levels in physically inactive participants and mitigated BMI *z*-score among participants with overweight and obesity.

Young people show a consistent desire to be active, but are often constrained by environmental factors, such as school policy or curricula and physical structure (3). However, to increase external validity, this intervention was primarily focused on education-based activities, since decision makers could consider robust changes in physical and social environment as not feasible, due to budget restriction and/or inflexible education-related laws. The current data, nonetheless, suggest that community-based interventions with a stronger educational component may be not sufficient to elicit major changes in PA and sedentary behavior at a city level if not supplemented with more pronounced environmental changes, such as increasing the number of physical education classes and promoting extra class activities (e.g., organized sports) (14).

Although the intervention was not able to increase the proportion of physically active individuals, adolescents, and physically inactive individuals increased PA levels (3.3 and 11.2 min/day). Despite the relatively low magnitude of changes (especially in the former), one may argue that these increases may be relevant in real-life, considering that even small increases in PA may result in benefits, especially for physically inactive individuals (10), who were the vast majority in this study (70.6%).

The proportion of sedentary lifestyle among youth was dramatically high in this study (76.8%), supporting previous Latin-American surveys (15, 16). Importantly, the intervention decreased time spent watching television (during weekdays) and playing videogames, whereas time spent on the computer was increased. It appears that, in a real-world scenario, different types of sedentary activities may be differentially affected by a lifestyle intervention, and possibly replaced one by another over the course of time through unknown circumstances. There has been a worldwide reduction in time spent watching television, in parallel to an increase in time spent on the computer, a pattern that has been observed in Brazil (15) and in other developing countries (17). This trend needs to be considered by policymakers while elaborating programs aimed at limiting the use of different screen-based entertainments.

The reduction in BMI *z*-score experienced by participants with overweight and obesity enhances the external validity of efficacy studies (18, 19). The lack of changes in PA or sedentary behavior allows speculating that BMI *z*-score improvements may be mainly attributed to changes in eating habits. Considering that parents and children mutually influence each other's behavior (20), one could speculate that the profound improvements in eating habits experienced by adults (unpublished data) could have also affected their children's habits, which was unfortunately not assessed.

The strengths of this study are (i) the real-world, city-wide nature of the intervention; (ii) the large sample enrolled (∼43% of total school-aged population) with a relatively low attrition rate (∼10.5%); and (iii) the intervention's dual-focus on tackling PA and sedentary behavior. However, this study has limitations. First, internal validity of this study may have been affected by the lack of a control city, which was not possible since São Paulo cities are highly heterogeneous regarding administration, public health policies, and demographic characteristics. Second, subjective measures of PA and sedentary behavior may have led to inaccuracies inherent to this sort of method. Third, it is possible that the intervention was too short to change behavior among children. Finally, heterogeneity across cities may demand further assessments of cross-community transferability and adaptability before implementation of policies.

This intervention was not able to change the proportion of physical inactivity and sedentary behavior in youth at a city level. Nonetheless, physically inactive individuals increased PA levels and participants with overweight and obesity experienced a reduction in BMI *z*-score, evidencing the relevance of the intervention. Education-based lifestyle programs should be supplemented with environmental changes to better tackle inactivity/sedentary behavior in the real-world.

ETHICS STATEMENT

This study was conducted in accordance with The Declaration of Helsinki and was approved by the local research ethics committee (Ethics Committee of the Centro Universitário de Jaguariúna approval #54320616.6.0000.5409).

AUTHOR CONTRIBUTIONS

MA, AP, FB, and BG participated in the conception and design of the study. MA, AP, FB, GM, EB, and BG were involved in the acquisition of study data, doing statistical analyses, and supervising and training teams to disseminate the intervention and gather data. AP, FB, and BG drafted the manuscript with critical revision from MA, GM, and EB. MA obtained funding. All authors have seen and approved the final version of the manuscript for publication.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2018.00298/full#supplementary-material

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Four Months of a School-Based Exercise Program Improved Aerobic Fitness and Clinical Outcomes in a Low-SES Population of Normal Weight and Overweight/Obese Children With Asthma

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Introduction: Fitness can improve asthma management. However, children from disadvantaged and minority communities generally engage less in physical activity, and have increased obesity and asthma disease burden. The goal of this pilot study is to evaluate (1) the feasibility of an exercise intervention program in a school-based setting (attendance and fitness improvement) and (2) the effect of the intervention on fitness, asthma, and clinical outcomes in normal weight and overweight/obese children with asthma from low-SES population.

Materials and Methods: Nineteen children, ages 6–13 years, from two elementary schools in Santa Ana, CA, a population with high percentage of Hispanic and low socioeconomic status, participated. Training sessions occurred at the schools during afterschool hours (3 sessions weekly × 4 months) and included mainly aerobic age-appropriate activities/games and a small component of muscle strength. Before and after the intervention, evaluations included pulmonary function testing, cardiopulmonary exercise testing (peak $\dot{V}O_2$), assessments of habitual physical activity, body composition (DXA), asthma questionnaires, and blood (cardiometabolic risk factors).

Results: Seventeen of 19 participants completed the study. Adherence to the program was 85%. Based on BMI %ile, 11 of the participants were overweight/obese and 8 were normal weight. Ten participants had persistent asthma and 9 children had intermittent asthma. Training was effective as peak $\dot{V}O_2$ improved significantly (8.1%, SD ± 10.1). There was no significant change in BMI %ile but a significant improvement in lean body mass (1%, SD ± 2.0) and decrease in body fat (1.9%, SD ± 4.6). Asthma quality of life outcomes improved following the intervention in symptoms, emotional function, and overall. There was no change in asthma control or pulmonary function. Five of 10 participants with persistent asthma decreased their maintenance medications. Lipid levels did not change except HDL levels increased (46.1 ± 8.4 mg/dL to 49.5 ± 10.4 mg/dL, $p = 0.04$).

Discussion: A school-based exercise intervention program designed specifically for children with asthma for a predominantly economically disadvantaged and minority population was feasible with good adherence to the program and substantial engagement from the schools, families and participants. The exercise intervention was effective with improvement in aerobic fitness, body composition, asthma quality of life, and lipid outcomes, setting the stage for a larger multicenter trial designed to study exercise as an adjunct medicine in children with asthma.

Keywords: asthma, obesity, school, low SES, aerobic fitness

INTRODUCTION

Asthma is the most common chronic disease of childhood, which, despite advances in therapy, continues to cause substantial morbidity among the 6 million children affected in the U.S. (1). Patients with asthma have not been spared by the unrelenting childhood obesity epidemic and it is well established that obesity is a significant risk factor for both asthma development and increased morbidity (2, 3). While the mechanisms linking asthma and obesity are likely multifactorial, poor fitness and physical inactivity may play a role (4, 5).

Studies suggest that better physical fitness can improve asthma symptoms and control in addition to the known benefits for cardiovascular health (6). Exercise intervention programs in children and adults with asthma have been shown to improve aerobic fitness, quality of life, asthma control, airway hyper-responsiveness, and airway inflammation (7). However, studies demonstrating the impact of improved fitness in children of low socioeconomic status (SES) and minority populations, which are disproportionately affected by higher asthma and obesity rates and morbidity, are lacking (8–10). The challenges faced in implementing sustainable lifestyle interventions in these communities include: (1). Accessible and safe venues for physical activity for children is limited and (2). Ensuring robust interventions (for example, training goals of at least 80% of maximum heart rate (HR) and a minimum of 3 sessions per week) to lead to measurable changes in physical fitness (11–13). Without a measure of physical fitness, unfortunately absent in many exercise training studies in children and adults, the impact of the intervention on conditions like asthma is uninterpretable. In a review of exercise training on asthma outcomes, Wanrooij et al concluded that training programs should last at least 3 months with at least 2 sessions per week with a personalized training intensity (at ventilatory threshold or 80% of HR max) (14). School-based intervention studies are appealing for these communities because schools are considered as safe places by parents. Moreover, as data continue to support the beneficial role played by exercise on academic performance (15), schools are increasingly motivated to host and sustain programs designed to enhance physical activity (16). To the best of our knowledge, no exercise intervention studies to date have targeted children with asthma in predominantly lower-SES communities.

The goal of this pilot study was to evaluate (1) the feasibility of an exercise intervention program in a school-based setting, specifically whether we were able to improve fitness in this setting and whether we had sufficient attendance of the training; and (2) the effect of the intervention on fitness, asthma, physical activity and clinical outcomes in a group of normal weight and overweight/obese children with asthma from a predominantly low-SES Hispanic population.

METHODS

Study Participants

Nineteen children, ages 6–13 years, participated in the study. Inclusion criteria included participants with a current physician diagnosis of asthma (asthma symptoms or medication use in the past 12 months) and no disease or disability that would impair participation in a vigorous exercise program. Participants with asthma exacerbation requiring systemic corticosteroids in the past month, any condition that would preclude exercise, obesity-related complications (i.e., type 2 diabetes), or pregnancy were excluded. This study was approved by the institutional review board at the University of California, Irvine (UCI), and informed consent and assent were obtained from all participants and their legal guardians. All participant expenses were covered by the research program.

Study Design

We developed relationships with two local elementary schools in Santa Ana, CA, a population with high percentage of Hispanic and low socioeconomic status. The schools contacted all students with diagnosis of asthma or albuterol prescription to attend information sessions regarding the research program. Approximately 30–40 total children/families attended the information sessions, with approximately 25 children eligible to participate (current physician diagnosis of asthma) and 19 children were consented to participate.

The study included two separate visits to the UCI Pediatric Exercise and Genomics Research Center (PERC) Human Performance Laboratory (HPL) before and after a 16-week school-based exercise intervention program. Each visit to the HPL included assessments of fitness and physical activity, body composition, lung function, and asthma questionnaires.

Anthropometric Measurements

Standard calibrated scales and stadiometers were used to determine height and body mass. Body mass index [BMI = weight/height^2 (kg/m^2)] percentile was calculated using the published standards from the Centers for Disease Control

(CDC), National Center for Health Statistics, USA (17). Normal weight is defined as BMI 5th to < 85th %ile, overweight is 85th to < 95th %ile, and obese is ≥ 95 %ile.

Dual x-ray absorptiometry (DXA) was used to determine body composition, including lean body mass and percent body fat, using a Hologic QDR 4500 densitometer (Hologic Inc., Bedford, MA, United States). Participants were scanned in light clothing while lying supine. The DXA instrument was calibrated using the procedures provided by the manufacturer, and DXA scans were performed and analyzed using pediatric software. Percent fat categories were calculated based on body fat reference curves for children (18). The 2nd, 85th, and 95th percentiles define the cut-off points for underfat, overfat, and obese.

Pulmonary Function Testing

Volunteers were requested to hold all medications, including inhaled corticosteroids, for at least 24 h prior to each visit. Spirometry was performed at baseline and 10–15 min following an exercise challenge (ramp test). Spirometry included FVC, FEV_1, forced expiratory flow, and mid-expiratory phase (FEF_{25-75}) measured in triplicate (V_{max}229; Sensormedics, Yorba Linda, CA) according to American Thoracic Society (ATS) guidelines (19). Exercise-induced bronchoconstriction (EIB) was present if participants demonstrated ≥ 12% decrease in FEV_1 following exercise challenge(19). If participants demonstrated EIB, they were given inhalation of albuterol and spirometry was repeated.

Asthma Questionnaires

Asthma control was assessed using the Childhood Asthma Control Test for participants ≤ 11 years and the Asthma Control Test if > 11years of age (20).

The Children's Health Survey for Asthma (CHSA) is a 48-item validated questionnaire completed by parents with 5 subscales: (1) physical health, (2) child activity, (3) family activity, (4) child emotional health, and (5) family emotional health (21). Primary caregivers were asked, using a 5-point Likert scale, how much of the time their child (or family) experienced each item as a result of asthma during the past 4 weeks. This self-report measure also assesses healthcare utilization, asthma triggers, and family demographics (21).

The Pediatric Asthma Quality of Life questionnaire, which assesses physical, emotional, and social impairment due to asthma over the previous week, was completed as well (22). There are 23 items distributed in three domains: activity limitations, symptoms, and emotional function. All items are similarly answered by means of a 7-point Likert scale, ranging from 1 (severely affected) to 7 (unaffected). The minimally important difference established for this instrument is 0.5 points.

Asthma classification (intermittent or persistent) was based on EPR guidelines (23). Caregivers also reported all current asthma medication prescriptions, which were brought to study visits for confirmation.

Physical Activity Monitoring

Habitual physical activity and sedentary time were assessed during awake time (8 am to 8 pm) for 7 days using Actigraph GTX3, which was worn on the waist at baseline and end of the study. Twelve-hour daytime activity data were analyzed for weekdays and weekends using Actilife software. Physical activity was classified into sedentary, moderate, and vigorous levels according to the cut points set by Evenson Children 2008 (24). Cut points based on vector magnitude <100 counts per minute (CPM) were scored as sedentary, ≥2,296 CPM were scored as moderate, and ≥4,012 CPM were scored as vigorous physical activity.

Cardiopulmonary Exercise Test (CPET)

Each subject performed a ramp-type progressive cycle ergometer exercise test using the SensorMedics metabolic system (Vmax 229, Yorba Linda, CA, United States). Following 3 min of sitting comfortably without pedaling (rest) on the cycle ergometer breathing through a mouth piece and 1 min of unloaded pedaling, the work rate (determined by weight and overall assessment of activity level) was incremented at 10–20 W/min to the limit of the participant's tolerance. Participants were vigorously encouraged during the high-intensity phases of the exercise protocol. Gas exchange was measured breath-by-breath and peak $\dot{V}O_2$ was determined when RER ≥1.0 (25) and was calculated as the highest 20-s rolling average in the last minute of exercise in absolute values (l/min), relative to body mass (ml/kg/min) and lean body mass (ml/kg/min). Percent predicted peak VO_2 was determined using published norms (26).

Blood Sample Collection

Participants arrived to PERC HPL in the morning following > 8-h fast. Blood was collected and sent to the UCI Clinical Pathology Lab for complete blood count (CBC) with differential, complete metabolic panel, lipid panel, and Immunoglobulin E.

Exercise Training Intervention

Participants completed a 16-week aerobic exercise training intervention (45 min session, 3 days a week) at their local schools during after-school hours. Prior to the beginning of exercise activities, the trainer ensured that the participants had their bronchodilator readily available. Participants were pretreated with bronchodilators prior to exercise activities if specified in their asthma action plan. Training was done in small groups of 4–6 children and included a variety of age-appropriate activities using small equipment (e.g., soccer, basketball and football balls, stability exercise balls, Bosu balls, jump ropes, hula hoops, cones, and scooter boards with safety handles. Training was led by experienced physical education specialists who were assisted by undergraduate student volunteers. Each session included a 5-m warm up, 5-min cool down (at the end), and a combination of aerobic and resistance exercises. Exercises were similar to activities in Physical Education classes. During weeks 1 and 2, aerobic activities (e.g., playing small group games and adapted ball games, basketball, soccer, badminton) were performed for 15 to 20 min. The duration of the aerobic exercises gradually increased up to 45 min by weeks 10 through 16. In addition to the aerobic exercises, participants performed resistance exercises (e.g., band exercises, push-ups, and pull-ups). These exercises were done in sets, starting from low number (4–6) of repetitions

TABLE 1 | Baseline demographics (n = 19).

Age in years, mean, and range	9 (6–13)
Sex, *n* (%)	
Male	13 (68)
Race/Ethnicity, *n* (%)	
Hispanic	19 (100)
Household income*, *n* (%)	
<$30,000	12 (63)
$30,000–60,000	2 (11)
>$60,000	3 (16)
BMI Categories, *n* (%)	
Normal weight (5–<85%ile)	8 (42)
Overweight (85–<95%ile)	5 (26)
Obese (≥95%ile)	6 (32)
Physical activity levels, median (IQR) in min per 12 h awake	
Sedentary time	515 (496, 549)
Moderate activity	33 (26, 39)
Vigorous activity	28 (17, 37)

Median household income in Orange County, CA is $81,837; median household income in Santa Ana, CA is $61,895 (2017 census data).

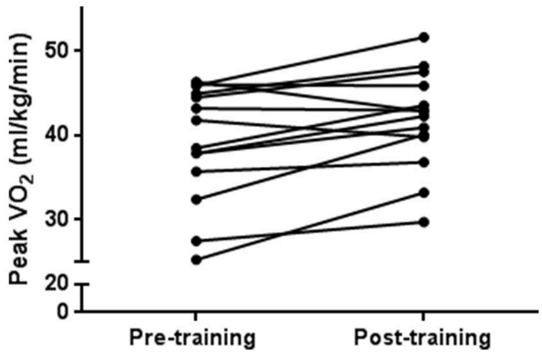

FIGURE 1 | Aerobic fitness improves following exercise training. Each black circle and line pair represents one participant from pre-training to post-training. There was a statistically significant training effect on peak $\dot{V}O_2$ (p = 0.008).

TABLE 2 | Aerobic fitness before and after training.

	Pre-training mean (SD)	Post-training mean (SD)
Absolute peak $\dot{V}O_2$ in L/min	1.5 (0.5)	1.7 (0.5)*
Peak $\dot{V}O_2$ (per body mass) in ml/kg/min	38.5 (7.1)	41.1 (6.2)*
Peak $\dot{V}O_2$ (per lean body mass) in ml/kg/min	57.4 (7.3)	60.9 (5.9)*

$^*p < 0.05$ paired t-test for training effect.

within each set, and gradually increased to 10–12 repetitions in a set. The number of sets was also gradually increased based on the participants' strength. Resistance exercises took approximately 20–25 min in the first few weeks and gradually decreased in time in parallel to the increase in time for the aerobic exercises.

To record exercise intensity, participants wore a heart rate (HR) monitor (PolarE600) during the sessions. Number of minutes spent on target HR (bpm) > 145 bmp (70–80% of maximum HR) are reported for sessions that had >40 mins of recording time as means ± standard deviations.

Statistical Analysis

Data are presented as mean [standard deviation (SD)], median [interquartile range (IQR)], or proportion (n, %). The effect of exercise training was assessed using a paired mean-comparison t-test or Wilcoxon's signed-rank test as appropriate. All tests were two-tailed and $p \leq 0.05$ were considered significant. Statistical analysis was performed using Stata version 11 (StataCorp LLC, College Station, TX, United States).

RESULTS

Demographics

Nineteen participants, mean age of 9 years and 68% male, participated in the study (**Table 1**). All participants were Hispanic and 63% with household income < $30,000. Ten of the 19 participants had persistent asthma and 9 participants had intermittent asthma based on NAEPP criteria (23).

Training Program

Seventeen of the 19 participants completed the 16-week exercise training intervention. Two participants did not complete the training intervention due to conflicts with other activities and did not complete any post-intervention measurements. There were no adverse events or injuries during the intervention. The average number of sessions attended by participants was 40 sessions with 85% attendance rate. During the training sessions, participants exercised for 29.3 (5.6) mins (average range per participant 18 to 42 mins/session) in the target HR >145 bpm (mean of 79% (8) of HR max).

Cardiopulmonary Fitness (Table 2)

Mean peak $\dot{V}O_2$ was 39.8 ml/kg/min (8.6) and 87.5% predicted (17.8) at baseline. Absolute peak $\dot{V}O_2$, peak $\dot{V}O_2$ (per body weight) and peak $\dot{V}O_2$ (per lean body mass) were all significantly improved [13.3% (22.6), 8.1% (10.1), and 5.2% (12.3), respectively, all $p < 0.01$] from baseline to after the training program (**Figure 1** and **Table 2**).

Body Composition

Forty two percent of participants were normal weight and 58% were overweight/obese. There was a change in weight ranging from 2 kg weight loss to 4.7 kg weight gain, as well as an increase in height ranging from 0 to 6 cm at the end of the training program. There was no significant change in BMI %ile following training.

At baseline, mean % of body fat was 33.8% (6.9) with all participants overfat (≥ 85th to <95th %ile) or obese (≥ 95th %ile) based on % body fat categories except for one participant in healthy fat category. Following the exercise training program,

TABLE 3 | Asthma characteristics.

	Pre-training	Post-training
Spirometry, mean (SD)		
FVC % predicted	107.8 (16.2)	104.3 (13.8)
FEV_1 % predicted	105.1 (19.1)	101.8 (17.2)
FEV_1/FVC	84.9 (7.1)	84.4 (9.2)
Exercise-induced bronchoconstriction, n (%)	3 (16)	1 (16)
Asthma related Quality of Life, median (IQR)		
Overall	4.5 (4.0, 6.4)	6.0 (4.4, 6.5)#
Activity limitations	4.6 (4.1, 6.0)	5.6 (4.3, 6.5)#
Symptoms	5.0 (4.0, 6.5)	6.2 (4.9, 6.5)*#
Emotional Function	4.8 (3.1, 6.4)	6.0 (4.0, 6.7)#
Asthma Control		
Mean score (SD)	21.2 (3.5)	22.1 (3.7)
Uncontrolled, n (%)	4 (24)	3 (18)
Children's Health Survey for Asthma, mean (SD)		
Physical Health	90.0 (12.2)	93.6 (7.2)
Activity (child)	86.8 (20.2)	95.6 (7.7)
Activity (family)	80.4 (15.4)	85.5 (4.4)
Emotion (child)	90.6 (15.7)	94.4 (11.4)
Emotion (family)	68.8 (20.8)	82.5 (14.3)*

*Asthma control: c-ACT, ACT. Uncontrolled score ≤19. Quality of life evaluated by PAQLQ, # minimally important difference = 0.5, *p < 0.05 paired t-test or Wilcoxon's rank sum test.*

TABLE 4 | Lipid levels before and after exercise training.

	Pre-training, mean (SD)	Post-training, mean (SD)
Lipid panel, mg/dL		
Total cholesterol	145.1 (25.4)	148.9 (21.5)
Triglycerides	79.5 (34.5)	78.6 (27.5)
HDL	46.1 (8.4)	49.5 (10.4)*
LDL	83.1 (26.2)	83.7 (20.2)

**p < 0.05 paired t-test.*

% of lean body mass increased by an average of 1.1% (2.0), $p = 0.04$, and % of body fat decreased by an average of 1.9% (4.6), $p = 0.04$.

Asthma Outcomes (Table 3)

Healthcare Utilization

There were no hospitalizations or emergency department visits during the study. One participant had a sick visit with their primary care physician before and after training.

Asthma Control

Seventy-six percent of participants had well-controlled asthma at baseline (ACT score > 19). There was no significant change in asthma control following exercise training intervention.

Asthma Quality of Life

Symptoms, activity limitation, emotional function, and overall score all improved with change in median PAQLQ score of ≥0.5, which is considered a clinically important improvement, following training. Using the Children's Health Survey for Asthma, the emotion (family) domain was significantly improved following training.

Medications

Five out of 10 participants with persistent asthma reduced their maintenance medications by the end of the exercise training intervention.

Pulmonary Function

There was no significant change in spirometry following the exercise training intervention. Three participants had exercise-induced bronchoconstriction at baseline that was not present after training. One participant had exercise-induced bronchoconstriction after training that was not present at baseline.

Physical Activity and Sedentary Time

Participants had a median of 28.6 min (IQR 25.4, 38.3), 30.2 min (IQR 14.7, 35.8) of moderate and vigorous activity time, respectively during weekdays and 37.2 min of moderate (IQR 25.8, 42.0), 26.7 min of vigorous (IQR 20.1, 35.6) activity during weekends at baseline. There was a median of 510.6 min (IQR 488.5, 529.6) of sedentary time during weekdays and 527.1 min (IQR 497.1, 574.6) during weekends at baseline. There was no significant difference in moderate, vigorous activity or sedentary time between normal weight and overweight/obese participants. Overall, there was no significant difference in moderate, vigorous activity time or sedentary time following the intervention. However, there was a trend of increased habitual physical activity time and decreased sedentary time on weekends in normal weight but not overweight/obese children with asthma following training.

Lipid Panel (Table 4)

Mean total cholesterol levels were 145 mg/dL (25.4) and one participant with elevated level at baseline (> 200 mg/dL). Mean triglycerides were 79.5 ml/dL (34.5) at baseline and one participant with elevated level at baseline (> 150 mg/dL). Mean LDL levels were 83.1(26.2) at baseline. Mean HDL levels were 46.1 ml/dL (8.4) with two participants with low levels at baseline (< 40 mg/dL). HDL levels improved from a mean of 46.1 to 49.5 mg/dL after training ($p < 0.04$). Participants with abnormal lipid levels were all obese (BMI %ile ≥ 95). Total cholesterol, LDL, and triglycerides levels were not significantly different after training; however, participants with elevated total cholesterol or triglyceride levels at baseline all improved to within normal limits following training.

DISCUSSION

This pilot study is the first to test a school-based program specifically designed to improve aerobic fitness in low-SES children with asthma. We found evidence that the 16-week aerobic exercise program was feasible in that there was a high attendance rate among participants for the training sessions and all but two participants completed the training. In discussions with families, the majority of participants enjoyed their involvement in the program, and parents/guardians were supportive of their children's participation. School personnel communicated to our team that they would welcome studies of this nature in the future. A major strength of the pilot was our ability to demonstrate improvements in cardiorespiratory fitness in a school-based setting (27). We showed significant increases in robust physiological metrics including $\dot{V}O_2$max, lean body mass, and an increase in HDL. Finding these measurable effects of the training program addresses a key deficiency in many previous exercise training studies in children because the exercise-training associated biological improvements can be used to gauge the impact of the training on disease related phenotypes, in this case, asthma-related metrics.

Previous lifestyle interventions have required participants to travel to centralized training facilities. This approach is not practical or sustainable in communities with high risk populations, particularly in lower-SES and minority areas. In contrast, school-based interventions, considered by parents and children as familiar, safe, and accessible venues, have been shown to improve cardiorespiratory fitness and physical activity in children by utilizing exercise sessions in addition to physical education classes (28, 29). Our project was possible only because of the strong relationships built with local schools and their active engagement with the families. In the communities where we partnered with the schools, the school grounds were among the only areas accessible and safe for the participants to engage in active play. We partnered with the after-school activities to coordinate space and time. While sessions were led by physical education specialists, these activities could be planned and executed by any trained staff. Utilizing HR monitors allowed the participants to get into the target zone. We found that utilizing array of small equipment and games (felt by the participants to be fun) from session to session was important to keep the children engaged throughout the length of the intervention.

Obesity and overweight status contribute to a wide range of health threats in children, ranging from increased cardiovascular disease risk to type 2 diabetes (30, 31). At baseline, 42% of our participants were normal weight using BMI %iles; however, when looking at body composition using % body fat (a metric obtained by DXA, not possible with BMI alone), all but one were equal to or greater than the 85th percentiles, highlighting the limitations of BMI in defining obesity in children during the period of growth and development in which rapid changes in body composition occur. Furthermore, BMI cannot distinguish between fat mass and lean mass and may fail to identify as many as 25% of children with excess body fat (32). Despite this, many health interventions in children target body composition (usually measured solely as BMI), most likely due to the relative ease of measuring height and weight and the additional expense and time required for assessments like DXA. These interventions are typically multifaceted, incorporating diet, physical activity, and motivational counseling. While the rationale for these complex interventions is understandable, multifaceted designs confound the investigators' ability to identify which component of the intervention (e.g., diet or exercise) led to the improved health outcome.

There are only a few studies targeting weight loss as a means to ameliorate asthma outcomes in obese asthmatic children (33–36). The interventions used varied from multifactorial interventions with both exercise and nutritional counseling to diet alone. Overall, weight loss was associated with improvements in asthma control, asthma-related quality of life, and exercise-induced bronchoconstriction (33, 37, 38). Jensen et al was the only pediatric study to measure body composition (using DXA) and found correlations between changes in % body fat or % lean mass and inflammatory markers (for example, C-reactive protein, exhaled nitric oxide). Lucas et al retrospectively compared healthy and asthmatic children in a 12-week nutrition and physical activity intervention in children who were overweight/obese or at risk of obesity and found significant improvements in BMI percentile or z-score as well as $\dot{V}O_2$max (39). Fifty-eight percent of the sample completed the program though there was no difference in attrition between healthy and asthmatic children. However, the study did not report any asthma outcomes. None of the previous studies focused solely on improvements in aerobic fitness or evaluated relationships between fitness and asthma outcomes. In our study, which primarily focused on aerobic fitness, we did not observe significant improvement in BMI %ile, but we did find improvements in lean body mass. The anti-inflammatory effect of routine physical activity and exercise may be mediated through several mechanism(s), including a reduction in NF-κβ levels, glucocorticoid receptor expression, or anti-inflammatory cytokines (40, 41). Other possible mechanisms of exercise training on asthma include increasing the ventilatory threshold, reduction in the perception of breathlessness, or improving exercise tolerance (42–44). Improving fitness may mitigate chronic inflammation, which is one of the key common features of both obesity and asthma (45), and reducing chronic inflammation may lead to improvements in asthma outcomes and overall health.

We found improvements in asthma quality of life in symptoms, emotional function, and overall score using the PAQLQ following the exercise program. We also found improvement in the emotion (family) domain using the Children's Health Survey for asthma. In contrast to the other intervention studies targeting obese asthmatic children, we did not find any significant difference in asthma control or pulmonary function following the exercise intervention (37). The majority of our study participants had well-controlled asthma as well as normal lung function at baseline. Additionally, half of the participants with persistent asthma were able to decrease or discontinue their daily medications which is consistent with other studies reporting a reduction in inhaled or systemic corticosteroids following an exercise training intervention (42, 46).

The exercise program was effective in improving aerobic fitness with no significant difference in habitual physical activity or sedentary behavior. Previous studies evaluating the relationship between CPET measures of physical fitness and habitual physical activity have consistently shown relatively weak correlations between these two variables (12, 47), dispelling the fear that an organized exercise intervention would reduce habitual physical activity. Sedentary behavior appears to be an independent risk factor for worse cardiometabolic health and obesity (48).

STUDY LIMITATIONS

Our project was targeted at a predominantly Hispanic, lower SES community in Southern California and our findings might not be generalizable to all children with asthma. However, we believe that there is a commonality in the willingness of all children, regardless of race or ethnicity to participate in fun exercise activities. Additionally, this was a pilot feasibility project with a small sample size and we cannot assess the effectiveness of our results in comparison to a control group that was not exposed to the exercise-training intervention.

CONCLUSION

A school-based exercise training intervention is a promising approach to promote fitness and health outcomes in children with asthma, including those from lower SES minority communities. Utilizing the schools provides a safe venue for children and serves as a potentially sustainable model for fitness interventions in children. Our study sets thestage for larger multicenter randomized controlled trials designed to improve fitness and study how exercise can be best used as an adjunct therapy to improve asthma outcomes.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of University of California Institutional Review Board Committee with written informed assent and consent from all subjects and their parents/guardians. All subjects and their parents/guardians gave written informed assent/consent in accordance with the Declaration of Helsinki. The protocol was approved by the University of California Institutional Review Board Committee.

AUTHOR CONTRIBUTIONS

KL and SR-A: Conception and design of the research study; KL, FH, DC, and SR-A: Data analysis and interpretation; KL, FH, DC, and SR-A: Review and approval of manuscript.

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Inhospital Exercise Training in Children With Cancer: Does It Work for All?

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Purpose: Physical exercise training might counteract the weakening effects of both pediatric cancer and anti-cancer treatment. We aimed to analyze the prevalence of "responders" and "non-responders" to inhospital exercise training in children with cancer and to identify the factors that could influence responsiveness, which might help personalize exercise interventions for this patient population.

Methods: We performed an ancillary analysis of the randomized controlled trial "Physical activity in Pediatric Cancer" (NCT01645436), in which 49 children with solid tumors were allocated to an inhospital exercise intervention or control group. The present study focused on the children in the former group ($n = 24$, 10 ± 4 years), who performed 3 weekly training sessions (aerobic + strength exercises). The intervention lasted 19 ± 8 weeks (i.e., from the start to the end of neoadjuvant chemotherapy treatment). A responder-vs-non-responder analysis was performed for physical capacity-related endpoints (five-repetition maximum strength, functional mobility tests, and cardiorespiratory fitness [CRF]). Only those participants showing improvements in a given test of a magnitude greater than both the random error and the threshold for clinically meaningful changes were considered responders.

Results: Most participants improved their performance in the strength tests, with 80, 88, and 93% of total showing a positive response for seated bench press, lateral row, and leg press, respectively ($p < 0.001$). No significant improvements were observed for the functional mobility tests or CRF ($p > 0.05$, rate of responsiveness $\leq$50%). No differences between responders and non-responders were observed for sex, age, type of cancer, or treatment (i.e., including or not anthracyclines/radiotherapy). However, significant differences ($p < 0.05$) were observed between responders and non-responders for baseline performance in all the tests, and a significant ($p < 0.05$) inverse relationship was found between baseline performance and relative improvement for most endpoints.

Conclusions: Although most children improved their muscle strength after the exercise intervention, a considerable individual variability was observed for the training responsiveness of functional mobility and CRF. A lower baseline performance was associated with a higher responsiveness for all the study endpoints, with the fittest children at the start of treatment showing the lowest responses. Efforts to individualize exercise prescription are needed to maximize responsiveness in pediatric cancer patients.

Keywords: fitness, pediatric cancer, functional mobility, physical activity, solid tumors, exercise is medicine

INTRODUCTION

With advances in cancer treatment, nowadays almost 80% of children diagnosed with cancer will survive the disease (1). However, anti-cancer therapies and the disease itself are associated with a deterioration of patients' physical fitness (2), as reflected by low levels of cardiorespiratory fitness (CRF) and muscle strength that are present both during (3, 4) and after the treatment (3, 5). Children with cancer also have a decreased ability to perform activities of daily living (6), which negatively affects their well-being and health-related quality of life (HRQoL) (7).

Although the impaired physical fitness of pediatric cancer patients is likely multifactorial, a main contributor is their typically reduced activity levels (4). In this context, meta-analytical evidence shows positive effects of exercise intervention on the CRF, muscle strength, functional mobility, HRQoL, and daily physical activity of children with cancer (8, 9). However, the great majority of studies in the field have been performed in children with acute lymphoblastic leukemia (10–18) and the evidence for the effects of exercise training interventions in children with other types of cancer is much scarcer (19–22). On the other hand, exercise benefits are typically reported under the assumption that the group average represents the response of most individuals. Yet, a wide inter-individual variability can be observed in the human response to a given training program, which results in subjects being classified as responders (i.e., those who achieve clinically meaningful benefits) or non-responders (i.e., those who experience a worsening or remain unchanged) (23, 24). Such individual variability has been reported in healthy people or in individuals with different disease conditions (25, 26) but not in cancer patients. Thus, the aim of this study was to analyze the prevalence of responders/non-responders to an inhospital exercise (aerobic + strength) training program for physical fitness and functional mobility in children with solid tumors, as well as to identify the factors that could influence individual responsiveness.

MATERIALS AND METHODS

Participants and Study Design

We performed an ancillary analysis of the randomized controlled trial "Physical activity in Pediatric Cancer" (NCT01645436), in which 49 children with solid tumors were randomly allocated to an inhospital exercise intervention or control group. The present study focused on the former group, with patients performing 3 weekly training sessions (aerobic + strength exercises) during 19 ± 8 weeks on average (i.e., from the start to the end of neoadjuvant chemotherapy treatment). All participants, together with their parents/guardians, gave their written informed consent, and the study was approved by the institutional Ethics Committee.

Exercise Intervention

Participants followed an inhospital training program, which took place during the entire neoadjuvant chemotherapy treatment period. The program has been previously described in detail (21). Briefly, the exercise intervention included three sessions per week (Monday-Wednesday-Friday), each lasting ∼60–70 min. Each session included a pre-conditioning period of ∼30 min of aerobic exercise (cycle-ergometer pedaling, treadmill running, or arm cranking in those children missing a lower limb due to the disease, and aerobic games). The training load was gradually increased depending on the age, physical capacity and health status of each child. Exercise intensity was recorded continuously with heart rate (HR) monitors and corresponded to 60–70% of the maximum HR value determined during the baseline tests for CRF assessment (see below). Aerobic exercise was followed by ∼30 min of strength training. The latter took place in the hospital gymnasium, which is appropriately equipped for this purpose (27) or in the ward room (especially during neutropenic episodes). Two to three sets (8–15 repetitions with a rest period of 1–2 min between sets) of the following exercises were performed in each session: shoulder, chest and leg presses, side-arm rowing extension and flexion, knee extension and flexion, and abdominal, lumbar, and shoulder adduction. The load was gradually increased as the strength of each child improved (i.e., by ∼2 kg after three training sessions with a given weight) and independently for each exercise, starting at 50% of the baseline five-repetition maximum (5RM). In the ward sessions, dumbbell exercises were similar to those performed in the gymnasium with weight training machines.

Before each training session, we enquired the medical staff about the children's health status in order to determine if they could exercise that day. No session started without medical permission. Depending on the clinician's recommendations, missing sessions were performed on another week day (Tuesday or Thursday).

Endpoints

Endpoints were assessed at baseline (i.e., upon initiation of neoadjuvant chemotherapy) and upon treatment termination (i.e., 19 ± 8 weeks later). Baseline assessment was preceded by three familiarization sessions with each test. The analyzed

TABLE 1 | Main demographic and clinical characteristics of the study participants at baseline (i.e., upon diagnosis).

	***n* = 24**
Male (%)	17 (71%)
Age (years)	10 ± 4
TANNER MATURATION STAGE	
I	42%
II	4%
III	21%
IV	8%
V	25%
TYPE OF TUMORS*	
Lymphomas and reticuloendothelial neoplasms	
Hodgkin lymphoma	4%
Non-Hodgkin lymphomas	34%
Soft tissue and other extraosseous sarcomas	
Rhabdomyosarcoma	8%
Other specified soft tissue sarcomas	
Non-rhabdomyosarcoma (synovial sarcoma)	4%
Malignant bone tumors	
Ewing's Sarcoma	25%
Osteosarcoma	13%
Neuroblastoma and other peripheral nervous cell tumors	
Neuroblastoma	4%
Germ cell tumors, trophoblastic tumors, and neoplasms of gonads	
Malignant gonadal germ cell tumors	
Germinomas	4%
Non-germinomas (embryonic carcinoma)	4%
Main treatment characteristics	
Total duration (weeks)	19 ± 8
Chemotherapy cycles (number)	7 ± 3
In-room isolation episodes due to neutropenia (number)	3 ± 2
Anthropometric variables	
Body mass (kg)	42.6 ± 19.9
BMI (kg/m^2)	19.2 ± 5.0

Data are mean ± SD.
**Type of tumors were classified according to the International Classification for Childhood Cancer. BMI, body mass index.*

endpoints have been previously described in detail (21, 27). Briefly, muscle strength was assessed in the hospital gymnasium with pediatric-specific weight training machines (Strive, Inc., McMurray, PA) (21, 27). We evaluated the 5RM for leg press, seated bench press and seated lateral row as previously described (28). Each subject was instructed to perform all the exercises to momentary muscular exhaustion. Any repetition not performed with a full range of motion was not counted. Children with an amputated lower limb did not perform the leg press test.

Functional mobility was assessed with the 3-meter Timed Up and Go (TUG) and Timed Up and Down Stairs (TUDS) tests (27). Performance time was measured by the same investigator with the same stopwatch to the nearest 0.1 s.

CRF (peak oxygen uptake, VO_{2peak}) was determined using "breath-by-breath" analysis with a metabolic cart (Vmax 29C; SensorMedics Corp., Yorba Linda, CA) and pediatric masks during a ramp-like treadmill testing protocol (Technogym Run Race 1400HC; Cesena, Italy) as previously described (27). For those children missing a lower limb and who were thus unable to perform the treadmill testing, we performed the test with an arm crank ergometer (Monark Rehab Trainer model 881E; Varberg, Sweden).

Responsiveness Analysis

Responsiveness was defined as positive changes whose magnitude exceeded both the random error (which includes the technical error of biological measurements and the day-to-day biological variability) and the expected threshold for clinically meaningful benefits.

Random error was defined as two times the typical error (TE) of measurement (29). The TE was calculated for each test as the standard error of within-subject standard deviation (SD) (30), obtained from previous reliability tests performed in the same hospital and with the same equipment by children with hematological cancer for leg press, bench press, lateral row TUGS, and TUDS tests (12). Participants performed each test twice separated by 48 h, and intra-class correlation coefficients and random error were calculated, yielding the following values: correlation coefficient of 1.00, 1.00, 1.00, 1.00, and 0.99 for leg press, bench press, lateral row, TUDS, and TUG, respectively; and random error of 7.3 kg, 3.2 kg, 4.5 kg, 0.3 s and 0.2 s, respectively (12). No reliability analysis (and consequently no random error) was available for CRF. Moreover, as no information was found in the scientific literature regarding the biological threshold of clinically meaningful changes for the tests and patient population of our study, one-fifth of the between-subject SD at baseline was taken as the as threshold for clinically relevant improvements as proposed by Hopkins et al. (31) and Hecksteden et al. (32).

The thresholds for clinically meaningful changes for leg press, bench press, lateral row, TUDS, TUG, and CRF were 5.0 kg, 3.7 kg, 3.7 kg, 1 s, 0.2 s, and 1.6 ml/kg/min, respectively. Only those children showing improvements in a given test of a magnitude greater than both the random error and the threshold for clinically meaningful changes were considered responders. A responder-vs.-non-responder analysis was performed only when more than 25% of participants were considered non-responders for a given endpoint.

Statistical Analysis

Data are presented as mean ± SD unless otherwise stated. The normal distribution (Shapiro-Wilk test) and homoscedasticity (Levene's test) of the data were checked before any statistical treatment.

Differences between mean values of baseline and post-intervention data were assessed using Student's paired *t*-tests. Differences between responders and non-responders were assessed using the Mann-Whitney *U* test for continuous variables (age, Tanner stage of maturation, training sessions, and baseline performance) and the Fishers' exact test for proportions (sex, type of solid tumor, treatment or not with radiotherapy or anthracyclines).

TABLE 2 | Effects of an inhospital exercise intervention on study endpoints.

Test	*N* with data	Baseline	Post-intervention	Change (SE)	*p*-value	β (95% CI)	Responders N (%)
Seated bench press (kg)	20	30 ± 18	40 ± 20	11 (1.9)	< 0.001	0.6 (0.4 ± 0.8)	16 (80%)
Seated lateral row (kg)	17	29 ± 19	43 ± 21	15 (2.1)	< 0.001	0.8 (0.6 ± 1.0)	15 (88%)
Leg press (kg)	14	35 ± 25	67 ± 35	32 (6.2)	< 0.001	1.3 (0.8 ± 1.8)	13 (93%)
TUG (s)	15	4.0 ± 1.1	3.8 ± 0.5	−0.3 (0.2)*	0.125	−0.3 (−0.6 ± 0.1)	8 (53%)
TUDS (s)	13	8.9 ± 5.0	7.0 ± 1.0	−1.9 (1.3)*	0.159	−0.4 (−0.9 ± −0.1)	4 (31%)
CRF (ml/kg/min)	21	25.0 ± 8.0	25.0 ± 5.2	0 (1.3)	0.960	0.0 (−0.3 ± −0.3)	8 (38%)

Data are mean ± SD. P-values were determined using student's paired t tests. β corresponds to the change expressed in standardized units (i.e., divided by baseline SD). Data for the strength tests correspond to the 5-repetition maximum. Changes are expressed as mean delta change along with the standard error (SE). Responsiveness was determined as a positive change greater than both the typical error of measurement and the minimal clinically meaningful change. CRF, cardiorespiratory fitness; ES, effect size; TUDS, timed up and down stairs test; TUG, timed up-and-go 3-meter test; VO_{2peak}*, peak oxygen uptake. Symbol: *a negative value presents an actual performance improvement in the test.*

The relationship between the different variables and the likelihood of being a responder was assessed using univariate logistic regression analyses, whereas the relationship between baseline performance and relative improvement was assessed using Pearson's correlation analysis. Correlation coefficients (*r*) values of 0.1, 0.3, 0.5, 0.7, and 0.9 were considered small, moderate, strong, very strong, and extremely strong, respectively (33). All statistical analyses were conducted using a statistical software package (SPSS 23.0, USA) setting the significance level at 0.05.

RESULTS

The mean age of the studied population was 10 ± 4 years, ranging from 4 to 16 years (**Table 1**). According to the International Classification of Childhood Cancer (34), five main diagnostic groups of cancer were included (i.e., lymphomas and reticuloendothelial neoplasms; soft tissue and other extraosseous sarcomas; malignant bone tumors; neuroblastoma and other peripheral nervous cell tumors; and germ cell tumors, trophoblastic tumors and neoplasms of gonads). The duration of the intervention was 19 ± 8 weeks, ranging from 9 to 41 weeks, and participants performed 35 ± 14 training sessions on average. Mean adherence to the intervention was 63% ± 21%. No major adverse events or health-related issues attributable to the testing or training sessions were noted.

A significant improvement in mean values was observed after the exercise intervention compared to baseline for all the strength tests ($p < 0.001$, rate of responsiveness >80%), but not for functional mobility tests or CRF ($p > 0.05$) (**Table 2**). However, the individual responsiveness analysis revealed that 31–53% of participants showed a meaningful improvement in TUG, TUDS, and CRF (**Tables 2**, **3**).

The results of the responder-vs.-non-responder analysis for functional mobility tests and CRF are shown in **Table 4**. No significant differences were observed between responders and non-responders for sex, age, biological maturity (Tanner stage), cancer type, or treatment (i.e., anthracyclines or radiotherapy) (**Table 4**). Significant differences in baseline performance were observed between responders and non-responders for all the tests ($p < 0.05$). Moreover, a significant and strong inverse relationships ($p < 0.05$) was found between baseline performance and relative improvement for both functional mobility tests and CRF (**Figure 1**). A significant inverse relationship between baseline and relative improvement was also observed for bench press and lateral row strength tests (**Figure 2**). Finally, a significant relationship between baseline performance and the likelihood of being responder was found for CRF (OR: 0.656, 95%CI: 0.449–0.958; $p < 0.05$), but no other descriptive value was found to increase the likelihood of being responder ($p >$ 0.05 for all).

DISCUSSION

The results of this ancillary analysis show that an inhospital exercise program can be safely applied to increase muscle strength in pediatric cancer patients with solid tumors undergoing neoadjuvant treatment, with a high prevalence of responders (i.e., >80%). The rate of responsiveness, however, was considerably lower for CRF or functional mobility tests (i.e., half and one third of the participants showed a meaningful improvement in the TUG test/CRF and in the TUDS test, respectively). On the other hand, significant differences were observed between responders and non-responders in baseline physical performance for all the tests: that is, non-responders had a better baseline performance.

A significant inverse relationship was found between baseline performance and relative performance improvement in both functional mobility tests, CRF, and in two of the three strength tests (bench press, lateral row), suggesting that a greater training stimulus might be needed in the fittest children. In fact, previous research has also found non-responders to training among children. For instance, ∼25% of children with insulin resistance who performed a short-duration (6 weeks) resistance training intervention showed a negative response for muscle strength (35). Others have reported a prevalence of non-responders for CRF of ∼20% among healthy young individuals (36).

Previous evidence shows that some exercise variables, such as training frequency and intensity, can be manipulated to enhance responsiveness. For instance, a systematic review concluded that intense aerobic exercise training elicits greater improvements in

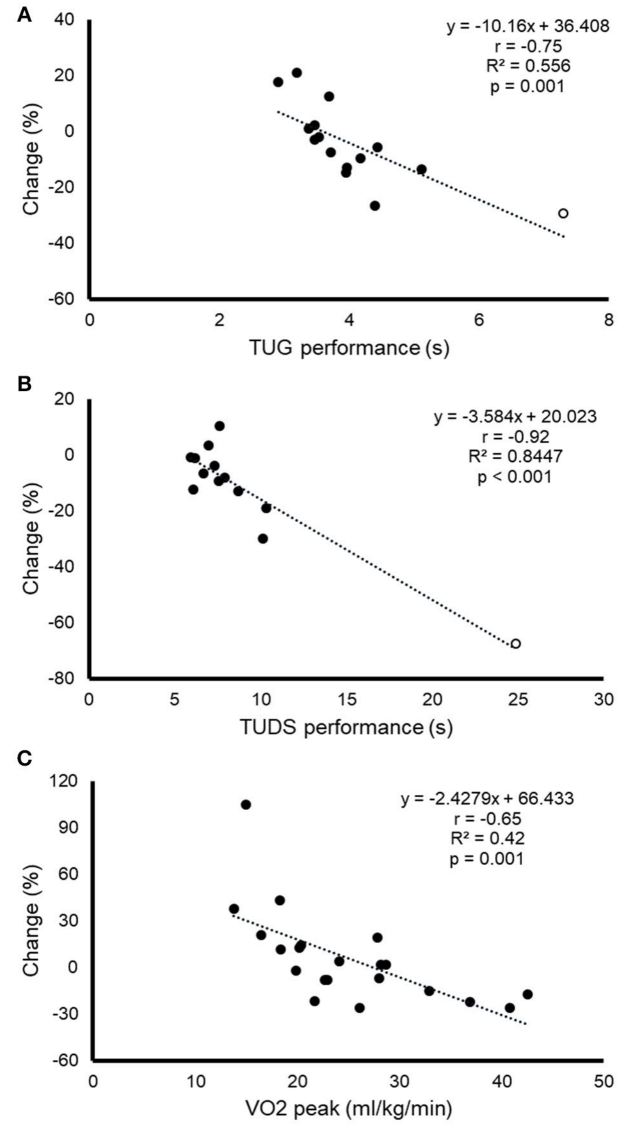

FIGURE 1 | Relationship between baseline performance in the timed up and go (TUG) test **(A)**, the timed up and down stair (TUDS) test **(B)** and cardiorespiratory fitness [CRF, expressed as peak oxygen uptake [VO_{2peak}]), **(C)**], on the one hand, and the relative change in performance for each test after the exercise training intervention, on the other. When outliers [white dots in **(A,B)**] were removed from the analysis, the relationship was still significant for both TUG ($r = -0.74$, $p = 0.002$) and TUDS ($r = -0.68$, $p = 0.01$).

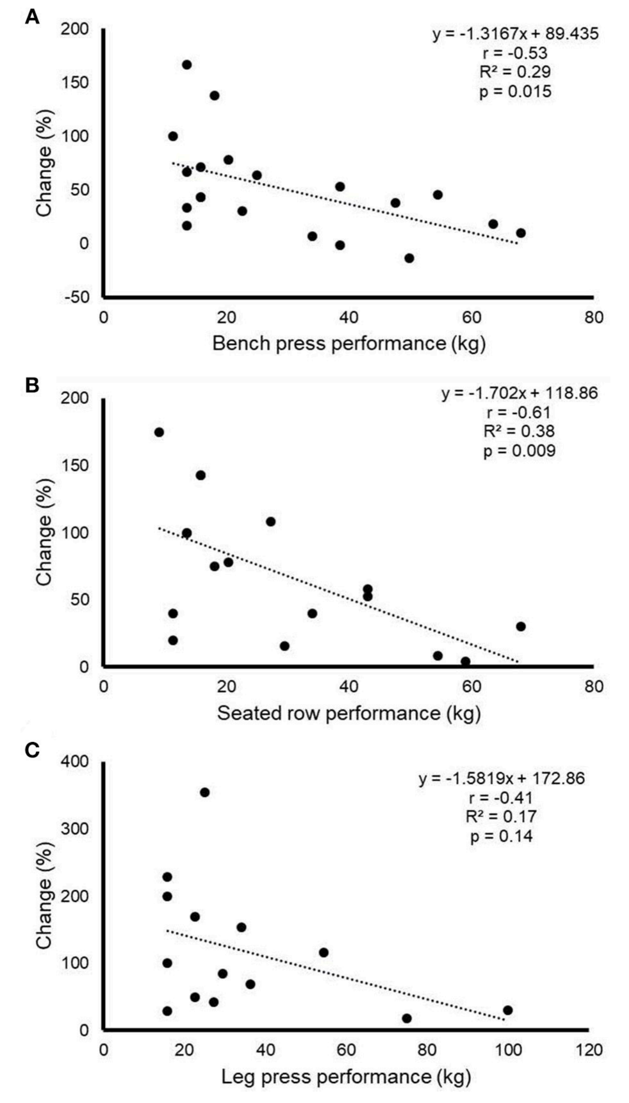

FIGURE 2 | Relationship between baseline performance in bench press **(A)**, seated row **(B)** and leg press **(C)**, on the one hand, and the relative change for performance in each test after the exercise training intervention, on the other.

fitness and cardiometabolic risk markers than moderate-intensity aerobic programs (37). Montero and Lundby (38) recently reported that the prevalence of non-responders for CRF after a 6 week endurance training program progressively declines with training duration (from 60 min per week to longer durations), with all the participants responding positively when exercising >240 min per week. Similarly, Ross et al. (39) found that, for a given exercise intensity, increasing exercise volume reduced the rate of non-responders by 50%, whereas increasing exercise intensity (from 50 to 75% of CRF) for a fixed exercise volume fully avoided non-responsiveness. Thus, an individual initially classified as non-responder to a certain training stimulus might actually respond to a different type of training program (40) or to a higher training volume (38, 39) or intensity (39). The children in our study who were non-responders had a poor baseline CRF (mean VO_{2peak} of 29 ml/kg/min) compared to children without a previous history of cancer of similar age, gender and sexual maturity (i.e., mean VO_{2peak} of 46 ml/kg/min) (41). Considering the importance of CRF as one of the strongest indicators of health status (42), efforts to enhance responsiveness in these patients are needed, which might probably involve applying a higher training stimulus (that is, higher intensity and/or volume) (24).

Our study has some limitations, including mainly heterogeneity in several participants' characteristics (i.e., type of solid tumor, age, or sexual maturity) and the small

TABLE 3 | Individual response to the different performance tests.

Subject	Seated bench press	Seated lateral row	Leg press	TUG	TUDS	CRF
1		N/A	+		N/A	+
2	+	N/A	+	+	N/A	+
3	+	+	+			+
4		+	+			+
5	+	+	+	+	+	+
6	+	+	N/A	N/A	N/A	
7		+	N/A	N/A	N/A	
8	N/A	N/A	+	N/A	N/A	N/A
9	+			+	+	
10	+	N/A	N/A	N/A	N/A	+
11		+	N/A			
12	+	+	+	+	+	+
13	+	+	N/A	N/A	N/A	+
14	+	+	N/A	N/A	N/A	+
15	+	+	+	+	+	
16	+	+	+			
17	+	+	N/A	N/A	N/A	N/A
18	+	+	+			+
19	+	N/A	+		+	
20	N/A	N/A	N/A	N/A	N/A	
21	+	+	+		+	+
22	+	+	N/A			
23	N/A	N/A	+		+	
24		N/A	N/A	N/A	N/A	N/A

Responsiveness (indicated as "+") was determined as a positive change greater than both the typical error of measurement and the minimal clinically meaningful change. CRF, cardiorespiratory fitness; N/A, not available; TUDS, timed up and down stairs test; TUG, timed up-and-go 3-meter test.

TABLE 4 | Differences between responders (R) and non-responders (NR).

	TUG			TUDS			CRF		
	R ($n = 8$)	NR ($n = 7$)	p-value	R ($n = 4$)	NR ($n = 9$)	p-value	R ($n = 8$)	NR ($n = 13$)	p-value
Male (%)	5 (62%)	7 (100%)	0.200	3 (75%)	8 (89%)	1.000	5 (63%)	10 (77%)	0.477
Age (years)	9 (6)	13 (7)	0.072	9 (6)	12 (6)	0.148	9 (6)	12 (6)	0.210
Tanner (stage)	1 (2)	3 (4)	0.152	1 (2)	3 (4)	0.148	1 (2)	3 (4)	0.185
Cancer type (% lymphoma)	4 (50%)	4 (57%)	1.000	2 (50%)	5 (56%)	1.000	3 (38%)	5 (38%)	1.000
Treatment with anthracyclines (%)	7 (87%)	5 (71%)	0.569	4 (100%)	7 (78%)	1.000	8 (100%)	11 (85%)	0.505
Anthracycline dose >300 mg/m^2 (%)	2 (25%)	1 (14%)	1.000	1 (25%)	2 (22%)	1.000	6 (75%)	4 (31%)	0.080
Treatment with radiotherapy (%)	4 (50%)	2 (29%)	0.608	2 (50%)	3 (33%)	1.000	3 (38%)	6 (46%)	1.000
Training sessions (n)	28 (24)	36 (27)	0.779	28 (32)	26 (26)	0.604	36 (15)	28 (28)	0.595
Baseline performance*	4.3 (1.0)	3.5 (0.3)	**<0.001**	10.2 (12.2)	7.0 (1.5)	**0.003**	18 (5)	28 (12)	**0.001**

*Data are shown as median and interquartile range (continuous variables) or as number and percentage (dichotomous variables). *Baseline performance is expressed in seconds for TUG and TUDS, and in ml/kg/min (peak oxygen uptake) for CRF. Differences were calculated using the Mann-Whitney U (continuous variables) and Fisher's exact test (proportions). The odds ratio (OR), calculated using univariate logistic regression, represents the likelihood of being responder attending to that specific variable. CRF, cardiorespiratory fitness; ES, effect size; N/A, not available; NR, non-responders; R, responders; TUDS, timed up and down stairs test; TUG, timed up-and-go 3-meter test. Significant P-values are in bold.*

sample size. However, heterogeneity in variables such as sexual maturity allowed us to account for the influence of maturation status on individual responsiveness, with the more sexually mature participants requiring a higher training stimulus. Further research with larger cohorts might allow for the examination of responsiveness predictors or for a prediction model. Concerning the low sample size, it should be noted that childhood cancer is a rare disease with pediatric solid tumors being particularly unusual (43), which implies an enormous recruitment challenge. In fact, it took more than 3 years to complete the participants' recruitment for this study (19–22). On the other hand, not all the participants could perform all the pre- and post-intervention tests. Another limitation was that no reliability analysis (and consequently no TE) was available for VO_{2peak}, and thus in the case of CRF responsiveness was solely determined attending to the minimal clinically meaningful change. Finally, the relationship between baseline performance and the observed improvement could be partly due to the learning of the technique (i.e., in those patients with the lowest baseline performance) and to statistical artifacts, especially for those subjects whose results are particularly far from the mean (whether too high or too low) (44). In this regard, we performed three familiarization sessions, and analyses were performed using percentage relative changes to minimize the influence of the "regression to the mean" phenomenon. In turn, major strengths of our study are the novelty of our approach and the clinical relevance of the topic.

CONCLUSIONS

The inclusion of inhospital exercise interventions in children with solid tumors undergoing neoadjuvant treatment improved muscle strength safely. However, a considerable individual variability was observed for the improvements in functional mobility and CRF. A lower baseline performance was associated with a better responsiveness for most tests, with those children with the best physical status at the start of treatment showing the lowest responses. Thus, our results might be taken into account in future efforts to prescribe effective, personalized exercise programs in pediatric cancer patients. Future research might determine if applying a higher training stimulus (i.e., higher intensity and/or volume) might maximize responsiveness in these patients.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Research Ethics Committee of the Children's Hospital Niño Jesús (Madrid, Spain). The protocol was approved by the Research Ethics Committee of the Children's Hospital Niño Jesús (Madrid, Spain; approval number R-0007/13). All subjects gave written informed consent in accordance with the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

AL, CF-L, JM, and PV conceived and designed the study. AH-O, AS, CR-C, ES-S, and JP supervised the training sessions and performed the evaluations. AS, AS-L, JM, and PV analyzed the data. AL, JM, and PV drafted the manuscript. AL, CF-L, and LM edited the final manuscript. All authors reviewed and approved the final version of the manuscript.

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REVIEW
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Exercise-Induced Laryngeal Obstruction: When Pediatric Exertional Dyspnea Does not Respond to Bronchodilators

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Exertional dyspnea is a common complaint in general pediatric practice. While a high proportion of the general pediatric population has asthma, other diagnoses, including exercise-induced laryngeal obstruction should be considered, especially when asthma therapy is not sufficient to control symptoms. This review describes some of the key clinical features of exercised-induced laryngeal obstruction as well as preferred diagnostic and therapeutic approaches. Importantly, current diagnostic technology has considerably improved in the last decade at specialty centers. At the same time, infrastructure for clinical trials is emerging and there is not strong evidence to support specific therapies at the current time.

Keywords: exercise-induced laryngeal obstruction (EILO), exertional dyspnea, continuous laryngoscopy during exercise (CLE), therapeutic laryngoscopy during exercise, Olin EILOBI breathing techniquest

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INTRODUCTION

Exertional dyspnea is a common presenting complaint in a general pediatric population. It is an important symptom regardless of cause because it may affect quality of life and willingness to exercise in an age characterized by concerns about decreased physical activity (1–3). It also may be a reflection of conditioning status or underlying pathology in a variety of organ systems (4). Finally, treatment of the conditions that cause exercise intolerance may safely increase a child's willingness to exercise, thereby optimizing normal growth and maturation and improving the child's cardiovascular risk profile later in life (5).

Among primary respiratory conditions leading to exertional dyspnea in pediatric populations, asthma is thought to be the most common cause, affecting nearly 300 million people globally and 10% of pediatric populations (6, 7). Exertional symptoms are present in the majority of patients, the impact of other diseases is important for clinicians, researchers, and the general population to consider.

Exercise-induced laryngeal obstruction (EILO) another common condition that causes exertional dyspnea and it is increasingly recognized for its impact on individual patients and populations. The disease is characterized by symptomatic upper airway obstruction at the level of the glottis or supraglottis during exercise in the absence of symptoms or obstruction at rest (8). In the evaluation of exertional dyspnea, EILO is a condition that warrants attention alongside asthma in selected populations, but our understanding of the condition is primitive when compared to asthma. This review will summarize this understanding of EILO and outline potential areas of high-yield scientific growth in the future.

DEFINITION, NOMENCLATURE, AND DESCRIPTION

In 2015, an international expert panel published a consensus document which discussed definitions and nomenclature related to episodic shortness of breath caused by the upper airway (8). "Inducible laryngeal obstruction" was introduced as the preferred term to describe glottic or supraglottic obstruction which occurred in response to a variety of environmental, psychologic, or exertional triggers. EILO is the term used to describe this phenomenon when the trigger is isolated to exercise. It replaces previously used terms including vocal cord dysfunction and paradoxical vocal fold motion.

EILO is defined by the presence of laryngoscopically visible upper airway obstruction that occurs during exercise before self-resolving (8). By definition, this same obstruction does not occur at rest. Historically, many of the descriptions of this condition highlighted involvement of the vocal folds. EILO can also be caused by a variety of structures in the supraglottic region including the arytenoid cartilages, tissue in the intra-arytenoid space, aryepiglottic folds, and rarely, the epiglottis. Although obstruction at either the glottic or supraglottic level is sufficient to make a diagnosis, the precise degree of obstruction at either anatomic level which differentiates 1) normal upper airway function from 2) an observed abnormality lacking clinical significance from 3) a clinical problem has not been defined.

EPIDEMIOLOGY AND IMPACT

The precise incidence and prevalence of this condition across a cross section of a population representing a variety of races and ethnicities has not been perfectly defined. Studies published to assess EILO prevalence have varied in terms of diagnostic methodologies. Nonetheless, in northern Europe, two studies both estimated that the population prevalence of EILO across adolescents and young adult seems to be in the range of 5% (9, 10).

Other studies have assessed sample EILO prevalence in referral clinics as well as patient characteristics among samples of patients previously diagnosed with EILO. Within clinics focused on refractory asthma or exertional dyspnea, EILO has been detected in a large, but highly variable proportion of patients (11–14). Many of these studies as well as others document and unequal gender distribution of identified subjects with a strong female predominance (15, 16). When race and ethnicity is reported, there is a notable Caucasian predominance (15, 16). There is not a clear understanding of changes in disease prevalence across the age spectrum.

PATHOPHYSIOLOGY

The mechanism of EILO is not completely understood. A variety of intrinsic and extrinsic contributors may be important. Anatomic factors, including airway size or airway pliability, logically impact the physics of airflow and may contribute to the frequency and severity of disease (17, 18).

Upper airway microanatomic factors could impact stimuli processing or the magnitude of inappropriate neuromuscular responses, possibly mediated through epithelial, neurologic, or muscular dysfunction (19).

The literature has highlighted a behavioral phenotype of EILO patients (20). Our understanding of the relevance of these behavioral observations is primitive and causality is certainly not proven.

Potential extrinsic contributors to the process of inappropriate upper airway obstruction during exercise include asthma, reflux, and nasal disease (21). Asthma triggers and EILO triggers are not necessarily identical (22). In EILO, upper airway abnormalities have been detected almost exclusively during high-intensity exercise (15). Surrogate testing has not yet been identified.

CLINICAL PRESENTATION

Many of the case reports and case series focusing on EILO discuss competitive young females presenting with frightening inspiratory stridor during strenuous exercise which resolves within minutes of exercise termination. Sometimes a personality phenotype characterized by perfectionistic or anxiety spectrum features co-travels with the description of symptoms (23).

In clinical practice, disease variability is likely extensive. The presence or absence of stridor may simply depend on disease severity and patient size (which is an important determinant of airflow) and extensive focus on stridor has the potential to mislead clinicians into discarding the diagnosis in smaller patients. Patient demographic features including age, gender, and athletic level have varied in the literature. A 32-year-old female presenting with long-standing exertional stridor secondary to supraglottic obstruction was one of the first cases presented in the literature (24). Young children with prominent supraglottic obstruction may also present with stridor, especially those known to have a degree of congenital laryngomalacia (18). The literature describes a female predominance, yet at the same time, males make up a large proportion of patients. Some cases come to light in the evaluation of "steroid-resistant asthma" (25, 26).

At an anecdotal level, our experience at a referral center that focuses on exertional dyspnea supports messages of EILO variability and the importance of curiosity during clinical histories.

We have recognized age as potentially misleading. Early school-age patients, later found to have prominent supraglottic EILO via continuous laryngoscopy during exercise (CLE), have initially presented with highly consistent exertional stridor which is not frightening to the patient, but highly concerning to observers. Patients in their 50s, later found to have prominent glottic EILO, have presented with "steroid-dependent asthma" and significant side effects from chronic oral steroid use including weight increases of over 50 kg over the course of therapy.

We are concerned that excessive focus on athletic level has the potential to unconsciously affect the rigor of diagnostic evaluation was performed by clinicians. In this line of thinking, we are concerned that patients not performing at a high level will be less likely to receive extensive exercise diagnostics because the perceived impact of exertional symptoms seems lower.

We have recognized descriptions of symptoms across the respiratory cycle as potentially misleading. Patients of almost all ages frequently refer to all audible respiratory noise as "wheeze," even those later to proven to struggle with isolated inspiratory obstruction with EILO. Many patients with severe obstructive disease, later proven to be unaffected by EILO, seem to describe symptoms as inspiratory despite the physiology of their diseases.

While not published, we have recognized excessive focus on audible stridor to be potentially misleading as well. Smaller patients may not have airflows sufficient to generate an audible noise or findings may be subtle (**Video 1**). Other patients, despite reproduction of obvious audible stridor during exercise testing, do not seem to be aware of the noise and subsequently do not report it to healthcare providers.

DIAGNOSTIC EVALUATION WITH CONSIDERATION OF DIFFERENTIAL DIAGNOSIS

The diagnostic evaluation of EILO should be one part of a general evaluation looking and causes of exertional dyspnea. In the pediatric population, as part of this evaluation, it is reasonable to consider both very common and potentially dangerous conditions.

When considering respiratory causes of exertional dyspnea, clearly asthma needs to be considered (**Figure 1**). In pediatric populations, many patients with exercised-induced bronchoconstriction struggle with non-exertional symptoms of cough and wheeze at baseline or during viral illness. As asthma is quite common, we recommend the use of spirometry and bronchodilator testing as an initial screen. At a more detailed level, and depending on available resources, provocative testing with methacholine challenge or eucapnic voluntary hyperventilation can be considered.

Cardiac causes of exertional dyspnea within pediatric populations, in whom congenital heart disease was presumably identified in infancy, are not as common as respiratory causes (given that asthma affects roughly 10% of the population). Importantly, identification of audible adventitial sounds should direct the clinical evaluation away from extensive cardiac testing because adventitial sounds are confined to the airway space. Syncope is a symptom that should always trigger a rigorous cardiac evaluation as left-sided obstructive lesions and dysrhythmias can be fatal.

Presyncope is a challenging coexisting complaint to evaluate. It can be associated with a number of cardiac, autonomic, and respiratory conditions. When clearly linked temporally with coexisting respiratory symptoms, such as described hyperventilation, it may be reasonable to defer extensive cardiac evaluation.

Once attention is turned to EILO, clinicians may be burdened by the relatively large number of methods described in the literature to evaluate the condition. Published case series have included subjects through the use of clinical history alone, flow volume loop analysis at rest, flow volume loop analysis during exercise, auscultation during exercise, ultrasound-based approaches, impulse oscillometry, resting laryngoscopy, post-exercise laryngoscopy, pre-and post-exercise laryngoscopy, and CLE (27–31).

CONTINUOUS LARYNGOSCOPY DURING EXERCISE

In centers with appropriate resources to perform safe and tolerable examinations, we recommend CLE as a preferred diagnostic approach over resting laryngoscopy and post-exertional laryngoscopy. In this procedure, a flexible laryngoscope is introduced prior to exercise and remains in place throughout an exercise challenge intended to reproduce characteristic field symptoms. CLE is reported in the literature as part of exercise testing in a variety of exercise modes including treadmill ergometry, cycle ergometry, rowing, and swimming (31–34). Each exercise modality presents unique challenges to proceduralists, with cycle ergometry likely being the safest and most feasible of the above exercise modes (**Figure 2**). Centers interested in pursuing this diagnostic approach also need to consider the relative likelihood of reproducing field symptoms across these different exercise modes in any given patient. Some authors have advocated for the use of treadmill ergometry as the preferred exercise mode for this reason (35).

There are multiple lines of reasoning that support the use of CLE as the preferred diagnostic method for EILO when available resources support the possibility. Importantly, the literature describes the visualized endoscopic findings of EILO patients as a function of exercise intensity (15). This study clearly describes an absence of resting findings as well as an absence of visualized findings during moderate exercise intensity. This study also describes a very rapid resolution of visualized findings upon exercise termination. Secondly, laryngoscopy can occasionally be an uncomfortable procedure if not performed by an experienced endoscopist. Performing a laryngoscopy after intense exercise during a period of shortness of breath has the potential to introduce abnormal laryngeal movements that do not accurately represent glottic behavior during intense exercise. Finally, although not quantitatively described in published literature, in our experience patients demonstrate an improved level of diagnostic acceptance and understanding after observing endoscopic and external video footage of observe symptoms which are perceived to reproduce characteristic field symptoms.

THERAPEUTIC OPTIONS

Medical Therapies

Currently, EILO therapies likely vary across centers and regions. Studies have documented case-based successes of medical, surgical, and behavioral therapies. There have not been published prospective randomized trials with well-described therapies on patients with symptoms isolated to exercise. There is a case series of patients with non-specific ILO in which tricyclic antidepressants were concluded to demonstrate potential benefit (36). This therapy is not recommended at the current time for EILO because patients with symptoms isolated to exercise were not a focus of this trial. The use of inhaled anticholinergic agents

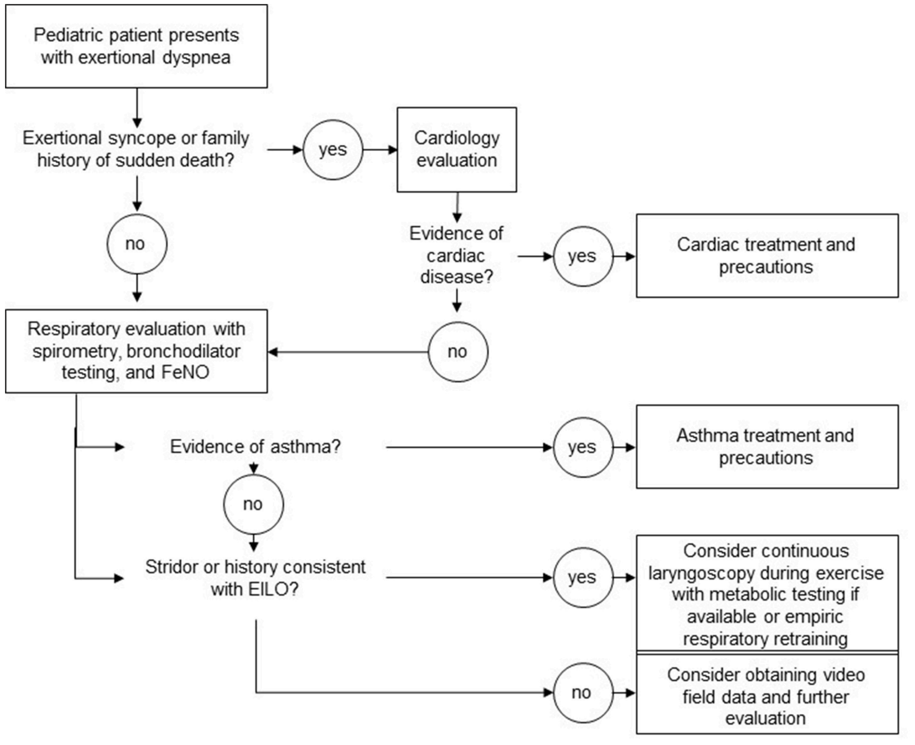

FIGURE 1 | A suggested diagnostic algorithm for young athletes complaining of exertional dyspnea.

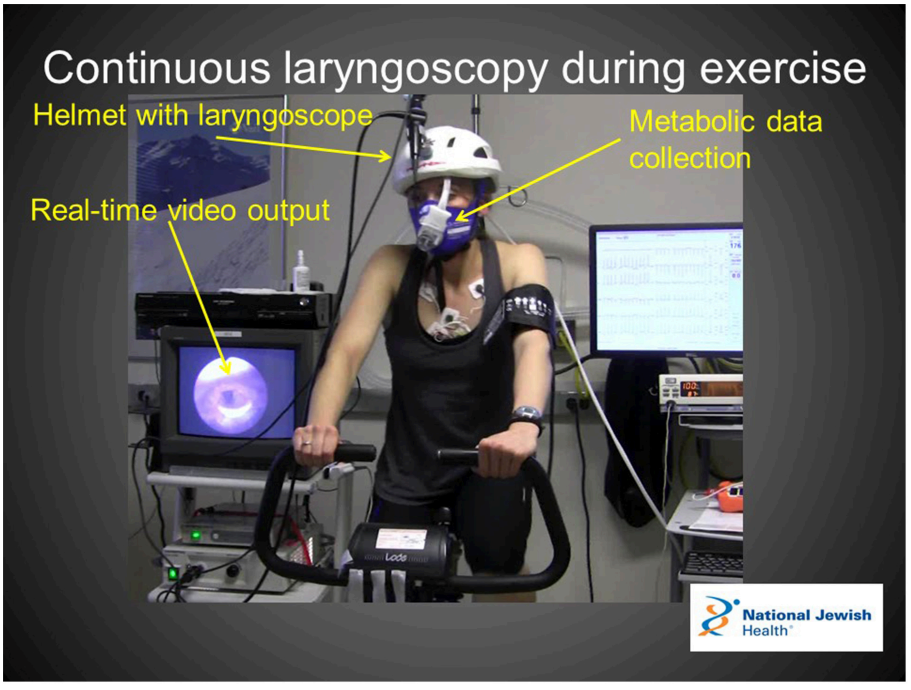

FIGURE 2 | Continuous laryngoscopy during exercise apparatus enables real-time visualization of the larynx with simultaneous ventilator and metabolic data collection. Verbal and written consent for the use of this image was obtained from the patient for use in this manuscript.

has also been proposed (37). Anticholinergic agents theoretically decrease muscarinic stimulus of laryngeal adductors and may favorably alter upper airway secretions.

Medical therapy may be more relevant for the treatment of conditions which may contribute to the presentation of EILO. Asthma, nasal disease, gastroesophageal reflux, and behavioral health disorders may theoretically affect EILO and may be amenable to medical therapy.

Surgical Therapies

Surgery may be a reasonable option for patients with EILO in patients with a prominent supraglottic component to the disease. Some European laryngology groups have used supraglottoplasty for selected patients because some of the laryngeal findings are reminiscent of patients with congenital laryngomalacia (38–42). The specific surgical approach includes release of the aryepiglottic folds and reduction in the size of the arytenoid towers. While initial reports of the approach seemed promising, it is important to understand that there is not a published body of data describing complications of the procedure.

Botulinum toxin, which can be injected into specific structures in the larynx, has been proposed as a potential therapy for patients that fail non-invasive therapies (43–45). As with medical therapies noted above, there is not sufficient evidence in patients with symptoms limited to exercise to warrant a recommendation for the use of this therapy.

Behavioral Therapies

Speech-language pathology intervention has been noted to be a potential therapy since the early reports of irritant-associated ILO were published (46). Specific breathing techniques taught by speech and language pathologists may differ across centers (47–50). General relaxation and biofeedback have also been incorporated in some of the therapies (16, 51). Behavioral therapies do not carry specific medical or surgical risks, but the potential positive effects of these therapies are challenging to study as they are likely multifactorial.

FUTURE

There are a number of very important gaps in our understanding of EILO. These range from basic science considerations to detailed treatment considerations.

Most importantly, the subtypes and associated mechanisms of EILO are very poorly understood. The impact of this problem is obvious when one considers the very broad spectrum of treatment approaches for the disease which may vary across regions of the world. As noted above, there are published schools of thought that focus on medical interventions with anticholinergic agents or reflux suppression, surgical interventions with supraglottoplasty, and behavioral health interventions with respiratory retraining, biofeedback, and psychotherapy.

Working backwards from these empiric therapies, is possible to hypothesize that the primary physiologic abnormality underlying the condition varies across different subtypes of disease yet to be identified definitively. It is also possible to hypothesize that the mechanism of disease relates to structural considerations of airway size and macro anatomy, epithelial integrity and micro-anatomy, airway muscles, airway nerves, intrinsic or extrinsic airway irritants, or central nervous processes.

At the current time, the hurdles to elucidating disease mechanism are numerous. They include the lack of a definitive categorization system of different disease subtypes and the lack of a widely-agreed-upon metric of disease severity. There is also a lack of feasible assays to assess airway size, airway pliability, airway irritability, epithelial integrity, muscle function, nerve function, and instantaneous central nervous stress.

In addition to a developing understanding of disease mechanism, there is a poor understanding of the differences observed across patients in terms of clinical presentation. For example, why do patients with similar degrees of airway obstruction observed on CLE present with seemingly different histories in terms of symptom quantity, sensation perception, and disease impact?

There are important gaps to fill in terms of diagnostic testing. While recent literature suggests that CLE is the preferred methodology for diagnosing the condition. There are still many unanswered question regarding exercise mode, exercise protocol, and environmental conditions, the answers to which will impact test sensitivity, specificity, and predictive value.

Finally, there are many unanswered questions related to disease treatment. It is possible to hypothesize that different schools of thought regarding disease treatment evolved across different medical specialties. As noted above, seminal literature on the condition developed within the fields of otolaryngology and pulmonology. Subsequently, authors from a number of different specialties including general medicine, allergy/immunology, sports medicine, and performance psychology have contributed to our collective knowledge of disease treatment. Ultimately, a better understanding of disease mechanism will lead to more personalized treatments.

In terms of quantifying the effects of these treatments and comparing them against one another, improved clinical trials infrastructure is required. Both physiologic in patient-reported measures of short-term and long-term disease impact will be required. Clinical trials will also rely on standardization of provocative protocols. Differences reported across centers will need to be understood as well.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2019.00052/full#supplementary-material

Video 1 | Field videos, such as this one demonstrating mild inspiratory stridor, can be a helpful diagnostic tool for clinicians. Verbal and written consent for the use of this video was obtained from the patient for use in this manuscript. Reproduced with permission from National Jewish Health.

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Participation in Physical Activity and Physical Education in School Among Children With Acute Lymphoblastic Leukemia After Intensive Chemotherapy

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Background: Low physical activity (PA) level has been reported among survivors of childhood acute lymphoblastic leukemia (ALL). The present study was performed to determine the level of participation in general PA and physical education in school (PES) among children with ALL who completed intensive chemotherapy and identify possible barriers that influence adherence to PA and PES.

Methods: A cross-sectional, single-center study was conducted over 1 year in a tertiary pediatric hematology and oncology referral center in Kuala Lumpur, Malaysia. A total of 47 children with ALL aged 7–18 years old who were off-treatment and attended school on a regular basis were recruited. A modified structured questionnaire adapted from the Youth Risk Behavior Surveillance System, Division of Adolescent and School Health, the Centers for Disease Control and Prevention (CDC) was used to assess the children's level of PA and PES participation.

Results: Among the 47 children will ALL included herein, 11 (23.4%) were physically active for at least 60 min a day for 5 days or more, following CDC recommendations. The median duration from completion of intensive chemotherapy was 4.95 years (25th, 3.29; 75th, 7.95). Younger age at study entry (median, 8.7 years old vs. 12.2 years old) and younger age at diagnosis (median, 2.9 years old vs. 4.3 years old) were significantly associated with higher PA level. Almost all children (45/47, 95.7%) participated in PES. Barriers to non-participation in PES mainly included exhaustion or fear of injury.

Conclusions: Majority of the children with ALL included herein had low levels of daily PA after intensive chemotherapy. Nonetheless, their participation in PES was encouraging. PA should thus be promoted during and after cessation of ALL treatment to prevent long-term health risks and improve overall quality of life.

Keywords: acute lymphoblastic leukemia, physical activity, physical education in school, off-chemotherapy, barriers

INTRODUCTION

Acute lymphoblastic leukemia (ALL), the most common childhood malignancy, has a 5 year overall survival of over 80% in developed countries (1, 2). Despite improved outcome, ALL survivors may experience long-term adverse effects of which some could be debilitating. Previous studies had reported that 62.3% of childhood cancer survivors suffered from at least one chronic condition, such as type 2 diabetes mellitus, obesity, and cardiovascular disease (2–6), one of the risk factors for such conditions being physical inactivity (3–7). Children with ALL have been reported to experience muscle strength deficits during and after treatment that could lead to deficits in physical activity (PA) (8). Dexamethasone-induced myopathy and vincristine-related peripheral neuropathy have also been shown to contribute toward the reduction in PA during and after completion of chemotherapy (9, 10). Previous studies had reported that childhood ALL survivors have a tendency to develop metabolic syndrome as a consequence of becoming overweight or obese due to reduced PA among other reasons (11–15).

Regular PA participation has been shown to induce protective effects by increasing muscle mass and improving strength and endurance, immune response, circulating hormones, and energy balance (16). According to a childhood cancer survivor cohort study, those with increased PA level have lower subcutaneous and body fat mass and greater lean body mass than those with low levels of PA (17). Moreover, the Centers for Disease Control and Prevention (CDC) has recommended that individuals over 18 years old should engage in 30 min of moderate to vigorous activity for at least 5 days a week (18). For children and adolescents below 18 years old, 60 min of moderate to vigorous activity at least 5 days per week is recommended (18). Moderate intensity activity refers to activities similar to a brisk walk, water aerobics, and biking on level ground with a few hills, whereas vigorous intensity activity refers to activities similar to a jog or run, hiking uphill, fast dancing, rope jumping, and swimming (19). However, a large number of childhood cancer survivors did not adhere to such recommendations (19–21). Reported barriers to PA participation included fatigue, concern regarding increased risk of infection, pain, low self-esteem, lack of time, and falling behind academically (17). Moreover, physicians provided insufficient exercise counseling to their patients and families (17).

PA programs in school have been shown to increase PA level and overall fitness in children, including childhood cancer survivors (17). However, during intensive chemotherapy, most children and adolescents do not attend school or participate in any PA. Prolonged hospital stay and frequent admissions could further reduce their level of involvement in PA (22, 23). Upon returning to school, many of them may be excluded from sports activities and physical education in school (PES). Kesting et al. reported that one in 4 children previously treated for childhood cancer was not being integrated into PES (22). Common reasons reported for non-participation in PES were prohibition from parents, teachers or attending physician, presence of an *in-situ* catheter, or problems related to prosthetic devices. Considering that PES is one of the compulsory subjects in both primary and secondary schools throughout Malaysia, it could be used as an initial step to promote active PA participation among the childhood cancer survivors upon returning to school. Therefore, we aimed to determine the level of PA and PES participation among children with ALL upon completion of intensive chemotherapy and identify possible barriers that may influence PA and PES adherence.

MATERIALS AND METHODS

This cross-sectional, single-center study was carried out at a tertiary pediatric hematology and oncology center in Kuala Lumpur, Malaysia over a period of 1 year. All children aged 7–18 years diagnosed with ALL who were post-intensive chemotherapy (maintenance or off-treatment) and attended school on regular basis were eligible for the study. The exclusion criteria included refusal of consent from parents or guardians. Ethical approval was obtained from the institutional Research and Ethics Committee prior to the study. Written informed consent was obtained from the parents/guardian prior to recruitment. The children and their guardian/parents (either mother or father) were given a questionnaire to answer under the guidance of the investigators.

ASSESSMENT TOOL

A structured questionnaire was used to assess the children's level of PA and PES participation. The questionnaire was adapted from the Youth Risk Behavior Surveillance System (1991–2015), Division of Adolescent and School Health, CDC and modified to suit the local population (24). The questionnaire consisted of 30 questions divided into six sections: (i) PA in general, (ii) PA in daily life, (iii) PES, (iv) PA during leisure time outside of school, (v) availability of sports facilities, and (vi) parental perception on their child's in PA and PES participation. Parts (i) to (v) were answered by the patients under the investigator's guidance, while part (vi) was answered by the parents or guardians. The original questionnaire was translated from English to Bahasa Malaysia by a bilingual translator and back-translated into English by another translator who had not seen the original questionnaire. Both independent translators were fluent in both Bahasa Malaysia and English. The translations retained the original meaning of the questionnaire and had been checked by two resident pediatricians. The content of the Bahasa Malaysia questionnaire was validated by administering it to a selected group of patients (10 subjects). The questionnaire was determined to have a Cronbach's alpha value of 0.8, showing high internal consistency and reliability. The approximate time to complete the questionnaire was 15–20 min. In this study, a patient who engaged in 60 min of moderate to vigorous activity at least 5 days per week was considered physically active as per CDC recommendations.

RESULTS

Subjects

A total of 108 eligible children were identified from the database during the study period. Among them, 55 (50.9%) (26 males and 29 females) met the inclusion criteria, and their parents/guardian completed the questionnaire. Among the 55 children, 8 (14.5%) were on maintenance chemotherapy, while the rest were off-treatment. The remaining 53 children (49.1%) could not be recruited due to scheduling reasons and investigators' time constraints. Children on maintenance chemotherapy were later excluded from analyses given that they were too few in number. **Figure 1** shows the flowchart of the study, while **Table 1** shows the characteristics of the 47 off-treatment children who completed the study.

Among the included children, 5 (10.6%) had underlying comorbidities: two have bronchial asthma, 1 has allergic rhinitis, 1 has HbE trait, and 1 has autism spectrum disorder. Moreover, three of the 47 children (6.4%) had complications during the intensive chemotherapy: one had vincristine-induced peripheral neuropathy, 1 had bilateral femoral head avascular necrosis, and 1 had right calf abscess with concomitant right tibia fracture.

Physical Activity

In a typical week, only 11 (23.4%; 6 males and 5 females) out of the 47 children were considered physically active following CDC recommendations (**Figure 2**). Moreover, 20 children (42.5%) were active for at least 60 min a day for 2 days or more but <5 days a week. Assessment of PA for the past 7 days showed that only 9 (19.1%) out of the 47 children were physically active. Eight children were found to be active both during a typical week and for the past 7 days. Concordance/agreement among the study participants was strong (kappa 0.84) for the level of PA participation during a typical week and for the past 7 days. Interestingly, the child who had both asthma and vincristine-induced neuropathy during intensive chemotherapy was physically active during a typical week despite his comorbidity.

Bivariate analyses revealed that age at study entry and age at diagnosis were statistically significantly associated with PA level. Accordingly, children of younger age at study entry (median, 8.7 years old vs. 12.2 years old) and diagnosis (median, 2.9 years old vs. 4.3 years old) were noted to be more active (**Table 2**). Duration from completion of intensive chemotherapy, off-treatment duration, risk stratification, ethnicity, gender, body mass index (BMI), and parental education level had no significant association with PA level (**Tables 2**, **3**).

Among the 47 children included, only 24 (51.1%) had easy access to sports facilities. Nearly half of the children (28/47; 59.6%) were members of at least one sports club, while the rest (19/47; 40.4%) were not involved in any sports club.

Physical Education in School

Majority of the primary school children (27/29; 93.1%) and all secondary school children (18 patients) participated in PES. The 2 children who did not participate in PES were treated for high risk ALL, one of whom had history of right calf abscess with concomitant right tibia fracture during intensive chemotherapy. One child did not participate in PES due to teachers' advice, while the other one did not participate due to parental restriction.

Out of the 45 children, 28 (62.2%) started to participate in PES within 6 months of returning to school. The remaining 17 children (37.8%) only took part in PES more than 6 months after returning to school (7 children participated in PES between

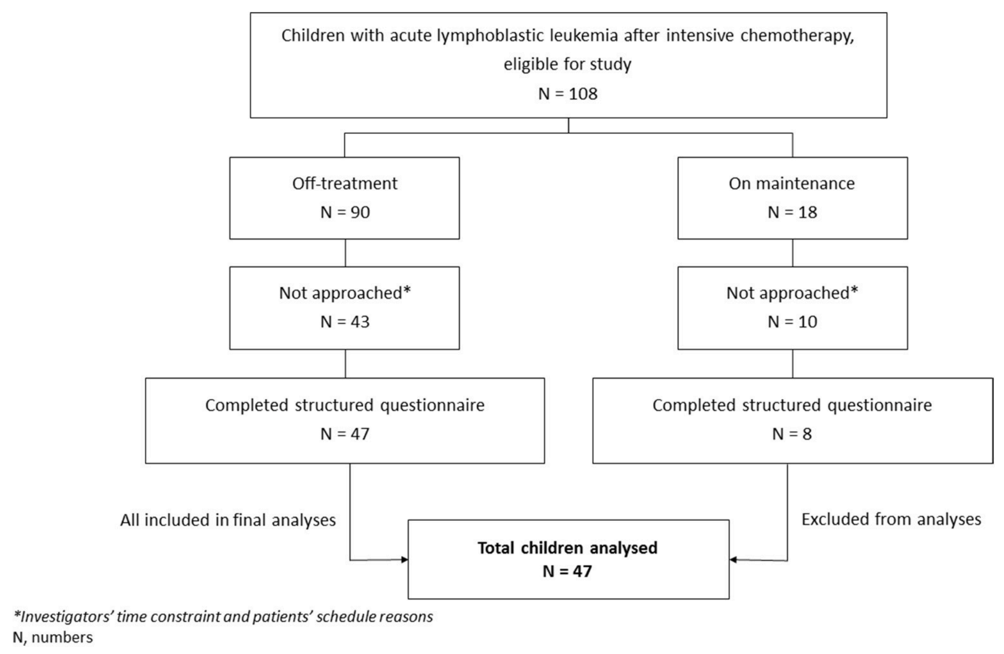

FIGURE 1 | Flow chart on the recruitment of study subjects.

TABLE 1 | Demographic and disease characteristics of the study population.

Characteristic	Patients ($n = 47$)
Age at study entry in years, median (IQR)	11.02 (25th 8.42; 75th 14.11)
Gender, *n* (%)	
Male	21 (44.7)
Female	26 (55.3)
Ethnicity, *n* (%)	
Malay	34 (72.3)
Chinese	9 (19.2)
Indian	3 (6.4)
Others	1 (2.1)
Education level, *n* (%)	
Primary	29 (61.7)
Secondary	18 (38.3)
Age at diagnosis in years, median (IQR)	3.53 (25th 3.06; 75th 6.15)
Duration from completion of intensive chemotherapy in years, median (IQR)	4.95 (25th 3.29; 75th 7.95)
Duration off-treatment in years, median (IQR)	3.03 (25th 1.61, 75th 6.09)
Risk stratification, *n* (%)	
Standard risk	36 (76.6)
High risk	11 (23.4)
Relapse, *n* (%)	
Yes	2 (4.3)
No	45 (95.7)
Craniospinal irradiation, *n* (%)	
Yes	1 (2.1)
No	46 (97.9)
Complication during treatment, *n* (%)	
Yes	3 (6.4)*
No	44 (93.6)
Comorbidities, *n* (%)	
Yes	5 (10.6)*
No	42 (89.4)
Body mass index (kg/m^2), *n* (%)	
<10th percentile	8 (17.0)
10–24.9th percentile	3 (6.4)
25–49.9th percentile	11 (23.4)
50–74.9th percentile	12 (25.5)
75–90th percentile	7 (14.9)
>90th percentile	6 (12.8)
Fathers' education level, *n* (%)	
Primary	1 (2.1)
Secondary	28 (59.6)
Tertiary	18 (38.3)
Mothers' education level, *n* (%)	
Primary	3 (6.4)
Secondary	21 (44.7)
Tertiary	23 (48.9)
Monthly income, *n* (%)	
<MYR1999	6 (12.8)
MYR2000–3999	16 (34.0)
>MYR4000	25 (53.2)

*n, number; IQR, interquartile range; MYR, Ringgit Malaysia. *One child with underlying comorbidity also had complication during treatment.*

6 and 12 months; 10 children participated after 1 year). The delay in PES participation was mainly due to restriction by either parents or teachers. Majority of the children participated in PES for more than 20 min per session (**Table 4**). Most of them (60.0%) participated in every game or exercises during the PES session with varying degree of exertion.

Parental Perception and Attitude Toward PES

All parents agreed that PA and PES are important for their children's health. However, when asked retrospectively regarding their children's participation in PES during maintenance chemotherapy, only 30 of the 47 parents (63.8%) allowed their children to participate. Of the 30 parents, 9 (30.0%) only allowed their children to participate in less vigorous activities during maintenance chemotherapy. Among the reasons given for not allowing their children to participate in PES while still on maintenance chemotherapy were fear of injury during the session (47.1%), child's complaint of fatigue (29.4%), and child's low self-esteem (5.9%). However, most of the parents (35/47; 74.5%) allowed their children to participate in PES upon completion of chemotherapy. Those who disagreed cited the following reasons: fear of overfatigue or infection (66.7%), presence of chemoport (8.3%), and fear of injury (8.3%). Of the 47 parents, 22 (46.8%) agreed that the best time for their children to participate in PES was within 6 months of treatment completion. Only 6 of the 47 parents (12.8%) concurred that their child should only be integrated back into PES 1 year after off-treatment.

DISCUSSION

The current study found that a high proportion of children treated for ALL were not physically active after intensive chemotherapy. Almost half of the children only engaged in PA <3 days a week. Our results are similar to findings from previous studies on reduced PA in children treated for ALL after completion of intensive chemotherapy or among the survivors (15, 25, 26). Another study reported that survivors of childhood ALL had PA levels similar to healthy children who met the recommended PA levels (27). The present study found that older age at study entry was associated with low PA levels. Similar findings had been reported in other studies where a decline in PA was observed with increasing age or during transition from middle school to high school (27, 28). Moreover, one study reported that regular and vigorous PA consistently reduced from 12 years old up to 21 years old (28). Although we postulate that preference for indoor activities and sedentary behaviors (e.g., watching television or playing computer games) could have contributed to this decline, other factors, such as psychological issues or lower self-esteem, may have played a role in the low level of PA among teenagers and young adults. However, such factors had not been investigated herein. Meanwhile, the increased likelihood of younger children being involved in outdoor activities like running, climbing, jumping, and cycling is consistent with their developmental milestone of being curious and eager to explore their surroundings at this

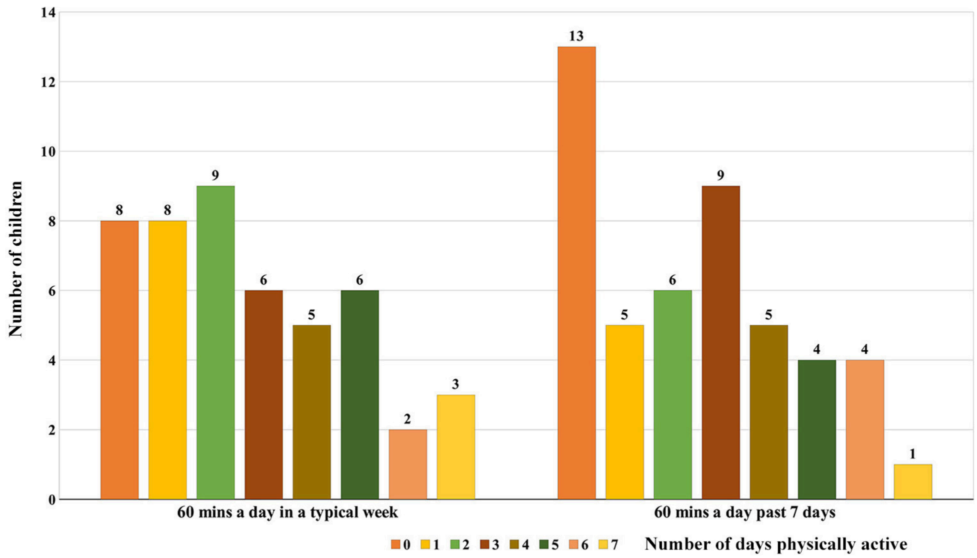

FIGURE 2 | Participation of the study population in general physical activity.

TABLE 2 | Factors affecting physical activity level among the ALL children.

	Typical week			Past 7 days		
	N	**Median (IQR)**	***p value***	***N***	**Median (IQR)**	***p value***
BMI (kg/m²)						
Inactive	36	18.68 (15.78; 21.77)	0.119	38	19.14 (15.82; 21.84)	0.119
Active	11	16.69 (14.00; 20.06)		9	17.00 (14.84; 19.69)	
Age at study entry (years)						
Inactive	36	12.16 (8.89; 14.61)	0.024*	38	12.19 (9.28; 15.00)	0.036*
Active	11	8.72 (7.33; 11.53)		9	8.79 (7.69; 11.58)	
Age at diagnosis (years)						
Inactive	36	4.26 (3.30; 6.59)	0.001*	38	4.36 (3.33; 6.61)	0.001*
Active	11	2.95 (2.30; 3.46)		9	3.04 (2.51; 3.46)	
Duration off treatment (years)						
Inactive	36	3.26 (1.18; 6.26)	0.900	38	3.03 (1.25; 5.88)	0.944
Active	11	2.98 (1.76; 4.70)		9	3.01 (1.72; 6.37)	
Duration from completion of intensive chemotherapy (years)						
Inactive	36	5.28 (3.23; 8.37)	0.782	38	4.95 (3.25; 8.23)	0.907
Active	11	4.76 (3.34; 6.72)		9	5.15 (3.30; 8.12)	

*Statistical analysis using Mann-Whitney U-test. *Significant p < 0.05.*

age. Younger age at diagnosis, and thus at completion of ALL treatment, could also lead to better recovery of overall health, early return to school, and active re-integration into PA and PES, all of which contribute to increased PA. To date, however, no study has reported on the correlation between younger age at diagnosis and higher level of PA participation. A larger study population would be needed to confirm this finding. No association had been observed between potential risk factors, like gender, ethnicity, children's education level, and BMI, and the level of PA.

To significantly reduce or prevent long-term health risks, our study supports the importance of promoting PA and healthy lifestyle habits among children treated for ALL. Studies have shown that exercise interventions in pediatric hematological cancer survivors promotes muscle strength and cardiorespiratory fitness, particularly if the training was conducted early in the hospital (29, 30). Tailored PA and exercise programs are important in certain subgroups of children treated for ALL to avoid injury and facilitate physical function. Thorsteinsson et al. reported that performing strenuous PA while receiving cancer treatment was safe and feasible for children and adolescents (31). Therefore, PA and physical training programs should be promoted among children with cancer immediately upon diagnosis to preserve premorbid physical function. Parents and family members should also be educated on the importance and safety of PA for their children. Furthermore, increased family engagement, especially mothers as exercise partners, plays an important role in influencing PA behavior in children (17). Other studies have also reported similar positive effects of parental participation on PA level among children (32, 33).

Although only 3 of the children included herein had complications during intensive chemotherapy, these complications involved the lower limbs (vincristine-induced peripheral neuropathy, bilateral hip avascular necrosis, and right calf abscess/tibia fracture), which could prolong their period of immobility and thus limit their PA. In this particular subgroup, a comprehensive rehabilitation program involving pediatricians, physiotherapists, occupational therapists, psychologists, and

TABLE 3 | Factors associated with physical activity level in a typical week.

		Physical activity level			
		Inactive	Active		
		n (%)	*n* (%)	χ^2	*p value*
Gender	Male	15 (41.7)	6 (54.5)	0.16	0.685
	Female	21 (58.3)	5 (45.5)		
Ethnicity	Malay	24 (66.7)	10 (90.9)	6.13	0.105
	Chinese	9 (25.0)	0 (0)		
	Indian	2 (5.5)	1 (9.1)		
	Others	1 (2.8)	0 (0)		
Risk stratification	Standard risk	26 (72.2)	10 (90.9)	0.76	0.382
	High risk	10 (27.8)	1 (9.1)		
Complication	Yes	2 (5.6)	1 (9.1)	0.00	1.000
	No	34 (94.4)	10 (90.9)		
Comorbidities	Yes	4 (11.1)	1 (9.1)	0.00	1.000
	No	32 (88.9)	10 (90.9)		
Education year	Primary	19 (52.8)	10 (90.9)	3.70	0.055
	Secondary	17 (47.2)	1 (9.1)		
Fathers' education	Primary/secondary	22 (61.1)	7 (63.6)	0.00	1.000
	Tertiary	14 (38.9)	4 (36.4)		
Mothers' education	Primary/secondary	17 (47.2)	7 (63.6)	0.37	0.543
	Tertiary	19 (52.8)	4 (36.4)		
Family income	<RM1999	4 (11.1)	2 (18.2)	1.65	0.438
	RM2000–3999	11 (30.6)	5 (45.4)		
	>RM4000	21 (58.3)	4 (36.4)		

Statistical analysis using chi square test. Significant $p < 0.05$.

family members should be initiated as early as possible to accommodate their health-specific limitations.

Our study nevertheless showed that majority of the children participated in PES. This finding is in contrast to the report by Kesting et al. where only 25% of the children previously treated for cancer were integrated into PES (22). The difference in the outcome could have been attributed to the heterogeneity of the study cohort considering that our study only involved children with ALL, whereas that by Kesting et al. included children with other types of cancers, such as bone, brain, and other solid tumors. Therefore, a higher number of patients who could not participate in PES due to physical disability, limb amputation, and endoprosthetic replacement could have been present in Kesting et al.'s study. Parental fear of their children being injured or overfatigued during treatment should be addressed accordingly to avoid unnecessary restriction to their PA participation. Other concerns regarding the risk of infection and *in-situ* catheters could be addressed during discussion to alleviate parents' and teachers' anxiety.

LIMITATIONS

The following are the limitations of the present study: (i) cross-sectional design with no control group, (ii) small sample size, (iii) recall bias when answering the questionnaire, (iv) items

TABLE 4 | Children's level of participation in Physical Education in School (PES).

Level of participation	*n* = 45
Duration spent on each pes session, *n* (%)	
>30 min	19 (42.2%)
20–30 min	20 (44.5%)
10–20 min	5 (11.1%)
<10 min	1 (2.2%)
Type of activity, *n* (%)	
Participate in every game/exercise	27 (60.0%)
Participate in some of the activities	18 (40.0%)
Degree of exertion, *n* (%)	
A lot of sweating and shortness of breath	19 (42.2%)
Slightly sweating and shortness of breath	20 (44.5%)
Without sweating and without shortness of breath	6 (13.3%)

n, number.

assessed in the self-report questionnaire may not reflect the actual PA level, (v) no objective measures of PA level were used, and (vi) lack of assessment on parental involvement in PA. The current study also excluded children with other cancer diagnoses. The main limitation of the present study is that PA was not objectively measured with any accelerometer. In addition, obtaining the children's attendance record for PES could have enhanced the understanding on their participation in such activities. Thus, the level of PA participation may have been under- or overestimated by the children. Future multi-center studies recruiting children with different types of cancer diagnosis or studies employing a longitudinal design would be more reflective of the PA status among the general pediatric oncology population throughout Malaysia. Nevertheless, our findings highlight the need for clinicians to recognize and address the issue of low PA participation among children with ALL. Our results also underscore the need for hospitals to create concepts and initiate programs mirroring those already established in developed countries.

CONCLUSION

The current study showed that majority of the children treated for ALL had low levels of PA after completion of intensive chemotherapy. However, their participation in PES was encouraging. The next logical step would be to conduct a longitudinal study including a larger cohort of children with different types of cancers; assess PA at diagnosis, during treatment, and after cessation of treatment using an accelerometer; and compare the findings with those from healthy controls.

DATA AVAILABILITY

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

ETHICS STATEMENT

Name of Ethics committee: Universiti Kebangsaan Malaysia Medical Center Ethics and Research; Ethics Committee/RB ref no: UKM PPI/111/8/JEP-2016-607; Research code: FF-2016-418.

AUTHOR CONTRIBUTIONS

DL and HA contributed to the conception and design of the study. NM and DL organized the database and performed statistical analysis. NM, DL, and HA drafted the manuscript. All authors contributed to the revision of the manuscript and have read and approved the submitted version.

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Assessing Exercise-Induced Bronchoconstriction in Children; The Need for Testing

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Objective: Exercise-induced bronchoconstriction (EIB) is a specific morbidity of childhood asthma and a sign of insufficient disease control. EIB is diagnosed and monitored based on lung function changes after a standardized exercise challenge test (ECT). In daily practice however, EIB is often evaluated with self-reported respiratory symptoms and spirometry. We aimed to study the capacity of pediatricians to predict EIB based on information routinely available during an outpatient clinic visit.

Methods: A clinical assessment was performed in 20 asthmatic children (mean age 11.6 years) from the outpatient clinic of the MST hospital from May 2015 to July 2015. During this assessment, video images were made. EIB was measured with a standardized ECT performed in cold, dry air. Twenty pediatricians (mean years of experience 14.4 years) each evaluated five children, providing 100 evaluations, and predicted EIB severity based on their medical history, physical examination, and video images. EIB severity was predicted again after additionally providing baseline spirometry results.

Results: Nine children showed no EIB, four showed mild EIB, two showed moderate, and five showed severe EIB. Based on clinical information and spirometry results, pediatricians detected EIB with a sensitivity of 84% (95% CI 72–91%) and a specificity of 24% (95% CI 14–39%).The agreement between predicted EIB severity classifications and the validated classifications after the ECT was slight [Kappa = 0.05 (95% CI 0.00–0.17)]. This agreement still remained slight when baseline spirometry results were provided [Kappa = 0.19 (95% CI 0.06–0.32)].

Conclusion: Pediatricians' prediction of EIB occurrence was sensitive, but poorly specific. The prediction of EIB severity was poor. Pediatricians should be aware of this in order to prevent misjudgement of EIB severity and disease control.

Keywords: asthma, EIB exercise-induced bronchoconstriction, children, disease history, pediatrician

INTRODUCTION

Exercise-induced bronchoconstriction (EIB) is defined as an acute narrowing of the airways that occurs as a result of exercise (1). Evaporative water loss during exercise inducing osmolarity and thermal changes of the airway epithelium plays a central role, leading to smooth-muscle contraction (2). EIB is a specific morbidity of childhood asthma and has a great impact on the quality of life, especially on the physical dimensions (3). Clinical symptoms include shortness of breath, chest tightness, wheeze, and cough in association with physical exercise (4). EIB reflects airway inflammation and is a sign of uncontrolled asthma (5, 6). EIB is diagnosed and monitored based on lung function changes after a standardized exercise challenge test (ECT) according to American Thoracic Society and European Respiratory Society (ATS/ERS) protocol (7, 8). However, in daily practice, ECT's are not often performed and pediatricians usually assess EIB based on a medical history, self- or parent-reported, a physical examination, and possibly lung function. This clinical strategy is in line with guidelines from The Global Initiative for Asthma (GINA), which recommends that an ECT should be undertaken if it is otherwise difficult to assess asthma control (6).

However, it is unclear if this approach is sufficient to properly assess EIB in children. Several studies have shown a poor relation between reported exercise-related symptoms in children and EIB as measured with an ECT (9–11), as well as between basic lung function tests and EIB (12–14). All previous studies focused on separate aspects of clinical information and EIB, while in daily practice, pediatricians combine available information to evaluate EIB and thus asthma control. This study aimed to determine the capacity of pediatricians to predict the occurrence and severity of EIB in asthmatic children, based on clinical information routinely available during an outpatient clinic visit.

METHODS

Study Design and Patients

This study had a cross-sectional design. Children 6–17 years old with pediatrician diagnosed asthma were recruited from the outpatient clinic of the pediatric department of Medisch Spectrum Twente, Enschede, The Netherlands from May 2015 to July 2015. Children with spirometry-induced bronchoconstriction or severe airflow limitation in baseline spirometry, defined as a forced expiratory volume in 1 s (FEV_1) $< 60\%$ of predicted, were not included. None used short- or long-acting bronchodilators for at least 24 h before the exercise challenge test. Children with other pulmonary or cardiac disorders were excluded. A STARD checklist (31) for this study can be found in the **Supplementary Material**.

Study Procedure

Clinical Assessment With Medical History, Physical Examination, Video Images, and Spirometry

The clinical assessments and ECT's were performed at OCON sport, in Hengelo. This was carried out by two healthcare professionals, one sports-physician, and one pediatric pulmonologist, with both extensive experience in the clinical assessment of asthma and EIB.

Before the start of the ECT, a medical history with specific focus on asthma symptoms was obtained (**Table 1**). Anthropometric measurements were taken (height, weight) and a physical examination (**Table 1**) including pulmonary auscultation was performed. During this clinical assessment, video images were made in order to provide the pediatricians an overall picture of the children. The video images included sound and were made using an iPad mini attached to a tripod, positioned to film the patients' head and bare chest (**Figure 1**). After this, baseline spirometry measurements were performed using a MicroLoop® MK 8 hand-held spirometer (ML3535) following standard ATS/ERS protocol (15). Baseline spirometry was measured in duplicate before exercise.

Exercise Challenge Test

The ECT's were performed in a climate chamber with cold (10.0–12.0°C), dry air following standard protocol (7). Children aged 8–17 years performed the ECT while running on a treadmill (H/P-Cosmos Quasar 4.0) for 6 min, with an inclination of 10% and with their nose clipped. The treadmill was accelerated until a steady heart rate around 85% of the maximal heart rate (220–age) was achieved in a time period of 2 min. Heartrate was measured with a radiographic ECG-device (Custo cardio 100 BT). Children aged 6 and 7 years performed the ECT on a jumping castle (16), also for a duration of 6 min. Post-exercise spirometry was

TABLE 1 | Elements of medical history and physical examination[a].

Medical history
General asthma symptoms
Exercise-induced symptoms
Nocturnal symptoms
Nasal symptoms
Atopy
Family history positive for asthma
Medication use
Physical examination
General impression
Nasal obstruction
Nasal crease (allergic salute)
Vesicular breath sounds
Inspiratory stridor
Expiratory wheezing

[a]*Part of the clinical assessment before the exercise-challenge test.*

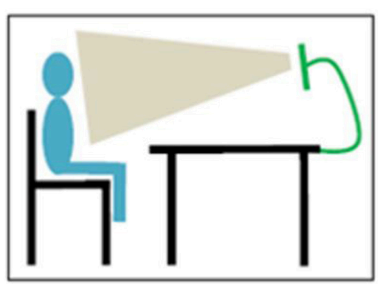

FIGURE 1 | Position of patient and camera while recording.

performed in duplo at 1, 3, 6, 9, 12, and 15 min after the ECT. After post-exercise spirometry, children inhaled 200 μg salbutamol, and 5 min later reversibility was measured. Children with a fall of ≥10% in FEV_1 post-exercise were considered to have EIB. EIB severity was classified as: 1. No EIB; 2. Mild EIB; 3. Moderate EIB; 4. Severe EIB (**Table 2**), as suggested by Anderson et al. (17).

The ECT results were interpreted by the above mentioned healthcare professionals.

Prediction of EIB by Pediatricians

Twenty pediatricians from three different teaching hospitals (Medisch Spectrum Twente, Isala Klinieken Zwolle, ZGT Almelo/Hengelo) participated in this study. Their average years of experience was 14.4 years (SD 9.8) and two pediatrician were subspecialized as pediatrician-pulmonologist. Each pediatrician independently evaluated five children that were randomly assigned to him or her, providing 100 evaluations in total. The evaluation procedure consisted of two steps.

First, occurrence and severity of EIB (**Table 2**) was predicted based on the information from the participants' medical history, anthropometric measurements, physical examination and video images. Second, additional information was provided to them in the form of spirometry results [flow-volume curve, FVC (forced vital capacity), FEV_1, PEF (peak expiratory flow)], after which the pediatricians again predicted occurrence and severity of EIB.

Statistical Analyses

Results were expressed as mean values ± standard deviation (SD) for the normally distributed continuous data and as median ± interquartile range (IQR) for not-normally distribute data. For nominal or ordinal data, numbers with corresponding percentages were used. The maximum fall in FEV_1 as a percentage of predicted was calculated and used for statistical analyses.

Sensitivity was calculated as the proportion of children with EIB, diagnosed with an ECT as reference standard, who were given an EIB diagnosis by the pediatricians based on the provided clinical information and spirometry results. Specificity was calculated as the proportion of children without EIB, who were not given an EIB diagnosis by the pediatricians.

The 95% confidence intervals (CI) for sensitivity and specificity were calculated using Episheet (18).

To assess the degree of concordance between the prediction of EIB severity by the pediatricians and the validated classification of EIB based on the ECT, a linear weighted Cohen's Kappa was calculated. Cohen's Kappa values were classified as: <0 = poor; 0–0.2 = slight; 0.2–0.4 = fair; 0.4–0.6 = moderate; 0.6–0.8 = substantial; 0.8–1.0 = almost perfect (19). To assess the difference between two correlated proportions, a McNemar test was used.

For these analysis all 100 evaluations were included, acknowledging the fact that each child was present multiple times in the dataset, albeit assessed by different pediatricians.

A two-sided $p < 0.01$ was considered statistically significant. Data analyses were performed with SPSS® Statistics, version 22.0, and www.vassarstats.net/kappa.html was used to carry out the weighted Cohen's Kappa analyses.

TABLE 2 | Classification of EIB severity[a].

Degree of EIB severity	Maximum fall in FEV_1 after exercise
No EIB	<10%
Mild EIB	>10% but <25%
Moderate EIB	>25% but <50%
Severe EIB	>50% for steroid-naïve patients >30% for steroid-treated patients

[a]*EIB severity classification, adopted from Anderson et al. (16).*

TABLE 3 | Characteristics of the study sample (n = 20)[a].

VARIABLES	
Sex[b]	
Female	10 (50.0%)
Male	10 (50.0%)
Age, years	11.6 (3.4)
BMI, kg/m^2	19.5 (4.6)
Atopy[b]	11 (55.0%)
Medication use[b]	
SABA	13 (65%)
LABA	2 (10%)
ICS	10 (50%)
LTRA	6 (30%)
NCS	5 (25%)
Exercise-induced symptoms	8 (40.0%)
FEV_1 predicted, %	92.7 (13.9)
Fall in FEV_1[c], %	15.1 (1.2–65.1)
EIB classification after ECT[b]	
No EIB (<10%)	9 (45.0%)
Mild EIB (10–25%)	4 (20.0%)
Moderate EIB (25–50%)	2 (10.0)
Severe EIB (>50% or ICS use with >30%)	5 (25.0)
Reversibility[c], %	18.9 (−11.0–62.3)

[a]*Values are presented as mean (SD), except when indicated otherwise.*
[b]*Value is presented as n (%).*
[c]*Value is presented as median (IQR). BMI, Body Mass Index (kg/m^2); SABA, short-acting β2-agonist; LABA, long-acting β2-agonist; ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonist; NCS, nasal corticosteroid; FEV_1, Forced Expiratory Volume in 1 s; EIB, exercise-induced bronchoconstriction.*

TABLE 4 | EIB occurrence after the exercise challenge test compared to the predicted occurrence of EIB.

EIB prediction		EIB after ECT		
		No	**Yes**	**Total**
	No	11	9	20
	Yes	34	46	80
	Total	45	55	100

Prediction by pediatricians, based on medical history, physical examination, pre-exercise video and spirometry results. EIB, exercise-induced bronchoconstriction; ECT, exercise challenge test.

Ethical Considerations

This study was approved by the Medical Ethics Review Board Twente. All children and parents/guardians received written patient information and provided written informed consent before participating in the study.

RESULTS

Of 24 children with usable consultation videos, three children had spirometry-induced bronchoconstriction, and one child used salbutamol shortly before the ECT. Twenty children completed the protocol and were included for statistical analyses. Twenty pediatricians independently assessed five children, providing a total of 100 assessments.

Characteristics of the Study Population

Baseline characteristics of the study sample [10 boys (50.0%)] are shown in **Table 3**. The mean age of our study group was 11.6 years (SD 3.4). The mean baseline FEV_1 was 92.7% of predicted (SD 13.9), with a median fall in FEV_1 after exercise of 15.1% (IQR 1.2–65.1). Nine children showed no EIB, four children showed mild EIB, two children showed moderate and 5 children showed severe EIB (for classification, see **Table 2**).

Prediction of EIB by Pediatricians

EIB occurrence after the ECT was compared with the predicted occurrence of EIB by pediatricians (**Table 4**). Based on clinical information and spirometry results, pediatricians detected EIB with a sensitivity of 84% (95% CI 72–91%) and a specificity of 24% (95% CI 14–39%).

Table 5 shows an overview of the EIB severity predictions by pediatricians based on the clinical assessment with and without spirometry data and the actual EIB severity after the standardized ECT. EIB was underestimated in the majority of patients with moderate EIB when based on the clinical assessment without spirometry data (14 out of 23 assessments). This improved slightly when spirometry data was added (underestimation in nine out of 23 patients). Without spirometry data, pediatricians underestimated EIB severity in all children with severe EIB. This improved barely when the clinical data was complemented with the spirometry data.

The agreement between the EIB classifications is shown in **Table 6**. Agreement between the predicted EIB severity classification based on the clinical assessment and the validated classification based on the ECT, was slight [Kappa = 0.05 (95% CI 0.00–0.17)]. This agreement still remained slight when the clinical assessment information was complemented with the spirometry data [Kappa = 0.19 (95% CI 0.06–0.32)].

Differences between the paired EIB severity classifications, analyzed with the McNemar test, are shown in **Table 7**. Pediatricians' prediction based on the clinical assessment with and without spirometry data was not significantly different ($p = 0.181$). There was a significant difference between the validated classifications based on the ECT and the predictions based on the clinical assessment, both with and without additional information on pre-exercise pulmonary function ($p < 0.001$).

DISCUSSION

This study aimed to evaluate the capacity of pediatricians to predict the occurrence and severity of EIB based on information routinely available during an outpatient clinic visit. In 100 evaluations, the sensitivity of a pediatricians' predicted diagnosis of EIB was 84%, compared to a specificity of 24%.

The prediction of EIB severity based on a clinical assessment including a medical history, physical examination, and video images of the assessment was poor, with an underestimation of EIB severity in children with moderate and severe EIB. This prediction remained poor when pediatricians were informed about pre-exercise pulmonary function.

To our knowledge, this is the first study that focused on the capacity of pediatricians to predict EIB based on merged data, rather than focusing on separate aspects, available during a routine clinical visit. Our results are in line with previous research that found that clinical information alone is unreliable to predict EIB, leading to both over- and underestimation.

Seear et al. (9) concluded that a respiratory history was unreliable, as it led to the overdiagnosis of EIB in schoolchildren. In a study by de Baets et al. (10) exercise-induced respiratory symptoms after a free running test had a poor positive predictive value for EIB in school-age children not previously diagnosed with asthma. Linna (14) however, was able to predict EIB severity in asthmatic children based on the frequency of general asthma symptoms, including exercise-related symptoms. This is in contrast with other studies that could not identify a relation between EIB and general asthma symptoms assessed with questionnaires, such as the ACT (Asthma Control Test) (20–22) and ACQ (Asthma Control Questionnaire) (23). Moreover, Rietveld et al. (11) did not observe a relation between self-reported dyspnea symptoms and lung function decline during a histamine-induced bronchoprovocation test in their cohort of asthmatic children.

Four studies found no relationship between pre-exercise spirometry values and EIB in children (12–14, 24). Linna (14) however, did find that EIB was related to the concavity of the pre-exercise flow volume curve. Holt et al. stated that spirometry is only meaningful during exacerbations where it influences patients' diagnosis and treatment (25), and not in periods without symptoms due to a low sensitivity.

Studies focusing on athletes with EIB are in line with our results. Hallstrand et al. (26) assessed the accuracy of a medical history and physical examination to diagnose EIB in adolescent athletes and found that half of the EIB diagnoses would have been missed without a standardized ECT. Another study focusing on athletes (27) found that the use of self-reported symptoms for the diagnosis of EIB resulted in both false positive and false negative results.

The unreliability of only using symptoms for the assessment of asthma control was demonstrated by Shefer et al. (28), who found a discordance between children's assessment of general asthma control and the opinion of their pediatricians, with more than 40% of the pediatricians indicating asthma as controlled based on symptom assessment when children

TABLE 5 | Overview of predicted and tested EIB severity classifications in participants.

		EIB severity after ECT				
		No EIB	**Mild EIB**	**ModerateEIB**	**Severe EIB**	**Total**
EIB prediction by pediatricians based on CA	No EIB	11	5	1	4	21
	Mild EIB	22	10	13	6	51
	Moderate EIB	10	5	8	2	25
	Severe EIB	2	0	1	0	3
	Total	45	20	23	12	100
EIB prediction by pediatricians based on CA + spirometry	No EIB	11	5	1	3	20
	Mild EIB	21	11	8	3	43
	Moderate EIB	10	4	11	5	30
	Severe EIB	3	0	3	1	7
	Total	45	20	23	12	100

EIB, exercise-induced bronchoconstriction; ECT: exercise challenge test. CA, clinical assessment (medical history, physical examination, pre-exercise video).

TABLE 6 | Agreement between pediatricians' prediction of EIB severity and EIB severity after an ECT.

	Kappa (95% CI)	**Significance**
Clinical assessment * ECT	0.05 (0.00–0.17)	$p = 0.400$
Clinical assessment + spirometry * ECT	0.19 (0.06–0.32)	$p = 0.005$

EIB, exercise-induced bronchoconstriction; ECT, exercise challenge test; Clinical assessment, medical history, physical examination, video images.

TABLE 7 | Differences between pediatricians' prediction of EIB severity and EIB severity after an ECT.

	Significance
Clinical assessment * clinical assessment + spirometry	$p = 0.181$
Clinical assessment * ECT	$p < 0.001$
Clinical assessment + spirometry * ECT	$p < 0.001$

EIB, exercise-induced bronchoconstriction; ECT, exercise challenge test; Clinical assessment, medical history, physical examination, video images.

indicated it was not. Overestimation of asthma control can lead to undertreatment and creates a potential risk for patients. Several studies have shown that poor asthma control is not only associated with an increased risk of exacerbations, a lower quality of life and increased health-care costs (29), but also with obesity and learning disabilities (30).

A major strength of this study is the standardized exercise challenge tests that were performed in a climate chamber with cold and dry air, following standard protocol. Young children (6–7 years old) performed the test on a jumping castle, a method that has previously been validated by members of our study group (16).

The main limitation of our study is that pediatricians predicted occurrence and severity of EIB based on clinical information not personally obtained. This information was obtained by the investigators of this study during the clinical assessments and ECT's. The pediatricians received this information afterwards and each assessed five children based on the provided information. We complemented this information with video images of the children so that the pediatricians could form a general impression of the children. This study setting is however not a perfect simulation of a real-life setting, and therefore could have led to a less accurate prediction of EIB by the pediatricians.

Another limitation of our study is the inflated sample size: 20 pediatricians each assessed five children (from a total study group of 20 children), providing 100 evaluations. We also acknowledge that therefore each child was present multiple times in our dataset, albeit assessed by different pediatricians.

In conclusion, this study shows that the clinical prediction of EIB occurrence by pediatricians is sensitive, but poorly specific. Furthermore, the prediction of EIB severity based on information routinely available during an outpatient clinic visit is poor. Pediatricians should be aware of this unreliability to prevent misjudgement of asthma control by evaluating EIB without an ECT.

ETHICS STATEMENT

This study was approved by the Medical Ethics Review Board Twente. All children and parents/guardians received written patient information and provided written informed consent before participating in the study. This study was registered on the Dutch Trial Registration under number NTR 5534 (www.trialregister.nl).

AUTHOR CONTRIBUTIONS

All except MB-K and JvdP contributed to data acquisition. NL, MB-K, and JvdP contributed to the data analysis. All authors contributed equally on the research protocol, the writing and editing of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2019.00157/full#supplementary-material

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Gymnastic-Based Movement Therapy for Children With Neurodevelopmental Disabilities: Results From a Pilot Feasibility Study

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Background: Developmental and behavioral issues often limit the participation of children with neurodevelopmental disabilities (NDD) in community-based activities with their peers, which decreases opportunities for their social learning and development. Parents of children with NDD seek out programs that address physical and psychosocial development. Several studies already support the positive effects for the child to attend physical activity programs (PAPs). However, these studies are highly prone to biases and Hawthorne effect. In the planning stage of a large prospective study to assess the effectiveness of PAPs we reviewed the records of children who participated in a gymnastic-based program, the Empowering Steps Movement Therapy (ESMT). Besides generating useful data for developing the prospective study we thought these data reflect the rate of changes in context of normal practice in a naturalistic environment; therefore protected from Hawthorne effect and other biases.

Design: This is a historical cohort: the files of 67 children with NDD were examined across a 2-year period (Jan 2011 to Jan 2013). As part of standard practice, the ESMT therapists document changes in motor function every 6 months, using the ESMT's proprietary motor scale. Parents also completed a parental questionnaire in June 2011 regarding their perceptions of changes in their child's physical and psychosocial function, as well as family functioning since their child started the program.

Results: Linear Mixed Effects Model clearly identified three groups according to changes in motor function: the ones with rapid changes (mostly functional children with autism spectrum disorder: $n = 13$), the ones with moderate changes (different types of NDD diagnoses: $n = 41$) and the ones that did not change or even decreased motor skills over the follow-up (children with complex diseases or uncontrolled epilepsy despite treatment: $n = 13$). Parental questionnaires ($n = 39$) reported improvement in most of the children's physical and psychosocial abilities; they also indicated improvement in some of the family parameters. There was no association between the changes in children's motor functions and parents' responses to the questionnaire.

Conclusion: Despite limitations due to the retrospective nature of the study, the absence of a control group and the absence of validated measurement tools, the observed positive effects of attending movement therapy center on motor performance and psychosocial development confirm in a naturalistic environment what has been shown in context of clinical trials or quasi-experimental studies. These results are not conclusive. They warrant further, rigorous investigation using validated instruments, independent assessors, and control groups.

Keywords: physical activity, movement therapy, children, neurodevelopment disability, child development, gymnastic, motor skill, activity theory

INTRODUCTION

The prevalence of neurodevelopmental disabilities (NDD) among children aged 4–14 years is ∼3.6–12.8% depending on the definitions, and is increasing (1, 2). Morris et al. defines NDD as "*a group of congenital or acquired long-term conditions that are attributed to impairment of the brain and/or neuromuscular system and create functional limitations*" [p. 1105, (3)]. The impact of NDD on family and society is important due to ongoing functional needs, high level of medical attention, and challenges related to behavioral and emotional adjustments (4–8).

The primary disability and the presence of behavioral issues, which often accompany NDD, limit or even preclude children's participation in typical social and recreational activities with peers (8–10); therefore, they tend to miss these important aspects of social learning during the developmental period (11–13). Child isolation is a source of concern for their parents (14). Families often seek and enroll their children in programs aimed at stimulating both motor skills and psychosocial development, with the goal of improving social integration reaching their potential and improving their quality of life.

Adapted community-based physical activity programs (PAPs) for children with NDD offer the appropriate environment for enjoyable and meaningful inclusive recreational activities, thereby creating a context for socio-cultural learning and development (12). Literature on the effects of physical activity in children with NDD has shown a positive impact of physical activity on variety of outcomes such as cognitive function, social integration, friendship development and physical ability (15–22). However, the majority of these studies are limited because of the high risk of Hawthorn effect as well as observation and selection biases in context of trials or quasi-experimental studies. Other limitations include short follow-up and a narrow focus on limited range of outcomes. Further, they describe a large variety of PAP structures and strategies with different aims such as motor development (e.g. sport activity), recreation/leisure (e.g. bowling, dancing, and horseback riding) or both, which limits inferences. In context of preparing a prospective study we extracted data from one center that collects systematically the child's motor changes in a systematic way. These data offer a unique opportunity to assess motor changes in context of usual practice in a naturalistic environment and 2 years follow up, protected from observation biases and Hawthorne effects.

The Empowering Steps Movement Therapy (ESMT) program is a gymnastics-based motor intervention that operates in the Greater Vancouver Area, as a private organization serving ∼125 children with NDD between 2 and 18 years of age, irrespective of diagnosis. The ESMT program employs a range of motor learning approaches, communication tools, and behavioral management techniques delivered by trained ESMT therapists. ESMT is an individualized, one to one, child-centered program that aims to enhance motor development, attachment and emotional state. Since its creation in 2002 as an offshoot of a large gymnastics center with a wide range of programs from early motor milestone programs to competitive gymnastics, ESMT has evolved and gained experience working with children with NDD. In January 2011, the program started to quantitatively measure each child's motor development every 6 months using a motor scale developed by VS. The ESMT motor scale (**S1 Appendix**) is comprised of eight progressive stages that are subdivided into 20 categories of movements that range from basic movements for non-ambulatory motor development, to more complex motor patterns and sequences designed to develop executive functioning. In 2011, based on the ESMT experience of observed changes, a developmental pediatrician (RW) developed a "Parental Questionnaire" to assess the parents' perception of ESMT on children and families. Parents completed this questionnaire in June 2011.

In 2015 our team at UBC British Columbia Children's Hospital Research Institute (BCCHRI) decided to conduct a prospective study of the children registered in the ESMT program with the objective of completing a rigorous review of the program's effects on children and parents. In the planning stage of this study, we decided to review the data collected on each child by RW and the ESMT staff during the period January 2011 to January 2013 to document the child's motor changes and the parents' perceived changes in child and family quality of life and functioning, collected in June 2011. We expected to observe improvement in complex motor functions, as well as in motivation, behavior, social integration, daily life functions, and quality of life, as perceived by parents. Finally, we anticipated a correlation between the improvement of motor functions and other psychological and social factors. However, our main objective was descriptive: to determine the reported magnitude of change, as well as identifying related factors, in preparation for the prospective study.

Despite the non-use of standard validated instruments to assess motor functions, we decided to publish these results because we feel they provide relevant information for the planning of other studies assessing the effects of community-based programs designed to improve daily function and quality of life of children with NDD and their families. Further, these data show the children's changes in context of usual practice over 2 years, therefore complementing the results from experimental studies, with the advantage of being protected from observation biases and Hawthorne effects. Finally, community-based PAPs are very unlikely to use standard motor assessment tools, because of the recurrent license fees that are not bearable for these organizations. This project was developed in collaboration with ESMT staff and RW, but the study design and data analysis were conducted in complete independence from the ESMT staff.

MATERIALS AND METHODS

Participants

The ESMT files of 67 children with NDD (2–18 years of age) who attended the ESMT program between January 2011 (when systematic assessments of motor function began at ESMT) and January 2013 were considered for the study, regardless of diagnosis, as long as parents had signed the authorization for secondary use of data for research purpose. If a child started the ESMT training before Jan 2011, he/she was exposed to the program but no rigorous assessments were done prior to this date. The age range of the participants was 24–221 months (median = 81, mean = 89.9, SD = 43), and 59.7% of children were male. Twenty-six children (38.8%) had a sole diagnosis of Autism Spectrum Disorder (ASD) while 20 (29.8%) had ASD associated with other diagnoses, such as Attention Deficit Disorder, Seizure Disorder, or Down Syndrome. Eighteen children (26.9%) had other diagnoses such as Fetal Alcohol Spectrum Disorder (FASD), Cerebral Palsy (CP), or rare genetic disorders. The remaining three children (4.5%) had undiagnosed neurodevelopmental conditions. These diagnoses are based on the de-identified information provided by ESMT from their files without medical verification.

To assess the possible relationship between the changes in motor function and perceived changes in daily life function and quality of life (i.e., using the parental questionnaire), we selected the subgroup of children/families that were registered in the ESMT program in Jan/Feb 2011 and completed the Parental Questionnaire in June 2011 (n = 39). In this subgroup, we could study both the changes in motor function from Jan to June 2011 and the perceived changes in quality of life and daily function assessed in June 2011 (**Figure 1**).

Procedures

The change in motor performance is based on the assessments made at 6-month intervals using the ESMT motor scale. The data were extracted from the chart by the ESMT staff. The researchers extracted information from the paper version of the anonymized completed parental questionnaires. The data analysis was conducted during the period of May-September 2015.

The study was reviewed and approved by the University of British Columbia/Children's and Women's Health Center of British Columbia Research Ethics Board. Since we received the de-identified data of children whose parents had signed authorization of use for research purposes, for our analysis, formal consent from families was not required under Canadian Tri-Council policy 2nd edition, article 5.5.

ESMT Program Exposure

Most children with NDD received one training session per week ranging from 30 to 60 min. Absences were not recorded by the ESMT team at this time. Children's records showed that 18, 24, and 16% of participants had been involved in the program for 6–12, 12–24, and >24 months prior to their first ESMT motor assessments, respectively. The ESMT program is a personalized one to one intervention based on each child's specific needs and abilities as determined at their initial assessment prior to beginning intervention sessions. At the end of each session, the child's performance is recorded to guide the next session's training activity. A refined scaffolding process is in place, to reach optimal performance through continuous improvement ensuring that the child is always in their zone of proximal development. More details about the ESMT program can be found in **Appendices S2,S3**.

Measures

Children's motor ability was measured using the ESMT® (V2.0) Motor Scale (hereafter referred to as the "ESMT scale") every 6 months starting January 2011. The ESMT scale is a physical literacy roadmap for assessing motor ability with eight progressive stages. Each stage has 20 assessment skills for a total number of 160 skills (**S1 Appendix**), which allow the ESMT team to observe how children best develop motor skills and enhance their functional motor development. The ESMT scale starts at stage 1 (building motor milestones for non-ambulatory children) and progresses to Stage 8 (children are executing skills of a typical 12-year-old such as complex sequencing and the memorization of 10 skill routines, e.g., the trampoline routine is based on the compulsory routine for entry level competitive Trampoline athletes). Two ESMT staff completed the semi-annual assessments for each child.

The parental questionnaire was used to assess the parents' perceptions of changes in their child and in the family. Parents were asked to report on any perceived change since their child started the ESMT program on (i) their child's behavior and activity at home, changes in their ability to manage daily life activities, recreational inclusiveness, sleep patterns, mood, self-esteem and their quality of life; and (ii) family functioning and quality of life. Each item represented one domain. Responses were based on a 5-point Likert scale ranging from 1 "marked improvement" to 5 "significantly worse."

The two instruments used for generating the motor function score and identifying changes in daily activities reflect the

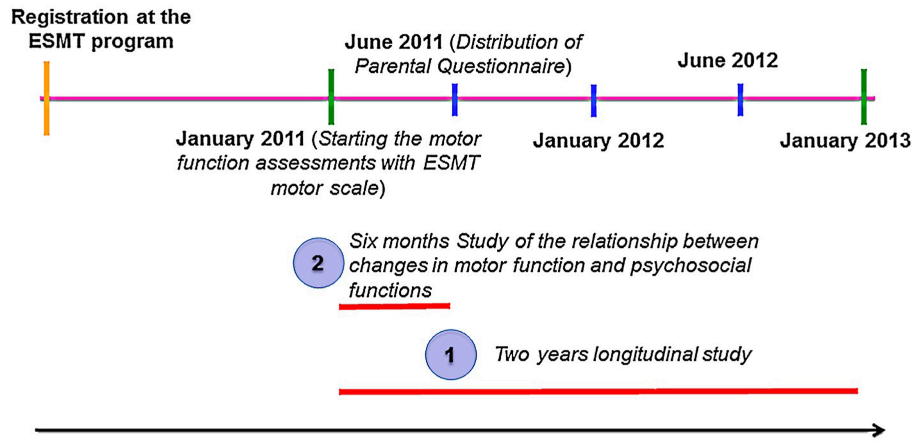

FIGURE 1 | Study process. Part 1 refers to the study of changes in children's motor abilities from January 2011 to 2013 assessed by the ESMT[TM] (V1.0) motor scale. Part 2 is related to the six-month study (Jan 2011–June 2011) of children with NDD whose parents also completed the Parental Questionnaire in June 2011.

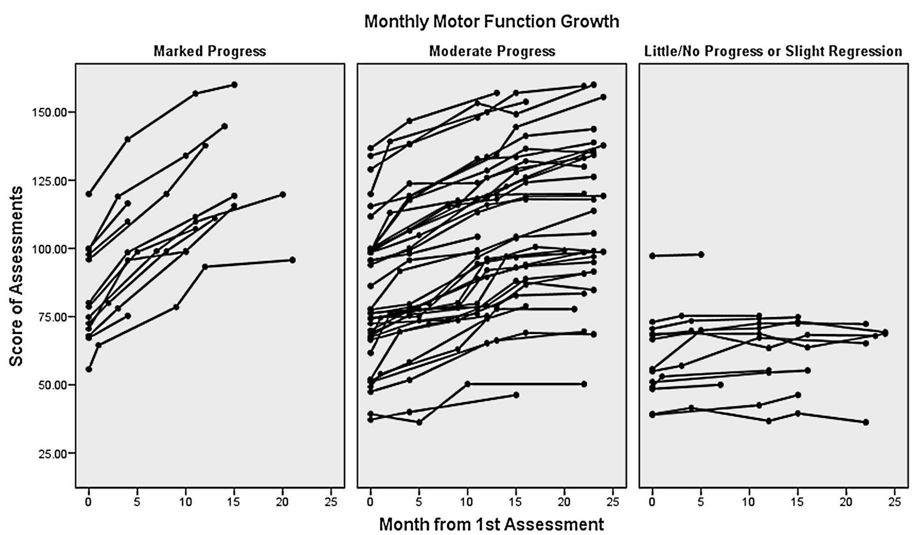

FIGURE 2 | Motor function curves of 67 children from 2011 to 2013. The Y axis represents motor function scores measured by the ESMT scale; X axis is the number of months that children were exposed to the ESMT training after the first assessment. Three graphs represent the progress level of children.

experience of the ESMT team, but neither the ESMT motor scale nor the parental questionnaire have been formally validated.

Data Analysis

The analysis was completed using SPSS version 20. The 2011-2013 historical cohort enabled computing the motor function curve of each child over 2 years. Using Linear Mixed Effects Model with random effects for subject, we identified growth patterns and predictors. We also investigated the association between children's exposure to the ESMT training and average growth in motor function within 2 years of study, considering the effects of age at study entry, diagnosis, baseline ESMT score and duration of program attendance before the study.

We also assessed the association between the children's changes in motor function for the period Jan/Feb to June 2011 (expressed as percentage of change from baseline) and the parents' perceived changes in both the children's and parents' daily life functioning and quality of life in June 2011. We computed the frequency distribution of parents' responses to each question. To assess the possible association between the changes in motor function (ESMT scale score) and parents' perceived changes, we performed a Spearman's rank test.

RESULTS

In total, 70 children with NDD were registered at the ESMT program during the period Jan 2011 to Jan 2013. Three did not sign the ESMT program's research release form; hence, data from 67 children were used in the longitudinal analysis of the changes in children's motor function while attending the ESMT program. From those, 79% started their ESMT training before Jan/Feb 2011, 10.5% started in Jan/Feb 2011, and 10.5% after

TABLE 1 | Linear mixed effects model.

Parameters	Estimate	Std. error	95% Confidence Interval		p-value
			Lower bound	Upper bound	
Intercept	1.93	57.91	−128.6	132.5	0.973
ESMT program exposure	**1.30**	**0.177**	**0.95**	**1.6**	**0.0001**
Baseline score at entry	1.00	0.926	−1.15	3.17	0.276
Previous attendance (months)	−0.014	1.72	−4.28	4.25	0.993
Age at study entry (months)	−0.0037	0.603	−1.5	1.50	0.995

The bold values show that the monthly growth in ESMT motor function score is 1.30 score point with 95% CI: 0.95–1.6 and p < 0.0001.

Jan/Feb 2011. **Figure 2** shows the motor function trajectories of the 67 participants for the period Jan 2011 to Jan 2013. Out of 67 study participants, 36 children had a full 2 years of motor function assessments (i.e., 5 data points), 11 children had 4, 14 children had 3, and 6 children had 2 data points. For two children whose second motor function assessment score (June 2011) was missing, we used the last-value-carried-forward method, which assumed no change during the 6-month period (a conservative approach) to replace the missing data.

The Linear Mixed Effects Model shows the relationship between the ESMT program and motor function improvement, along with the respective effects of age at study entry, baseline score and duration of exposure to the ESMT program before the study: the monthly growth in ESMT motor function score is 1.30 (95% CI: 0.95–1.6); $p < 0.0001$. We categorized participants' progress level into three categories: the lowest 20th percentile (little/no progress or slight regression), the highest 20th percentile (marked improvement), and those in between (moderate progress). Neither age at study entry, baseline score or previous exposure to the program was associated with the change in motor function during the study (**Table 1**).

Linear Mixed Effects Model showing the effects of ESMT program exposure, age at study entry, previous attendance at the ESMT program and Baseline score. The Estimate describes the monthly change in ESMT scale score.

The Parental Questionnaires was completed by 39 parents (out of 67) in June 2011. The reasons 28 families did not complete the questionnaire include: lack of time or interest or absence from the program when the questionnaire was offered. There were no significant differences in the age and gender between children whose parents completed or did not complete the questionnaire. Completers were significantly more likely to have a sole diagnosis of ASD (56.4% for 39 compared to 17.8% for 28). Among 13 children who showed marked progress in motor function, 6 were in this subgroup of 39. Similarly, 2 children with no change and the one with a regression of motor functions were also part of this subgroup.

Parents reported improvement in most of the child's physical and psychosocial abilities (**Table 2**). They also indicated some improvement in few family parameters (**Table 3**). We did not find any association between the changes in children's motor functions and parents' responses to the questionnaire.

DISCUSSION

This pilot observational feasibility study was conducted with a mixed group of children with NDD followed prospectively over 2 years while attending the ESMT program to assess changes in motor function and perceived changes in a wide range of outcomes in both children and families. Historical cohort design was possible because of the systematic semi-annual recording of motor performance by the ESMT therapists.

This feasibility study confirms the association observed in previous intervention studies (15–22) between participation in physical activity and improvement in motor performance among children with ASD ($n = 46$, with 20 having other conditions), as well as other NDD (18 with FASD, CP, or rare genetic disorders and 3 with undiagnosed conditions). The motor function curves (**Figure 2**) show consistent progress with large variations between children. The average monthly change in the motor function score during the 2-year study is independent of age at first assessment, baseline score and duration of previous exposure to the program. The 13 children with the most rapid change in motor functions (highest slope) had autism only. The children who regressed ($n = 1$) or did not improve ($n = 2$), had similar characteristics: they were young (between 2 and 7 years of age), non-cooperative during the sessions, and were complex cases, two with multiple NDD conditions and one with severe ASD combined with epilepsy. In the future, it will be important to determine whether the program can adequately address these more complex cases.

Parents report perceived benefits for children with NDD in a wide array of outcomes (**Table 2**).

These results however, need to be interpreted in light of numerous limitations, including the absence of a control group, possible selection biases, and the use of not validated measurements. The main reason for not using validated instruments in usual practice is budgetary, due to the scales' license fees. ESMT developed proprietary instruments in order to evaluate their children and assess the changes. We recognize the limitation of using an instrument that has not been properly evaluated, but we also recognize the unique data provided by this study because, to our knowledge, there is no community-based study of PAPs that followed all participants using costly standard tools. Further, many study results like the comparisons of different diagnosis categories; the absence of effects of previous ESMT attendance, or the minor role of the diagnosis compared to severity, are somewhat independent of the type of scale used. However, it is not the purpose of this article be conclusive with strong causal inference at this stage; our results rather confirm in natural context of normal practice the positive effect of attending PAPs for children with NDD. They also call for the conduct

TABLE 2 | Percentage of parents reported perception of changes in their child after attending the ESMT program ($n = 39$).

Items	A	B	C	D	Items	A	B	C	D
Fitness	47.2	44.4	8.3	–	Participation in school sports	42.9	23.8	33.3	–
Balance	60.5	31.6	7.9	–	Participation in school classroom activities	31.0	44.8	17.2	6.8
Coordination	54.1	40.5	5.4	–	Play skills	20	54.3	22.9	2.9
Muscle strength	48.6	42.9	8.6	–	Interest in other children	30.8	28.2	38.5	2.6
Anxiety	38.9	47.2	11.1	2.8					
Motivation	20.5	56.4	17.9	5.1	Forming friendships	22.9	31.4	40	5.7
Cooperation	25.6	53.8	15.4	5.1	Academic performance	32.1	39.3	25	3.6
Mood	23.1	43.6	25.6	7.7	Participation in community based sports	26.7	20	53	–
Self-confidence	39.4	45.5	12.1	3	Involvement in other recreational activities	20	44	36	–
Attention	28.9	52.6	15.8	2.6	Manual skills	21.2	48.5	30.3	–
Transitioning to a new activity	26.3	50	21.1	2.6	Sleep problems	10.3	24.1	51.7	13.7
Frequent or abnormal movements	6.9	34.5	51.7	3.4	Eating problems	8	44	48	–
Frequency of muscle spasm	0	50	50	–	Behavioral problems	20.6	38.2	38.2	2.9
Communication skills	27.8	52.8	19.4	–	Sibling Relationships	20.8	41.7	37.5	–
Participation in school physical education	36.0	44	15	4	Activities of daily living	21.1	44.7	31.6	2.6

Column A: Percentage of parents that indicated "Marked improvement." Column B: Percentage of parents that indicated "Some improvement." Column C: Percentage of parents that indicated "About the same (no change)." Column D: Percentage of parents that indicated "Somewhat worse" and "Significantly worse." "No response," "I don't know," and "Not applicable" were not valid responses and were not taken into consideration for the calculated percentages.

TABLE 3 | Percentage of parents reported perceptions of changes regarding their child and family after attending the ESMT program ($n = 39$).

Items	A	B	C	D
Your level of childcare stress	10.5	47.4	36.8	5.3
Level of concern about your child's health	14.3	34.3	45.7	5.7
Feelings about your child's quality of life	15.8	44.7	34.2	5.3
Feelings about your quality of life	14.7	35.3	41.2	8.8
Relationships within your household	17.1	34.3	42.9	5.8
Safety concerns about your child	7.9	47.4	42.1	2.6
Feelings about your child's future	15.4	35.9	35.9	12.8
Concerns about siblings	4.2	37.5	45.8	12.5

Column A: Percentage of parents that indicated "Marked improvement." Column B: Percentage of parents that indicated "Some improvement." Column C: Percentage of parents that indicated "About the same (no change)." Column D: Percentage of parents that indicated "Somewhat worse" and "Significantly worse." "No response," "I don't know," and "not applicable" were not valid responses and were not taken into consideration for the calculated percentages.

a large prospective study with appropriate control groups and validated measurement tools.

From the literature, several short-term studies have shown improved motor functions of children with CP attending different community programs (15, 16, 19, 20). In a randomized controlled trial ($n = 99$) Davis et al. showed the positive effect of a 10-week horseback riding on quality of life and physical functions (20). Another study showed the positive effect of a 6 months movement and swimming intervention on respiratory functions and water orientation skills of 46 children with CP (23). Similarly, a few studies showed the positive effects of horseback riding in children with autism using wait-time as control period (21, 22). One study with 42 children showed improvement in self-regulation, adaptive skills and motor skills over a 10-week period (21). Another study of 34 children showed improvements in their social function after 12 weeks, but the authors did not assess the changes in motor function (22). A small study ($n = 3$) examined the effects of a therapeutic skating intervention for children with ASD and showed improvement in physical functions (17). Finally, one study conducted in 90 young individuals (12–25 years of age) with physical disabilities showed the beneficial effects of a 6-months reverse-integrated basketball activity on quality of life and perceived social competence (24). These studies on children with different types of disabilities are interesting, but they generally focus on the changes of a limited number of outcomes in context of a specific intervention and do not assess the impact on families; the follow-up is generally not long (<6 months), which increases the risk of a Hawthorne effect. Finally, in context of not blind randomized trial, observation bias is possible, besides Hawthorne effect.

Our study is more naturalistic and the historical design makes it less prone to observation biases: the ESMT therapists collected motor performance data for their internal use, 2 years before the study. The observed improvement in motor function over 2 years is certainly expected in context of an intervention which is one to one, personalized and based on each child's needs, with weekly evaluation to plan the next session for more efficient scaffolding (25, 26). It was interesting to also observe the parents' perceived positive change in a large range of psychosocial and daily function outcomes in both children (**Table 2**) and families (**Table 3**), at least in the subset that completed this measure. Conceptually, outcomes such as the ones reported in **Table 2** are consistent with Activity Theory's social cultural model of learning and child development (27, 28). According to this theory, a child's learning happens in the context of social environment and community through a series of activities in which the child develops high executive functions such as self-regulation or working memory, and higher levels of social integration, communication, self-esteem, and daily life functions. The ESMT program offers an ideal, inclusive environment to foster the development of each child as a whole thereby creating a context for socio-cultural learning and development. As per the Transactional Model Theory (29) the child's improvement may have a positive impact on anxious and depressed parents, and subsequently the whole family system as evidenced in **Table 3** (30). Improvement in the family's quality of life is an important outcome to consider in future studies. According to the World Health Organization's International Classification of Functioning, Disability and Health for Children and Youth (ICF-CY) (31, 32), family is the most important environmental factor for child development. (33).

The absence of association between changes in motor function over 6 months and parents' responses to the questionnaire likely reflects the complexity of child development with NDD, which is a dynamic, multifactorial and interactive process rather than fixed and predictable (34, 35). Therefore, it is difficult to associate the psychosocial changes to a single factor. The absence of an association may also reflect a lag time between changes in motor function and changes in psychological, functional or social outcomes that may take more than 6 months. Moreover, since the parental questionnaire was only conducted once, we could not assess the dynamic of changes and possible interactions between these factors. Lastly, although developed by field experts, we do not know the psychometric properties of the two instruments used to assess changes, which limits our understanding.

As already stated, the present study has important limitations. Four particular matters of concern are the absence of a control group, the possible selection bias, the absence of formal validation of the measurement tools and possible co-interventions that were not assessed. The absence of a control group limits the interpretation, as the observed changes in motor function are due in part to normal progression when aging. Consequently, we cannot precisely determine the program's effect. More useful than the average growth however, is the wide range of changes observed among children that may lead to the identification of children that may benefit most from the program, and a more accurate correspondence between specific program features and the type of NDD. Also, the fact that the motor change during the 2-year follow-up is independent of age and duration of program attendance is encouraging as it indicates that motor function may improve whatever the age, and does continue after several years in the program. Selection bias is another concern. Attending the ESMT program is voluntary for parents/families, which most likely self-select and pay to attend if they perceived the benefits. This possible prevalence bias however, did not remove heterogeneity in the study population as demonstrated by the large distribution of personal growth curve with no progression in a few children (**Figure 2**). Another self-selection bias may have occurred when 28 families did not complete the parental questionnaire, with participating parents being the ones most satisfied with the program, leading to a positive inflation of the results. However, there are also studies that show the reverse, with unsatisfied participants being the sub-group that self-selects. (36, 37) Overall, we believe this subgroup of 39 families (56%) is a fair representation of the population that attended the program in 2011.

Furthermore, the evaluation tools used by the ESMT program have not been formally evaluated for their psychometric properties. This limitation raises questions regarding the meaning of a change in motor functions. Also, it does not authorize a valid comparison with other studies that used standard tools like BOT-2 for instance. We already stressed the fact that the use of validated tools by community sites in usual practice is not a real option for most sites because of the recurrent license's fees. It is for this specific reason that ESMT developed its own proprietary scale as a practical tool to evaluate the children's progress and guide the intervention. The ESMT motor scale, has been developed by experienced professionals with a solid background in child development, kinesiology and gymnastics, to assess motor performance changes and guide practice, which ensures high content validity. In addition, the same motor scale was used from Jan 2011 to Jan 2013, therefore ensuring consistency in the assessments. This contextual information suggests that a scoring bias is not likely. Finally, many useful results are independent of the scale used such as the poor progress of children with complex disease, the relative limited importance of diagnosis category compared to disease severity to explain the change, or the continuous change whatever the duration of previous ESMT attendance, which is encouraging.

The parental questionnaire developed by RW, an expert in Pediatric Medicine, also bears high content validity; the questions were focused and clear with simple wording to prevent misinterpretation. RW used the method we use when we adapt a "satisfaction survey" to a new population. The specific wording is changed to reflect the new context, but the validity of the modified instrument is not questioned.

Finally, Because of the retrospective nature of this study, we have not been able to collect information regarding the other concurrent activities of children. Without having precise assessment of possible co-interventions, interpreting the meaning and significance of observed changes is challenging.

CONCLUSION

Results from this feasibility pilot observational study cannot be taken as solid evidence of a causal relationship between the ESMT training and changes in children/youth's and families' function and quality of life. The main limitation is the use of measurement instruments that had not been validated before. Therefore, study results should be considered with precaution, because we do not know whether they reflect a real change (i.e., a true ESMT outcome) or they are still in the area of the measurement errors of the ESMT scale. Despite this major limitation the study shows that over 2 years of practice children with different diagnosis progress at different pace and few of them regress. It shows the importance of disease severity in limiting motor skills improvement and it shows that improvement is independent of previous attendance of the program. This study is aimed at stressing the importance of considering physical activity for children with NDD and to promote research in this area. Further studies might consider assessing different sub-groups defined by diagnosis, severity, or age, for instance. Besides assessing changes in motor abilities, we also suggest assessing psychosocial and mental outcomes in both the child and the family.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Canadian Tri-Council Policy. The protocol was approved by the University of British Columbia/Children's and Women's Health Center Research Ethics Board.

Since we worked with data extracted from patients' files and data were anonymized, there was no need to obtain consent from families (article 5.5 of the 2nd edition of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans of Canada).

AUTHOR CONTRIBUTIONS

MG and J-PC took a leadership role in developing proposal and getting funding as well as managing the project. MG conducted the statistical analysis. J-PC reviewed results and commented. Both MG and J-PC took Leadership in developing the article. WM, AMi, JW, AMa, LM, and RW reviewed protocol for grant submission, reviewed analyses results, and actively participated in reviewing and commenting the article. RW led the initiative as community pediatrician. RB developed the analysis section of the protocol and supervised the statistical analysis. VS facilitated the research organization at Club Aviva.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2019.00186/full#supplementary-material

S1 Appendix | Introduction to the Empowering Steps Movement Therapy® (V2.0) Motor Scale.

S2 Appendix | ESMT scientific protocol: visual representation.

S3 Appendix | Overview of the ESMT program.

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A Six Week Therapeutic Ballet Intervention Improved Gait and Inhibitory Control in Children With Cerebral Palsy—A Pilot Study

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Children with cerebral palsy (CP) have motor impairments that make it challenging for them to participate in standard physical activity (PA) interventions. There is a need to evaluate adapted PA interventions for this population. Dance can promote coordination, posture, muscle strength, motor learning, and executive functioning. This pilot study evaluated the feasibility and the effects of a new therapeutic ballet intervention specifically designed for children with CP.

Methods: Eight children with CP (9–14 y/o; 75% female) participated in a 6-week therapeutic ballet intervention. Outcomes were measured in multiple domains, including body composition (DXA), muscle strength (hand-grip dynamometer), habitual physical activity, gait and selective motor control functions, and executive functioning. Follow-up assessments of habitual physical activity, gait, and executive functioning were completed 4 to 5 weeks post-intervention.

Results: Five of the eight participants were overfat or obese based on DXA percentage of body fat. All participants were below the 50th percentile for their age and gender for bone density. Four participants showed a trend to improve hand-grip strength in one hand only, while one improved in both hands. There were significant improvements in gait across time points (pre, post, and follow-up), specifically in time of ambulation ($X_{\text{pre}} = 4.36$, $X_{\text{post}} = 4.22$, $X_{\text{follow-up}} = 3.72$, $d = 0.056$, $p = 0.02$), and in step length (cm) on the right: $X_{\text{pre}} = 48.29$, $X_{\text{post}} = 50.77$, $X_{\text{follow-up}} = 52.11$, $d = 0.22$, $p = 0.027$, and left stride: $X_{\text{pre}} = 96.29$, $X_{\text{post}} = 102.20$, $X_{\text{follow-up}} = 104.20$, $d = 0.30$, $p = 0.027$, indicating gait changes in bilateral lower extremities. There was improvement in inhibitory control ($d = 0.78$; 95% Confidence Limit = ±0.71, $p < 0.05$) with large individual responses primarily among those above the mean at baseline.

Conclusions: Therapeutic ballet may prove to be a useful intervention to promote physiological and cognitive functions in children with CP. Results demonstrated feasibility of the physical, physiological, and cognitive assessments and suggested improvements in participants' gait and inhibitory control with large individual responses. Modifications to personalize the intervention may be needed to optimize positive outcomes.

Clinical Trial Registration: www.ClinicalTrials.gov, identifier: NCT03681171

Keywords: pediatric, rehabilitation, dance, exercise-medicine, executive functions, arts, physical activity, cerebral palsy

INTRODUCTION

Cerebral palsy (CP) is a neurobiological disorder that is induced by injury to the brain during prenatal and early postnatal development. CP is characterized by disturbance in movement that is usually accompanied by impairments in cognitive and behavioral functions. There is evidence suggesting that early intervention with children with CP may promote functional connectivity in the brain, which may in turn improve prognosis over time (1, 2); thus, interventions during childhood should be a high priority for CP research.

It is well established that physical activity (PA) interventions can improve both motor and cognitive functions in healthy children (3) and children with special needs (4). Among the various physical activity interventions that have been previously studied in children with CP, therapeutic ballet, which combines body movements and artistic expression appears to be a promising practice (5). In a pilot study that assessed the perceived benefits of a ballet intervention for children with CP, children reported enjoyment and interest in continuing ballet classes, and their parents perceived therapeutic benefit (5). Therapists involved in the study perceived benefits beyond traditional physical therapy in self-confidence, in the use of the body as instrument for creative expression, in the exposure to music and rhythm to guide movement, and in providing an alternative structure for physical rehabilitation interventions. The balletic foundation of this therapeutic intervention was theoretically supported, in part, by the modular and hierarchical organization of the conservatory style instruction of ballet technique, which has been in development during the last five centuries. This type of instructional organization allows for rationally organized motor learning, promoting a larger and more complete repertoire of available motor actions (5). The effectiveness of this modular approach to improve balance was tested in a randomized controlled clinical trial in children with CP (ages 7–15 y/o) consisting of a 12 h of targeted ballet in a studio over a 4 week period. This study reported improvements post-intervention in the Pediatric Balance Scale for the ballet group that were retained at 1 month follow-up (6).

Although disruptions in motor functioning are often the most recognizable feature of CP, executive function impairment is also a central feature of CP (7). Recent studies have indicated that dance may be an example of a cognitively complex and social physical activity that could be expected to improve executive functions (8, 9). Thus, in the current pilot study, we aimed to study the impact of a therapeutic ballet intervention on motor and executive functioning. We characterized anthropometric, body composition, bone health, muscle strength, and habitual physical activity in a group of children with CP and evaluated for the first time the effects of a 6-week therapeutic ballet intervention on gait, motor, and executive functioning.

METHODS

Participants

Eight children with CP (9–14 y/o; 75% female) completed a 6-week (three times per week) therapeutic ballet intervention that included live piano music. The inclusion criteria were: (1) cerebral palsy spastic diplegia and/or hemiplegia; (2) absence of health problems that would preclude participation in exercise; (3) male or female age 9–14 years; (4) ability to read and complete study measures; (5) ability to participate in dance classes conducted in English; (6) interest in learning ballet; (7) intact vision; (8) ability to ambulate independently in the community with or without a device; (9) intact proprioception in lower extremities; and (10) ability to complete assessment measures and consents in English. Five of the participants had a history of prematurity (26–34 weeks gestation), one participant had a history of congenital heart defect (double outlet right ventricle), and one participant was born full term with microcephaly of unclear etiology. The Institutional Review Board at the University of California Irvine approved the study, and written informed consent and assent were obtained from all participants and their guardians upon enrollment.

Assessment Procedures

Physical, physiological and cognitive assessments were conducted in two sessions before and after the ballet intervention. Session one included clinical, anthropometric, body composition, muscle strength and cognitive (executive functioning) assessments and was completed in the PERC Human Performance Laboratory. Session two included an evaluation of gait and physical functioning in a movement laboratory. In addition, habitual physical activity was assessed over 7 days during the first and last weeks of the intervention. A follow-up assessment with a subset of measurements was conducted 4 to 5 weeks after the post-intervention assessment and included measures of motor function, habitual physical activity, and executive functioning.

Measures

Anthropometric Measurements

Standard calibrated scales and stadiometers were used to measure height and body mass. Body mass index [BMI = wt/ht^2 (kg/m^2)] percentile and stature percentile were calculated using the online calculators from the Centers for Disease Control (CDC) (10–12).

Body Composition and Bone Health

Body composition and bone density were determined by a Dual X-ray Absorptiometry (DXA), using Hologic QDR 4500 densitometer. Participants were scanned in light clothing while lying supine. The DXA instrument was calibrated using the procedures provided by the manufacturer, and DXA scans were performed and analyzed using a pediatric software. Percent fat categories were calculated based on body fat reference curves for children (13). The 2nd, 85th, and 95th percentiles define the cut off points for underfat, overfat, and obese.

Hand Grip Strength

Grip strength was measured using a Jamar handgrip dynamometer, which evaluated maximum isometric strength (Kg) of the hand and forearm muscles. The participants sat comfortably in a chair with a back support, with elbow at 90°, and squeezed the dynamometer with maximum isometric effort that was maintained for 3 to 5 s. No other body movements were allowed. Three trials, with brief pauses, were done for each hand alternately. The best result at each assessment was chosen for analyses. Participants were strongly encouraged to exert maximum effort. Results are presented as absolute values in kg and relative to norms of healthy boys and girls of the same age (14).

Selective Control Assessment of the Lower Extremity (SCALE)

To assess the selective voluntary motor control [SVMC; (15)] participants were asked to perform specific isolated movements at each joint to bilaterally assess the movements of the hip, knee, ankle, subtalar, and toe joints. Evaluation was performed in the sitting position, except for assessing hip flexion, which is tested in side-lying for proper joint excursion. For each joint, the participants were asked to perform a task by moving their limbs through the desired movement sequence using a 3-s verbal count. The SCALE score for each limb is the sum of all the points given to each joint, up to a maximum of ten points per limb.

Gait Function

The GAITRite© system (16) was used to collect temporal and spatial gait parameters. Each participant ambulated for a total of four trials at each testing time point. The GAITRite is an 8.3 m long and 0.89 m wide carpet that forms an electronic walkway with pressure sensors embedded into the carpet in a horizontal grid. As the participant walks over the carpet mat, the sensors are triggered when mechanical pressure is applied (17). The active area of the mat is ~7.32 m long and 0.61 m wide. A distance of 12.7 mm separates the sensors between one another. The data was sampled at a frequency of 80 Hz, allowing a temporal resolution of 11 ms from the carpet mat runway (16). Each participant ambulated barefoot for a total of four trials at each testing time point. As defined by the GAITRite© system (16), stride length is measured on the line of progression between the heel points of two consecutive footprints of the same foot. Step length is determined by the distance from the heel center of the current footprint to the heel center of the previous footprint on the opposite foot.

Executive Functions: Hearts and Flowers Tasks

The Hearts & Flowers EF tasks (18, 19) are tasks that measure executive functions, including attention, inhibitory control, working memory, and shifting/cognitive flexibility. These tasks were administered to participants individually by a researcher using a touch-screen laptop computer. All participants completed the task on the same laptop computer and placed their hands in the same position on a resting bar in front of the screen in order to maintain equal distances from the screen across all participants. Completion of the task (consisting of three blocks of trials) required about 7 min per child, including set-up, instructions, and practice. In the first block (Congruent), children were asked to press a button on the screen on the same side as the stimulus (a heart). Following practice, there are 12 trials in which the heart appears on either the left or right side of the screen. For the second block (Incongruent), children were asked to press the button on the opposite side of the stimulus (a flower). After practice, there were 12 trials. The final block (Mixed) consisted of 33 trials in which the child is presented with either a heart or flower; children are required to inhibit automatic responses, retain rules in working memory, and quickly shift between rules to press the correct button. Performance was evaluated using accuracy scores and median response time (in milliseconds) for each of the three blocks. The first trial of each block was omitted from analysis for both accuracy and response time scores. Accuracy scores were based on the percentage of correct responses in a given block (number of correct responses divided by the number of trials). To reduce the effects of outliers, a median response time was calculated for each block (18); analysis is based on response times for correct responses.

Habitual Physical Activity

Activity monitors (Actigraph GT3X) were worn on the waist during awake time during the first and last weeks of the ballet intervention and at the time of the follow up visit 4 to 5 weeks after the completion of the intervention. Twelve hour daytime activity data was analyzed for 3–4 weekdays using Actilife software. Physical activity was classified into sedentary, light, moderate, and vigorous levels according to the cut-points set by Mattocks Children 2007 (20). Cut points based on vector magnitude <100 counts per minute (CPM) were scored as sedentary, 3581–6129 CPM were scored as moderate, and >6130CPM were scored as vigorous physical activity. Results are presented as moderate, vigorous and moderate to-vigorous physical activity (MVPA).

Intervention

Following the baseline assessments, participants attended 1-h ballet sessions three times per week for 6 weeks. Sessions were held in a university dance studio. Make up sessions were held to ensure all participants attended a minimum of 16/18 h of the intervention. Licensed physical therapists and experienced dance teachers delivered the ballet intervention. Physical therapy and dance students also were present to assist the children, resulting in a minimum of a 1:1 child to assistant ratio. The assistants provided physical support as needed, to help the child initiate and perform the dance steps. Each participant wore a gait belt during all weight bearing activities to enhance overall safety.

The adapted ballet classes mirrored components of typical ballet classes, including warm-up, stretching, barre exercises, and center floor exercises, with reverence to finish each class. Specific exercises addressed CP-related gait issues, such as out-of-pattern movement, postural alignment, endurance in sitting and standing, weight shifting, and out-of-phase motion in lower extremities. Engaging exercises promoted selective motor control, balance, and coordination. Each class was augmented with live piano music and prop targets (such as wands, bean bags, hula hoops, chalk, and stickers) to improve motor approximation and maintain participants' attention and motivation. For novelty and challenge, as participants repeated and learned steps, the next session's exercises increased in difficulty, adding more complex steps and combinations. The intervention concluded with a class demonstration for parents and members of the community where the children's accomplishments were celebrated.

Exercise Intensity During Ballet Sessions

Intensity of the activities during two of the ballet sessions was assessed using Polar E600 heart rate monitors. Minimum, maximum, and average HR (bpm) during the ballet sessions are reported as means ± standard deviations.

Analyses

To analyse data collected to characterize participants, scores were generated according to measurement protocols and were evaluated for change over the three time points. Paired t-tests were used to evaluate changes in BMI percentile, percent body fat, bone density, and grip strength (using the significance level of $p < 0.05$). Repeated measures ANOVA was used to evaluate moderate-to-vigorous physical activity (MVPA) over the three time points.

Primary outcomes were analyzed using several methods selected based on their appropriateness for the data, study design, and sample size. Data from the SCALE was analyzed using a Fisher's Exact Test in R (21). Gait function data was analyzed with GraphPad Prism (La Jolla, CA) and Practical Meta-Analysis Effect Size Calculator (22) using Friedman's test (significant $p < 0.05$) to determine effect size for specific gait parameters (using means and Cohen's d).

Data from the executive functions computer tasks were analyzed in SAS Studio using a mixed linear model (Proc Mixed). A multi-level growth model was used, where repeated measurements were nested within individual subjects and where change over time was specified to vary across participants (23). Effects (Cohen's d) were derived via standardization: i.e., mean change over time divided by the standard deviation at baseline. A process outlined in Hopkins (24) and Joseph et al. (25) was implemented to remove the small sample-size bias in these estimates of standardized effects. Inferences were derived using a magnitude-based inference (MBI) approach to likelihood estimation. This approach [outlined in Hopkins et al. (26)] is a supplement to null-hypothesis testing and a refinement of Cohen's d. It ensures that the outcomes were interpreted according to both statistical significance and the likelihood that they were a substantial-sized effect. The size of standardized effects were evaluated according to the following scale: <0.2, trivial; 0.2–0.6, small; 0.6–1.2, moderate; >1.2, large (26, 27). The accompanying magnitudes express the likelihood of these effects and are presented as qualitative probabilistic inferences according to the following scale: 25–75%, possibly (*); 75–95%, likely (**); 95–99%, very likely (***); >99.5%, most likely (****). Uncertainty in the estimate is expressed using 95% confidence limits.

Due to the lack of available control group data in this study, further precision of the estimate was achieved by estimating the presence and extent of (i) regression toward the mean and (ii) individual responses and responders in significant outcomes. The process for calculating (i) and (ii) followed the steps outlined in Hopkins (28–30), respectively. Reliability data from the control group in Schonert-Reichl et al. (31) were obtained and used to facilitate these estimations.

RESULTS

Participant Characteristics

Anthropometric, Percent Body Fat, and Bone Health

Table 1 presents anthropometric characteristics, percent body fat, and bone health of the eight participants. Based on BMI percentile, five participants had normal weight, one was overweight (90th percentile), and two were underweight (1st percentile). Based on percent body fat measured by DXA, three participants were obese, two overfat, and three normal fat. All participants were below the 50th percentile for their age and gender for bone density. No significant changes were observed in BMI percentile, percent body fat, or bone density from before to after the intervention.

Habitual Physical Activity

On average, in the first week of the intervention, participants spent 44 ± 22 min/day on moderate physical activity and 21 ± 10 min on vigorous physical activity (65 ± 28 min/day MVPA), with no significant change at the end of the intervention (60 ± 22 min/day MVPA) and 4–5 weeks following the intervention (58 ± 24 MVPA).

Muscle Strength

At baseline, six participants had asymmetric right/left hand grip strength (**Table 2**). On average the group performed 61% ± 33 of predicted values on the right hand and 53% ± 25 of predicted values on the left hand. Four participants showed a trend to

TABLE 1 | Baseline anthropometric, percent body fat, and bone density data.

Age range (years)	Height (cm)	Weight (Kg)	BMI %ile	Stature for age %ile	% Fat (DXA)	Fat category* (based on % fat)	Total body BMD** *z* score	Total hip BMD z score	Total spine BMD *z* score
12–14	160.7	59	90	76.9	29.9	Obese	−1.1	−0.8	0.4
9–11	139.4	34	47	17.8	35.7	Obese	−0.7	−1.7	−2.2
9–11	132.7	26	14	24.9	34.3	Obese	−2.4	−2.9	−2.1
12–14	156.7	45	33	13.5	18.9	Normal	−0.1	−1.3	−0.7
9–11	137.1	28	16	50.2	30.7	Overfat	−1	−0.2	−1.5
9–11	134.7	25	1	9.9	24.4	Normal	−2.3	−1.4	−1.8
9–11	123.1	20	1	0.8	29.1	Overfat	−3	−4.6	−1.1
9–11	142.53	34	38	75.7	27.1	Normal	−0.7	−1.4	−0.7

The 2nd, 85th, and 95th percentiles define the cut offs for underfat, overfat, and obese (13).
***BMD, Bone Mineral Density.*

TABLE 2 | Hand grip strength at baseline and post intervention.

Age range (years)	Dominant hand	Baseline right hand (Kg)/(% predicted)	Post right hand (Kg)/(% predicted)	Baseline left hand (Kg)/(% predicted)	Post left hand (Kg)/(% predicted)
12–14	Right	32/(120)	30/(112)	14/(56)	13/(52)
9–11	Right	12/(53)	14/(68)	12/(53)	10/(44)
9–11	Right	9/(56)	9/(56)	6/(40)	5/(33)
12–14	Left	34/(97)	31/(58)	28/(96)	30/(102)
9–11	Right	12/(75)	11/(69)	4/(27)	5/(33)
9–11	Left	7.5/(33)	9/(44)	15/(73)	16/(78)
9–11	Right	10/(44)	8/(35)	2/(10)	2/(10)
9–11	Left	2/(9)	1/(4)	14/(68)	16/(78)

improve handgrip strength in one hand only, while one improved in both hands.

Intervention Adherence

All 8 participants adhered to the intervention and participated in at least 16 out of the 18 intervention sessions.

Heart Rate (HR) Evaluation During the Ballet Sessions

The average HR recording time was 54 ± 6 min per session. Average HR during the session was 97 ± 10 bpm ranging from 74 ± 10 to 133 ± 15 bpm and reflects light aerobic activity.

Primary Outcomes

Selective Control Assessment of the Lower Extremity (SCALE)

There were no significant group changes in the selective control at any joint. Changes were noticed in individual participants (see **Figure 1**). It is noteworthy to mention, that 62.5% of the participants improved on their total limb score unilaterally or bilaterally with majority of the improvements observed in the hip and ankle.

Gait

There were significant differences between pre, post, and follow-up assessments of time of ambulation ($p = 0.02$). The participants were able to ambulate with a decreased time after the intervention and follow-up testing sessions ($X_{\text{pre}} = 4.36$, $X_{\text{post}} = 4.22$, $X_{\text{follow-up}} = 3.72$, $d = 0.056$). There was a trend across all time points that the participants exhibited increased velocity. There were significant differences in the percentage of gait cycle ($p = 0.008$, $X_{\text{pre}} = 36.50$, $X_{\text{post}} = 38.23$, $X_{\text{follow-up}} = 38.76$, $d = 0.41$) spent in left single support, indicating more time was spent executing gait function on the left after participating in the intervention. There were significant differences in step length (cm) on right ($p = 0.027$, $X_{\text{pre}} = 48.29$, $X_{\text{post}} = 50.77$, $X_{\text{follow-up}} = 52.11$, $d = 0.22$) and stride length (cm) on left ($p = 0.027$, $X_{\text{pre}} = 96.29$, $X_{\text{post}} = 102.20$, $X_{\text{follow-up}} = 104.20$, $d = 0.30$), indicating gait changes in bilateral lower extremities. It is noteworthy to mention that there also was a positive trend in increased stride length on the right ($p = 0.052$, $X_{\text{pre}} = 95.74$, $X_{\text{post}} = 102.50$, $X_{\text{follow-up}} = 103.20$, $d = -0.34$).

Executive Functioning

The Hearts and Flowers test has three tasks (congruent, incongruent, and mixed) that yield six scores (a response time and an accuracy score for each of the three tasks). The results of these three tasks and six scores are summarized in **Table 3**.

Results for the incongruent task indicate that participants were more accurate (Cohen's $d = 0.78$; 95% Confidence Limits

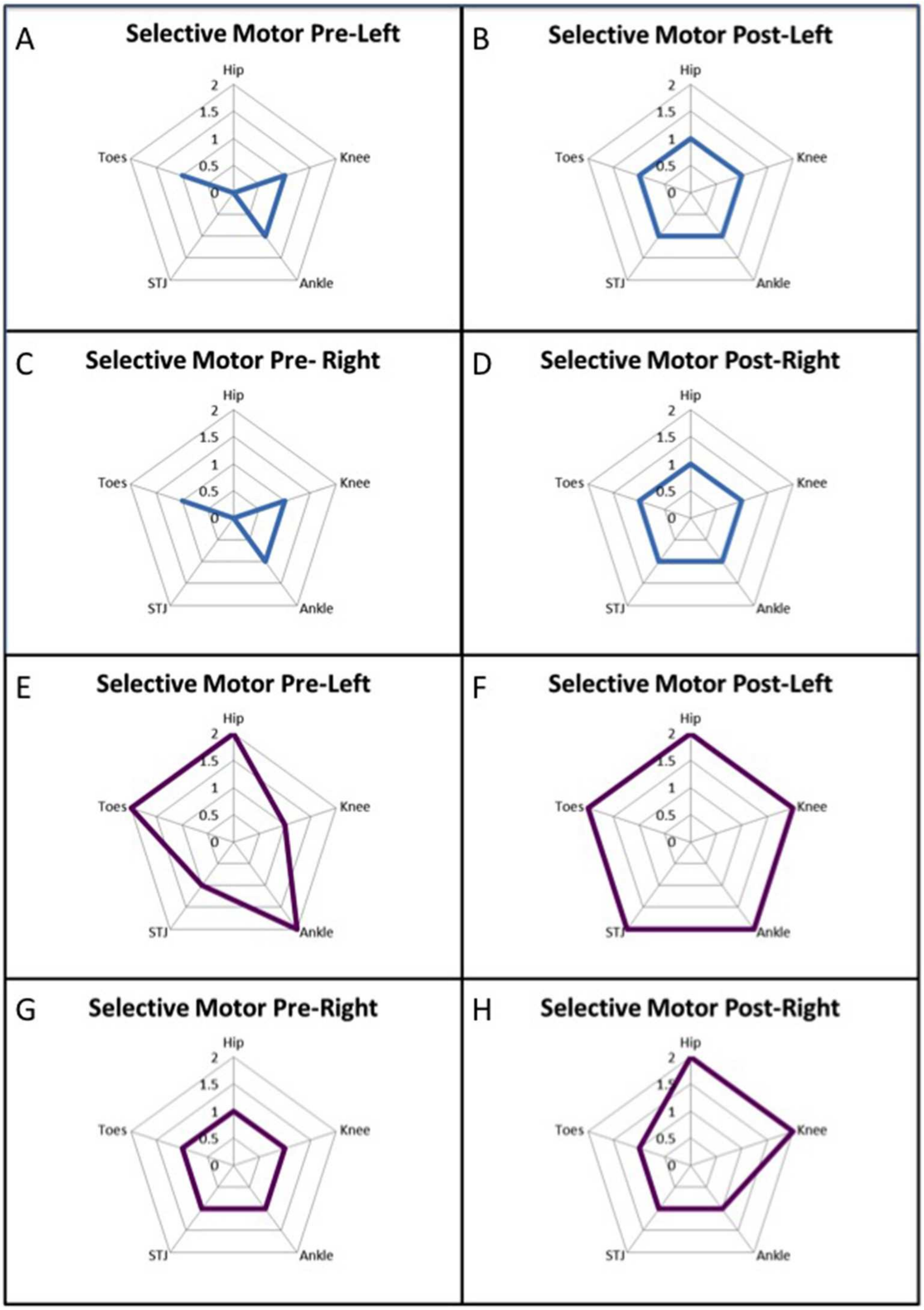

FIGURE 1 | Data from two participants who demonstrated increased total limb score for the Selective Control Assessment of the Lower Extremity (SCALE). **(A–D)** illustrate the participant improved in bilateral hip and subtalar joint (STJ), where as in panels **(E–H)** a different pattern of improvement was observed in the left knee and subtalar joint and right hip and knee.

= ±0.71) and had faster response times (0.89; ±0.45) at post-test. These results were both statistically significant ($p < 0.05$) and substantial, with outcomes for accuracy and response time very likely and most likely moderate in terms of their effect size, respectively. Results for the mixed task indicate that the group were also more accurate upon retest. This change in mixed accuracy, while statistically significant ($p = 0.047$), was likely small (0.38 ± 0.37) in terms of its effect size. All other outcomes were either trivial or trivial-sized and unclear and not statistically significant and are, therefore, not presented here.

TABLE 3 | Pre- and Post-intervention executive function scores with Magnitude-based Inferences (MBI) for the standardized difference (Cohen's *d*) in means.

		Baseline mean ± SD $n = 9$	Follow-up mean ± SD $n = 9$	Cohen's *d* [95% CI]	*p*-value	Inference
Inhibitory control, working memory, and cognitive flexibility (hearts and flowers computer task)						
Congruent trial (hearts)	Accuracy	87.96 ± 21.29	87.50 ± 11.79	0.02 [−0.22, 0.26]	0.86	Trivial***
	Response time	797.56 ± 142.89	798.25 ± 148.00	0.02 [−0.63, 0.65]	0.95	Unclear
Incongruent trial (flowers)	Accuracy	52.77 ± 23.20	71.86; ± 24.37	0.78 [0.07, 1.49]	0.03	Moderate***
	Response time	903.11 ± 183.79	745.86 ± 111.87	0.89 [0.44, 1.33]	<0.001	Moderate****
Mixed trial (hearts and flowers)	Accuracy	51.52 ± 19.64	58.44 ± 21.12	0.38 [0.01, 0.75]	0.05	Small**
	Response time	886.67 ± 144.83	916.29 ± 109.39	0.12 [−0.43, 0.67]	0.64	Unclear

*Inferences were derived by means of standardization (mean difference divided by the between-groups SD at baseline). Magnitude-based inferences were evaluated according to a revision of Cohen's d: <0.2, trivial; 0.2–0.6, small; 0.6–1.2, moderate; >1.2, large (26, 27). CI, Confidence interval. Asterisks indicate effects clear at the 95% level and likelihood that the true effect is substantial, as follows: **likely, ***very likely, ****most likely (26).*

Post hoc analyses were conducted to (i) assess the presence and extent of regression toward the mean in substantial effects, (ii) estimate the presence and extent of individual responses to the intervention and (ii) identify individual responders. A lack of available reliability data for response time trials meant that the *post-hoc* analyses are only conducted on accuracy outcomes.

(i) There was evidence of substantial regression toward the mean in both the incongruent and mixed accuracy trial. That is, once the change scores were corrected for the presence of statistical artifact, the substantial large moderating effect of baseline scores was removed. Follow-up estimates of effect were calculated for participants at −1 standard deviation (SD) below and +1 SD above the mean at baseline to further assess the effects of the intervention. These outcomes indicate that it was most likely only participants at +1 SD above the mean on incongruent trials at baseline whose accuracy improved. Whilst these outcomes were not statistically significant ($p = 0.06$), they were likely moderate (1.01 ± 1.06) when assessed via MBI estimation. Outcomes for participants at −1 SD below the mean at baseline on incongruent accuracy, whilst small-sized (0.34 ± 1.09), were neither statistically significant ($p > 0.05$) nor clear when assessed via MBI. Outcomes for participants at −1 SD below (0.22 ± 1.52) and +1 SD above (0.12 ± 1.42) the mean at baseline on mixed accuracy trials were neither statistically significant nor clear.

(ii) The standard deviation representing individual responses in the incongruent accuracy trial was very large ($d = 0.93$; 95% Confidence Interval = 0.24, 1.29). This outcome is corroborated by the estimates derived for individual responders illustrated in **Figure 2**. **Figure 2** indicates that there were four clear positive, one clear negative, and three non-responders to the intervention. Of the positive responders, there were three large responders and one moderate responder. The negative response was moderate-sized, and the estimates for the three non-responders were unclear. These estimates for individual responders with confidence limits are summarized for each participant in **Table 4**.

DISCUSSION

This study is the first to evaluate the effect of a therapeutic ballet intervention on gait, motor and executive functions in a group of children with CP. It is well established that physical activity (PA), a critical concern in the care of children with CP, is important for physical health. Hillman et al. hypothesized that PA in childhood could optimize brain development, but that for children with disabilities, the greatest challenge may be how to increase their PA (32). Plowman argued that PA is critical during childhood when brains are highly plastic, and that this is especially true for children with disabilities (33). However, motor impairment in children with CP appears to make participation in PA more challenging. As scientific evidence highlights the importance of PA for both motor and cognitive development (especially the development of executive functions), there is a critical need to develop and study PA interventions designed specifically for children with CP.

Verschuren et al. (34) reviewed PA and exercise intervention research for children and adolescents with CP, focusing on cardiovascular fitness using aerobic training, anaerobic training, lower-extremity muscle strength and mixed training, and found that most of the 20 studies they identified had been observational, with only five published randomized clinical trials (RCTs) at the time. Sample sizes across studies were relatively small, ranging from 3 to 46. Overall, these exercise interventions (most lasting 6 to 8 weeks) have been shown to improve a variety of outcomes, including muscle strength and tone, gross motor function, social acceptance, academic performance, posture, body image, and aerobic capacity. A pilot study for children with CP (ages 7–15) reported improvements in the Pediatric Balance Scale following 12 ballet sessions that was retained at 1 month follow-up (6). Our study extends prior research by examining the feasibility and outcomes of a therapeutic ballet intervention designed to meet the needs of children with CP (ages 9–14) on motor functioning, gait, and executive functions.

Physical and Physiological Characteristics of Participants (Tables 1, 2)

As previously reported in children with CP (35), most of the participants in our study presented abnormalities in growth (stature for age: 0.8–76.9%ile) and body composition (**Table 1**). While based on BMI percentile, five participants had normal weight, one was overweight (90th percentile) and two were underweight (1st percentile), a DXA scan revealed that most

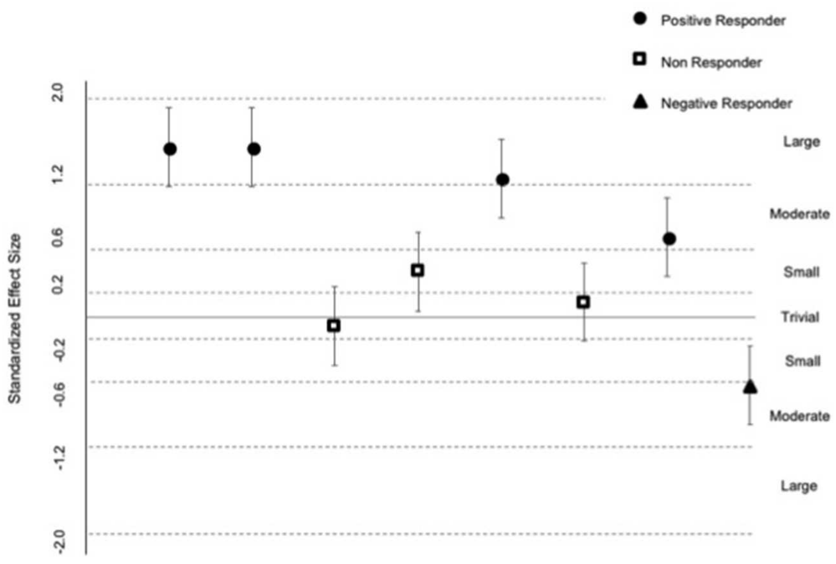

FIGURE 2 | Standardized effects for individual responders. Data are individual participant change scores. Uncertainty in each change score (95% Confidence Limits) was derived by multiplying the standard error of measurement from a reliability study (31) by the t-statistic produced in the mixed model (Proc Mixed) [see (30)]. Standardized effects were derived by dividing each change score and its CL by the baseline standard deviation for incongruent trial accuracy. The size of the effects are evaluated against the following scale: <0.1, trivial; 0.1–0.2, small; 0.2–0.6, moderate; 0.6–1.2, large; >1.2, very large (26).

TABLE 4 | Individual incongruent trial change scores with 95% confidence limits for the standardized difference (Cohen's *d*) in mean.

ID	Change score [95% CI]	Cohen's *d* [95%CI]	Response	Size
Incongruent trial (flowers)—accuracy				
1	46.72 [35.91, 57.53]	1.68 [1.29, 2.06]	Positive	Large
2	46.97 [36.16, 57.78]	1.69 [1.30, 2.07]	Positive	Large
3	−2.26 [−13.07, 8.55]	−0.08 [−0.47, 0.31]	Non	Unclear
4	12.63 [1.82, 23.44]	0.45 [0.07, 0.84]	Non	Unclear
5	38.14 [27.33, 48.95]	1.37 [0.98, 1.76]	Positive	Large
6	4.30 [−6.51, 15.11]	0.15 [−0.23, 0.54]	Non	Unclear
7	22.22 [11.41, 33.03]	0.80 [0.41, 1.19]	Positive	Moderate
8	−18.69 [−29.50, 7.88]	−0.67 [−1.06, −0.28]	Negative	Moderate

*For inferences, see **Table 3**.*

participants were overfat or obese based on percent body fat (including one of the participants with a BMI in the 1st percentile), indicating the importance of evaluating body composition in a clinical setting. All participants were below the 50th percentile for their age and gender for bone density suggesting poor bone density content. Poor bone density is common in children with moderate to severe CP and increases the risk of painful, pathological fractures. Interestingly, higher body fat has also been identified as one of the risk factors for fractures in this population (36). We found no significant changes in BMI percentile, percent body fat, or bone density from before to after the intervention. However, a longer duration of the intervention may be more likely to benefit both body composition and bone health (37, 38).

To assess habitual physical activity (HPA), defined as any bodily movement in daily life which results in energy expenditure, all participants were given accelerometers to wear on a belt around the waist during wakening time for 7 days. On average, in the first week of the intervention participants spent 65 ± 28 min per day on MVPA, which is 52 ± 25 percent of the time observed in typically developing children of the same age and sex (39). Our results match data presented in a systematic review of physical activity and sedentary behavior in CP which reported that across all ages and levels of motor function, young people with CP participated in 13–53% less HPA than their typically developing peers (40). In a review that included 10 studies with children with CP (mean age of 8.4 years), Keawutan et al. indicated that all but one study showed a direct association between motor ability and HPA (41). There was no significant change in MVPA time at the end of our ballet intervention and 4–5 weeks following the intervention, indicating that the brief ballet intervention in and of itself was not enough to promote HPA. A longer intervention and/or more specific instructions and education on HPA during leisure time might better promote HPA in this population.

Hand-grip dynamometer is a simple and easily accessible way to assess muscle weakness in children with CP, and the overall reliability is considered to be good (42). Muscle strength measured by hand-grip dynamometer was 61% ± 33 of predicted values on the right hand and 53% ± 25 of predicted values on the left hand, with great variability among participants and dominant and non-dominant hands (**Table 2**). Four participants showed a trend to improve hand-grip strength in one hand only, while one improved in both hands. While maximal grip strength can provide valuable insight into the maximal strength of the muscle groups involved, there is a need to perform other assessments as well to evaluate muscle coordination and endurance, which are important for the performance of skilled manual tasks in daily activities of children with CP.

Improvements in Selective Control and Gait

It is well established that individuals with CP, a non-progressive neurological disorder, have impaired motor function and selective motor control, but it is important to note that it is not an unchangeable condition with respect to gross motor and selective motor control (43, 44). Increased ambulation speed, increased left single limb support, increased stride length on the left and step length on the right, all suggested an improved ability to coordinate the out of phase or alternating control between the limbs. In addition, these improvements may be the result of the intervention's focus on weight shifting and selective movement of the ankle and foot in single limb stance practice. Improvements observed in the SCALE data suggest improved selective voluntary motor control, which could improve gait speed and control and is consistent with previous correlations between SCALE data and movement during gait (15). Shuman et al. recently published further support for the ability for enhanced gait function, with increased gait speed and gait parameters in children with CP with standard of care (45).

Improvements in Executive Functions (Inhibitory Control)

Although disruptions in motor functioning are often the most recognizable feature of CP, executive function impairment is also a central feature of CP. Bodimeade et al. compared executive functions (EF) in children with CP (mean age 11 y/o) to typically developing controls (7). The performance of children with CP was worse in all areas of EF measured, including attentional control, cognitive flexibility, goal setting, and information processing. Bottcher et al. evaluated EF in children with spastic CP and found impairments in sustained and divided attention, inhibitory control, shifting, and general executive functioning (46). They noted that these impairments were associated with social and learning problems. Bottcher noted that there is extensive developmental research indicating that children's activities and play are critical to social and cognitive development, and as children with CP may have difficulties (motor or other) that restrict participation, it results in limited opportunities for learning and cognitive development (47).

PA interventions, particularly cognitively engaging interventions, can improve EF in children (3, 48). Thus, PA interventions for children with CP could simultaneously target motor and executive functioning. Evidence indicates that not all forms of exercise benefit EF equally (3, 9, 49, 50), and that "*the degree to which the exercise requires complex, controlled, and adaptive cognition and movement may determine its impact on EF*" (51). Diamond argued that moving without thought produces little change in executive functions and that practices like yoga, martial arts, and dance—which require both thought and movement—are likely to have a stronger positive effect on EF (8), and recent research has suggested that dance—or music and movement—interventions can be beneficial for other clinical populations of children (52).

Thus, one of the aims of the current study was to evaluate the impact of a dance intervention on EF in children with CP. The only EF task with substantial improvement after intervention was the Incongruent Accuracy task, which measures primarily inhibitory control (i.e., the ability to focus on relevant simuli in the presence of irrelevant stimuli) and revealed large individual responses. Those who were above average at baseline improved substantially, but there was little improvement among those below the group average at baseline. This likely reflects differences in impairment in this group of children and suggests that much greater tailoring of the intervention may be required for those who start with greater impairment in EFs. Physical education research has highlighted the importance of differentiation, which refers to the process of assessing a learner's starting point and to adapting or modifying tasks in order to ensure that each individual progresses (53, 54). In future studies, different lengths and type of exercises should be evaluated to gain more information that can be translated to personalize prescriptions with a goal to improve the benefits for individuals with varying levels of impairment.

Conclusion

Therapeutic ballet may prove to be a useful intervention to promote gait and inhibitory control in children with cerebral palsy. Overall, results indicated improvements in participants' gait and inhibitory control with large individual responses. Modifications to the intervention might be needed on individualized basis to optimize health benefits, particularly for those with a greater level of initial impairment. This study provides support for further research, including the development of a randomized intervention study to systematically evaluate the effects of ballet intervention on physical, physiological, and cognitive functions in children with CP.

ETHICS STATEMENT

The study was approved by the Institutional Review Board (ethics committee) of the University of California, Irvine.

AUTHOR CONTRIBUTIONS

KS, MG-B, SS, JP, AA, KC, and CL-O: conception, design, delivery of the 6 week intervention. KLa, KS, MG-B, SS, and SR-A: conception and design of the research study. KLa, KS, FH, MG-B, KLu, and SR-A: data collection. KLa, KS, MG-B, RN, FH, KLu, and SR-A: data analysis and interpretation. KLa, KS, RN, SS, CL-O, and SR-A: drafting the manuscript. KLa, KS, MG-B, FH, CL-O, and SR-A: critical revision of the manuscript. KLa, KS, MG-B, RN, FH, SS, JP, KC, KLu, AA, CL-O, and SR-A: approval of the final version. RS, DH, and MS add to both data collection and data analysis.

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Lower Extremity Biomechanics Are Altered Across Maturation in Sport-Specialized Female Adolescent Athletes

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Sport specialization is a growing trend in youth athletes and may contribute to increased injury risk. The neuromuscular deficits that often manifest during maturation in young, female athletes may be exacerbated in athletes who specialize in a single sport. The purpose of this study was to investigate if sport specialization is associated with increased lower extremity biomechanical deficits pre- to post-puberty in adolescent female athletes. Seventy-nine sport-specialized female adolescent (Mean $\pm$ SD age $= 13.4 \pm 1.8$ years) basketball, soccer, and volleyball athletes were identified and matched with seventy-nine multi-sport (soccer, basketball, and volleyball) female athletes from a database of 1,116 female adolescent basketball, soccer, and volleyball athletes who were enrolled in one of two large prospective, longitudinal studies. The athletes were assessed over two visits (Mean $\pm$ SD time $= 724.5 \pm 388.7$ days) in which they were classified as pre-pubertal and post-pubertal, respectively. Separate 2×2 analyses of covariance were used to compare sport-specialized and multi-sport groups and dominant/non-dominant limbs with respect to pubertal changes in peak knee sagittal, frontal, and transverse plane joint angular measures and moments of force recorded while performing a drop vertical jump task. The sport-specialized group were found to exhibit significantly larger post-pubertal increases in peak knee abduction angle ($p = 0.005$) and knee abduction moment ($p = 0.006$), as well as a smaller increase in peak knee extensor moment ($p = 0.032$) during landing when compared to the multi-sport group. These biomechanical changes are indicative of potentially compromised neuromuscular control that may increase injury risk pre- to post-puberty in sport-specialized female athletes. Consideration of maturation status may be an important factor in assessing the injury risk profiles of adolescent athletes who specialize in sport.

Keywords: sport specialization, female, maturation, biomechanics, injury risk

INTRODUCTION

Sport specialization, or a year- or near year-round commitment to one sport at the exclusion of others (1), is becoming increasingly prevalent among pre-adolescent and adolescent athletes (2). This trend may be driven by a number of factors, including an overall decrease in unstructured physical activity (i.e., "free play"), an increase in structured activity among youth (3), and an increased pressure on youth athletes to excel in sport (4). The latter of these is underscored by the potential economic benefit of sport success [e.g., college scholarships, elite achievement, or high professional sports salaries (5, 6)] and the theoretical competitive advantage that deliberate practice might give youth athletes. These potential benefits are reinforced by the media and public perception (7) and the influence of coaches, parents, and peers (8). Consequently, there is concern that youth athletes are not only specializing in greater numbers, but also at earlier ages (7, 9), which can contribute to adverse outcomes in these athletes, such as psychological burnout and an increased risk of musculoskeletal injury (10, 11). Given the nearly 10-fold increase in female sports participation since the inception of Title IX (12), young female athletes may be specializing in sport at an increasing rate (2, 13, 14).

Recently, there has been an increased emphasis to discern the implications of early specialization in sport with the goal of educating practitioners and parents to ensure safe sport involvement in youth athletes (15, 16). Specialized athletes typically engage in a large volume of year-round, intensive, often technical or otherwise specialized, sport-specific training (10, 11), and as a result, sport specialization has been associated with an increased risk for overuse injury (2, 14, 17, 18). This increased risk may be related to the homogeneity of movements associated with highly specialized training regimens that repeatedly stress the same musculoskeletal tissues (19). For young, developing athletes, physiological immaturities in bone and connective tissue may not allow these individuals to adequately handle the homogenous and repetitive stresses that result from continual practice of a small set of sport-specific skills, which can lead to accelerated rates of fatigue and injury in this population (20, 21). This increased risk may also be due in part to compromised motor ability stemming from the inadequate development of or practice of motor skills that come alongside repetitive, non-variable practice of specialized sport movements. Multi-sport participation at a young age has been shown to improve gross motor competence and overall motor ability (22), and may lead to improved neuromuscular control (23) and more effective sport performance as exhibited through more optimal lower extremity biomechanics, as well as more balanced physiological responses to sport participation (24, 25). It therefore may be beneficial for young athletes to engage in a variety of sports and/or physical activities to facilitate more comprehensive physical and motor development.

Biomechanical risk factors that predispose sport-specialized youth athletes to overuse injury may be compounded by maturation. Developing female athletes, who are already at an increased risk of musculoskeletal injury relative to males (26, 27), may be especially susceptible to the factors underlying increased musculoskeletal injury risk relative to early sport specialization. Adolescent females are more likely than males to exhibit decreased neuromuscular control and aberrant biomechanics, particularly at the knee (28–30), that can lead to a decreased ability to modulate forces during dynamic movements that occur during sport, like landing (31) and cutting (32). Moreover, during maturation, these deficits persist and are often exacerbated by structural changes, such as increases in height, mass, height of the center of mass, etc., that can lead to increases in the magnitude of external forces experienced during dynamic activity (31, 33–35). These movement patterns can lead to increased risk for both acute and chronic knee injury in these athletes (29, 36).

Given the increased rate of sport specialization in youth athletes and its association with knee injury risk, and the potential for young, developing female athletes to be especially susceptible to increased injury relative to males, it is important to identify potential mechanisms that might amplify biomechanical risk factors in this group. Identification of these mechanisms may serve to educate parents, coaches, and other practitioners and improve prevention efforts targeting neuromuscular control during maturation. The purpose of this study was to examine the knee biomechanical changes that occur pre- to post-puberty in adolescent female athletes and the effect of sport specialization on these changes. The hypothesis tested was that sport specialization would be associated with increased propensity toward knee joint biomechanical changes that underlie an increased risk for musculoskeletal injury.

MATERIALS AND METHODS

Participants

The cohort for this study was selected from a database of 1,116 female, adolescent basketball, soccer, and volleyball athletes (Mean $\pm$ SD age $= 13.4 \pm 1.8$ years) who were enrolled in one of two large prospective, longitudinal studies that were conducted over the course of 4 years (29, 37). The athletes were 93.6% Caucasian, 3.0% African-American, 1.0% Asian, 0.2% Native American, and 0.1% Hawaiian, with 2.3% declining to or failing to report their ethnicity. Each testing session occurred at the beginning of the athletes' respective competitive sports season.

Prior to data collection, the study protocol was approved by the Cincinnati Children's Hospital Medical Center Institutional Review Board (IRB 2008-0023 and IRB 2009-0602, respectively), and informed written consent, along with child assent, was obtained from participants and their parents or legal guardians if under 18 years of age.

Data Collection

Testing consisted of participant characteristics, including questionnaires to determine anthropometric measurements, medical history, indicators of sport participation and pubertal development, as well as a three-dimensional biomechanical analysis of a drop vertical jump (DVJ) task. The same research assistant administered the questionnaires and obtained anthropometric measurements, and a trained research biomechanist collected the data from the biomechanical analysis using pre-specified standard operating procedures.

From the initial cohort of 1,116, athletes were excluded if they were not classified as either sport-specialized or multi-sport as indicated from the sport participation questionnaire, had poor or missing biomechanical data, and who were classified as post-pubertal at the initial visit or did not have a follow-up visit in which they were classified as post-pubertal. After exclusion, 183 athletes met the criteria for inclusion into the study; athletes were selected such that there were equal numbers of sport-specialized and multi-sport athletes and then age-, height- and weight-matched based on their measurements at their initial visit, leaving 158 athletes in the final cohort (**Figure 1**). Each participant's initial and follow-up visits were separated by at least 6 months (sport-specialized M $\pm$ SD days = 773 $\pm$ 405, range = 293–1,827; multi-sport M $\pm$ SD days = 696 $\pm$ 373, range = 280–1,812).

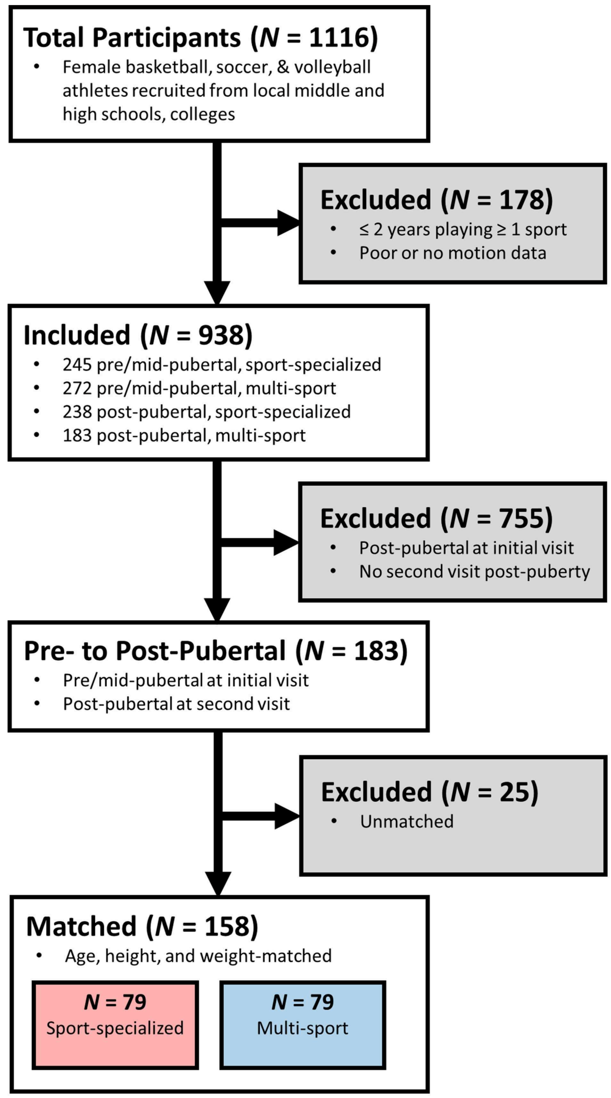

FIGURE 1 | Flowchart illustrating the selection process for the cohort of sport-specialized and multi-sport athletes. Athletes were selected if they were classified as either "sport-specialized" or "multi-sport," had longitudinal data ($\geq$2 visits to the laboratory), were classified as "pre-pubertal" or "mid-pubertal" at their first visit, and had at least one longitudinal visit in which they were classified as "post-pubertal".

Anthropometric Measurement

Height and weight were recorded for each participant using a standard medical scale, and body mass index (BMI) was computed from these measures. Each participant's dominant limb was also recorded by asking the participant which leg she would use to kick a ball as far as possible.

Sports Participation and Pubertal Questionnaires

During each testing session, both the sport specialization status and the maturational status of the athletes were assessed. Sport specialization status was determined by having participants complete a sports participation questionnaire, which asked athletes to report their participation in their current sport (i.e., basketball, soccer, or volleyball), as well as any additional sports, and the number of years in which they have participated in each sport. Participation was defined as having at least been a member of a competitive, organized team for an entire season in a given year. In the present study, participants were classified as "sport-specialized" if they had $\geq$2 years of participation in 1 sport and < 2 years participation in any other sports, and "multi-sport" if they had $\geq$2 years of participation in each of at least 2 sports. While the questionnaire did not include an assessment of year-round participation (i.e., $\geq$8 months out of the year) by single-sport athletes, which is a necessary component for classifying an athlete as truly sport specialized (1), this classification scheme was similar to that which was reported by Hall et al. (18), albeit differing slightly. Specifically, in contrast to Hall, single-sport athletes—regardless of the number of years they participated—were classified as "sport-specialized," and athletes who competed in more than one sport were classified as "multi-sport." The classification in the present study was used because of the ambiguity surrounding the sports participation questionnaire that was administered to participants. With respect to current sport involvement, the questionnaire did not differentiate between first-time athletes and athletes who had at least 1 year of participation (i.e., in both scenarios, their years of participation were recorded as "1").

Consequently, it was unclear at what point athletes who listed their number of years of participation as "1" began participating in that sport. As a result, the present study used 2 years of participation as the threshold for involvement in a given sport.

The pubertal status of each participant was determined with the modified Pubertal Maturation Observation Scale (PMOS) questionnaire (34, 38). The PMOS was developed by Davies et al. (38) as a clinician-friendly, unobtrusive tool to differentiate between pubertal stages without physical examination. This scale is based on several indicators of pubertal maturation, including growth spurt, menarcheal status, body hair, sweating, and muscular definition (39), and it can be used to reliably classify subjects into developmental stages based on a parental report and investigator observational report (38). The PMOS was completed by each participant's parent(s) or legal guardian(s). Positive answers to each of the questions in the PMOS were scored as a point, with $\leq$1 points, 2–4 points, and $\geq$5 points used to classify participants as "pre-pubertal," "mid-pubertal," or "post-pubertal," respectively (40). To investigate the biomechanical changes to female athletes through maturation, athletes were selected if their maturational status was classified as being either "pre-pubertal" or "pubertal" during their first visit to the laboratory and they had at least one follow-up visit during which they were classified as "post-pubertal" based upon PMOS score (i.e., their maturational status changed between the time of their first visit and some future visit) (34). If the participants had more than one longitudinal visit in which they were classified as "post-pubertal," the first visit in which they reached "post-pubertal" status was selected for analysis. Using these classifications, at the time of their first testing session, athletes were required to be classified as "pre-pubertal" or "pubertal," and at the time of the second testing session, they were required to be classified as "post-pubertal." Sport specialization status did not change between testing sessions for any participants.

Biomechanical Analysis of the DVJ

Data were collected on participants with a standard biomechanical assessment that utilized three-dimensional motion analysis (41). Participants were first instrumented with 37 retroreflective markers with a minimum of three tracking markers per segment. Markers were placed on the lower back between the S5 and T1 vertebrae, and bilaterally on the acromio-clavicular joint, lateral epicondyle of the elbow, mid-wrist, anterior superior iliac spine, greater trochanter, mid-thigh, medial and lateral femoral condyles, tibial tubercle, lateral and distal aspects of the shank, medial and lateral malleoli, the heel, the dorsal surface of the midfoot, the lateral foot (fifth metatarsal) and central forefoot (between the second and third metatarsals). A 10-camera, high-speed, passive optical motion capture system (Motion Analysis Corp., Santa Rosa, CA) sampled at 240 Hz was used to record the three-dimensional marker trajectories from each participant. Ground reaction forces in Newtons were collected with two embedded force platforms (AMTI, Watertown, MA) sampled at 1200 Hz that were synchronized with the motion capture system.

Before dynamic motion trials were collected, a static trial was conducted in which the participant was instructed to stand in anatomical pose with foot direction and placement standardized to the laboratory's global coordinate system to define the participant's neutral kinematic posture. Participants then performed a minimum of three trials of a drop vertical jump (DVJ) task, a commonly used motor task in lower extremity biomechanical assessments (29, 36, 42). During the DVJ, participants positioned themselves on top of a 31-cm box with their feet aligned with tape placed at the edge of the box, situated approximately shoulder-width apart. Participants were instructed to drop off the box with both feet at the same time, land on the force platforms in front of the box, and immediately perform a maximum effort vertical leap to attempt to grasp a maximally positioned overhead target. Each trial was performed with minimal rest in between (10–15 s). Trials were repeated if the participant did not leave the box with both feet at the same time or paused upon landing before performance of the maximum vertical leap, and the participant kept performing trials until three acceptable trials were obtained.

Data Processing

Marker trajectories and ground reaction forces were filtered using a low-pass, fourth-order Butterworth filter with a cutoff frequency of 12 Hz. A six-degree-of-freedom skeletal model was applied to the marker data to determine the position and orientation of all segments at each time sample, and the model was scaled to the participant's height and weight. Three-dimensional lower extremity joint angles were calculated with an XYZ Cardan rotation sequence, and ground reaction forces were used to calculate joint moments of force using an inverse dynamics analysis in Visual3D (C-Motion, Inc., Germantown, MD) and were referenced to coordinate axes systems about the proximal limb. Joint angles and moments were extracted from the stance phase, which was defined as the period of time from when subjects made initial contact with the force platforms (determined when the normal ground reaction force exceeded 10 N) until toe-off occurred. The joint angles and moments were then time-normalized to 101 data points (representing 0–100% of stance) using custom MATLAB (MathWorks, Inc., Natick, MA) software. Each participant's time-normalized waveforms were averaged across the three DVJ trials for each joint and plane of motion. In addition, the stance phase was further divided into the landing and propulsion sub-phases, respectively, differentiated by the point during normalized stance at which the participant's center of mass reached a minimum vertical height. Peak knee kinematic (joint angular motion) and kinetic (joint moments of force) measures in both the dominant and non-dominant limbs were extracted during the time-normalized, meaned landing sub-phase.

Statistical Analysis

One-sample Kolgomorov-Smirnov (K-S) tests for normality were conducted for anthropometry and knee biomechanical measures at each visit. Independent *t*-tests were used to ensure no differences existed between the sport-specialized and multi-sport groups in age, height, weight, BMI, and sport participation years at either the initial testing session ("pre-pubertal") or follow-up testing session ("post-pubertal"). Average years of

TABLE 1 | Mean ± SD pre- and post-pubertal anthropometry and sport participation years in the sport-specialized and multi-sport groups.

	Pre-pubertal		Post-pubertal	
	Sport-specialized	**Multi-sport**	**Sport-specialized**	**Multi-sport**
Age (years)	12.2 ± 0.8	12.3 ± 0.9	14.3 ± 1.2	14.2 ± 1.1
Height (cm)	155.0 ± 7.7	155.0 ± 7.5	1.6 ± 5.2	1.6 ± 5.9
Weight (kg)	47.1 ± 10.1	47.6 ± 10.7	55.9 ± 7.5	55.7 ± 8.7
BMI (kg × m^{-2})	19.4 ± 3.0	19.5 ± 3.0	21.2 ± 2.8	21.1 ± 2.4
Sport participation (years)	4.5 ± 1.4	4.3 ± 2.1	6.2 ± 2.1	6.0 ± 2.3

TABLE 2 | Mean ± SD pre- and post-pubertal peak knee kinematic and kinetic measures in the sport-specialized and multi-sport groups.

	Pre-pubertal		Post-pubertal	
	Sport-specialized	**Multi-sport**	**Sport-specialized**	**Multi-sport**
Dominant limb				
Knee flexion (°)	−83.2 ± 8.2	−82.9 ± 9.2	−82.1 ± 9.0	−82.7 ± 9.6
Knee abduction (°)*	−8.9 ± 6.6	−7.6 ± 4.8	−11.3 ± 6.7	−8.6 ± 5.3
Knee internal rotation (°)	6.8 ± 5.7	7.0 ± 5.8	5.6 ± 4.4	6.5 ± 6.1
Knee extensor moment (Nm)*	89.3 ± 23.6	87.6 ± 27.1	107.3 ± 23.4	112.3 ± 28.0
Knee abduction moment (Nm)*	−15.2 ± 11.6	−13.9 ± 9.1	−23.8 ± 14.7	−19.6 ± 11.4
Knee internal rotation moment (Nm)	3.0 ± 2.8	3.6 ± 3.5	3.7 ± 4.5	4.4 ± 4.1
Non-dominant limb				
Knee flexion (°)	−84.2 ± 8.5	−84.4 ± 9.6	−83.3 ± 9.0	−84.2 ± 9.7
Knee abduction (°)*	−10.1 ± 6.2	−8.2 ± 5.5	−11.6 ± 5.1	−9.5 ± 5.1
Knee internal rotation (°)	7.6 ± 5.1	8.4 ± 5.7	6.8 ± 5.7	7.9 ± 5.3
Knee extensor moment (Nm)*	83.8 ± 22.5	83.4 ± 25.0	103.1 ± 21.8	108.7 ± 24.5
Knee abduction moment (Nm)*	−19.9 ± 11.1	−18.8 ± 12.8	−26.9 ± 12.6	−23.0 ± 14.2
Knee internal rotation moment (Nm)	6.4 ± 4.3	7.2 ± 4.3	6.4 ± 4.8	7.6 ± 5.1

**Indicates statistically significant differences pre- to post-puberty.*

sport participation was determined by summing the total number of years reported participating in all sports divided by the number of unique sports.

Post-pubertal knee kinematic and kinetic differences between sport-specialized and multi-sport athletes were determined using separate 2 × 2 (group × limb) analyses of covariance (ANCOVA) with their pre-pubertal measures and days between testing sessions being included as covariates to the model. Days between testing sessions was included as a covariate because of the wide time range (i.e., 280–1,827 days) between visits; this occurred because while many participants had multiple visits to the laboratory, only the first visit in which the participant was classified as "post-pubertal" was used in the analysis, which did not occur at the same time for all participants. Bonferroni corrections were used to control for multiple comparisons, and an alpha level of.05 was selected *a priori* to indicate statistical significance.

RESULTS

Table 1 describes the mean age, height, weight, BMI, and years of sport participation recorded for the sport-specialized and multi-sport groups during both testing sessions. Age, height, weight, and average sport participation were all found to be normally distributed (K-S; all $p > 0.05$), and no differences existed between any of these measures at the time of either testing session (t-test; all $p > 0.05$).

Figures 2, **3** show the mean time-normalized waveforms for the dominant limb knee joint moments of force, respectively, for the sport-specialized and multi-sport groups pre- and post-puberty. The mean peak knee kinematic and kinetic measures for both groups and limbs pre- and post-puberty are shown in **Table 2**. All knee kinematic and kinetic measures were found to be normally distributed (K-S; all $p > 0.05$) except for transverse plane knee joint moment ($p = 0.011$), which had moderate positive skewness; this variable was subsequently square-root-transformed before being submitted to ANCOVA. The analysis revealed significantly larger post-pubertal increases for the sport-specialized group in peak knee abduction angle [$F_{(1,310)} = 8.077$, $p = 0.005$] and knee abduction moment [$F_{(1,310)} = 7.807$, $p = 0.006$]. In addition, the sport-specialized group exhibited a significantly smaller increase in knee extensor moment [$F(1, 310) = 4.616$, $p = 0.032$] (**Figure 4**). No other main effects were observed the other kinematic and kinetic measures for either group or limb, or the group × limb interaction (all $p > 0.05$).

DISCUSSION

The aim of the present study was to examine the influence of sport specialization on knee injury risk biomechanics across

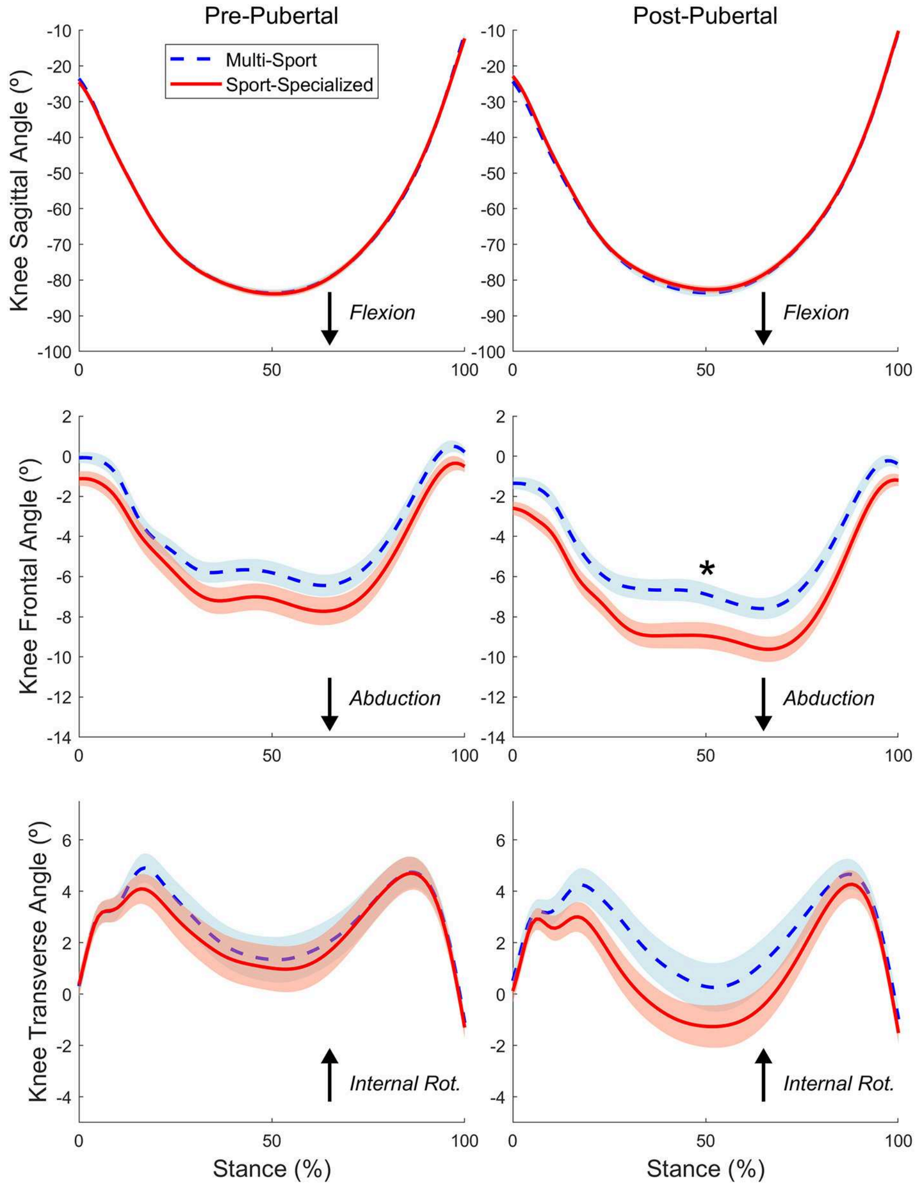

FIGURE 2 | The time-normalized knee joint angular motions in the sagittal (Top), frontal (Middle), and transverse (Bottom) planes during the stance phase of the DVJ task for the sport-specialized (red) and multi-sport (blue) groups pre (Left) and post-puberty (Right). The waveforms represent the average joint angular motions between dominant and nondominant limbs. The shaded region represents standard error of the mean. "*" indicates statistically significant differences pre- to post-puberty.

puberty. The main finding of our study showed that sport-specialized female athletes exhibited knee kinematic and kinetic changes pre- to post-puberty that may increase risk for injury when compared to multi-sport female athletes (29). Specifically, the sport-specialized female athletes exhibited larger post-pubertal increases in peak knee abduction angle and knee abduction moment and a smaller increase in knee extensor moment during landing while performing the DVJ task than multi-sport athletes. The results indicate that female athletes who specialize in sport may amplify an increased risk for injury across puberty due to compromised neuromuscular control when compared to female athletes who chose not to specialize in early sport.

The competitive demands of many sports necessitate movement patterns and coordination strategies that accommodate high external forces experienced by adolescent athletes during dynamic activity. These external forces are magnified through maturation because of structural and inertial changes to the body, such as increases in mass, height, and segment length(s). In the present study, sport-specialized athletes exhibited larger post-pubertal increases in knee abduction angle and moment during landing when

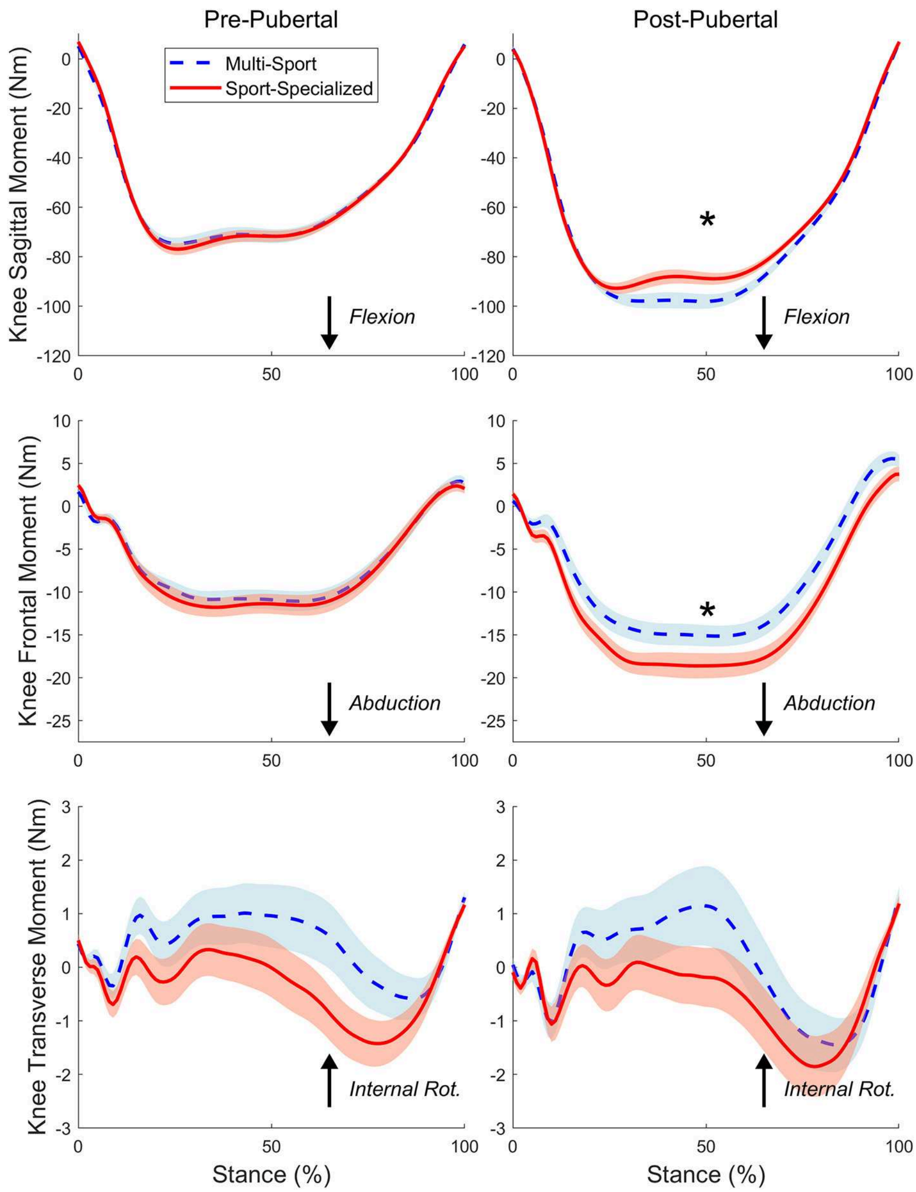

FIGURE 3 | The time-normalized knee joint moments of force in the sagittal (Top), frontal (Middle), and transverse (Bottom) planes during the stance phase of the DVJ task for the sport-specialized (red) and multi-sport (blue) groups pre (Left) and post-puberty (Right). The waveforms represent the average net external moments between dominant and nondominant limbs. The shaded region represents standard error of the mean. "*" indicates statistically significant differences pre- to post-puberty.

compared to multi-sport athletes. The relationship between sport specialization and knee abduction moment is particularly novel, as most previously described risk associations for sports specialization are for overuse injuries, such as patellofemoral pain (17, 18). However, demonstrating increased knee frontal plane moments associated with sport-specialized female athletes may have great implications in injury prevention of acute injuries such as anterior cruciate ligament tear, medial collateral ligament tear, and patellar instability. High knee abduction moments have been established previously as risk factors for both acute and chronic knee injury (29, 36) and thus, larger increases in this variable—as exhibited by the sport-specialized group across puberty—might be linked to increased injury risk. It is unclear what level of change in or magnitude of this variable can be considered meaningful as it pertains to knee injury; however, some studies differentiated athletes into low- and high-risk categories based on specified thresholds. For example, the maximum sensitivity and specificity to classify adolescent female athletes at high-risk for an ACL injury as having exhibited knee abduction moments greater than 25.25 Nm (29); in the present study, sport-specialized athletes exhibited average post-pubertal knee moments of 24 Nm and 27 Nm for the dominant and

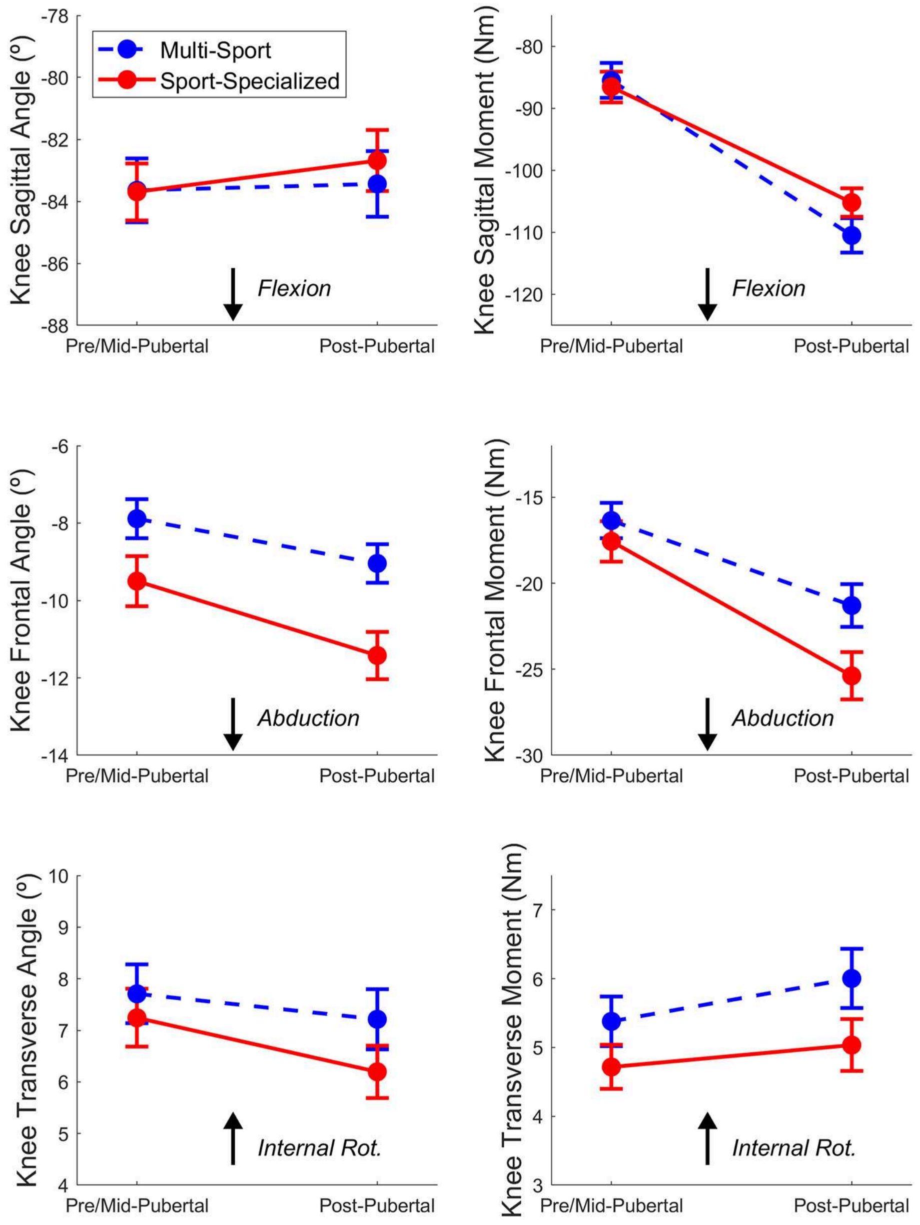

FIGURE 4 | Mean peak knee kinematic (Left) and kinetic (Right) measures in the sagittal (Top) frontal (Middle), and transverse (Bottom) planes during the stance phase of the DVJ task for the sport-specialized (red) and multi-sport (blue) groups. The error bars represent standard error of the mean.

non-dominant limbs, respectively (as opposed to 19 Nm and 23 Nm, respectively, for the multi-sport group), which would classify these individuals at or near "high-risk" for ACL tear.

Prior studies investigating similar high-risk biomechanics in female athletes through maturation have shown maturation can underlie increased proliferation of lower extremity frontal plane mechanics that underlie increased injury risk. While these prior investigations did specifically examine sport specialization, the findings of this study support that the biomechanical changes through puberty that occur may in fact be compounded by early sport specialization (28–31, 33–35). This finding indicates that early sport specialization may be an additive factor for increased injury risk or that multi-sport diversity mitigates the development of insufficient neuromuscular control throughout the maturation process (28, 31). In addition, there is consistent evidence that indicates that youth should be involved in periodized strength and conditioning (e.g., integrative neuromuscular training) to help them prepare for the demands of competitive sport participation (24, 25). The current results may suggest that young females who specialize in a single sport can benefit from focused integrative neuromuscular training to enhance diverse motor skill development to reduce the proliferation injury risk factors particularly during maturational development (15, 23).

Sport-specialized athletes also experienced a smaller increase in knee extensor moment during landing. While over-reliance on the knee extensors during landing can be an indicator of decreased hip control and subsequent lower extremity injury risk (43), it can also indicate improved task performance, particularly during the DVJ (44). For the multi-sport group, these results (i.e., greater increase in knee extensor moment, smaller increase in knee abduction moment, and trend toward a greater increase in hip extensor moment (**Figure 2**) indicate that multi-sport athletes tend to exhibit more improved landing performance during the DVJ. These results may also indicate that multi-sport involvement may help adolescent athletes modulate and possibly ameliorate the inability to manage inertial demands that occur across puberty leading to decreased injury risk.

For young athletes, sport performance is greatly influenced by the amount of sport-specific practice and competitive sport participation. As a result, the perception among many coaches, parents, and athletes is that constant, and intensive training, beginning at a young age, will ultimately lead to significant sport achievement. However, currently there is no evidence to support the notion that early specialization in sport results in greater success. To the contrary, achieving elite status in sport has been shown to be related to young athletes participating in multiple organized sports, followed by sport specialization later in adolescence (5, 6, 45). Some individualized sports, like tennis, swimming, and gymnastics, involve early and intensive training by youth, and early sport specialization is becoming increasingly prevalent in some team sports such as basketball, soccer, and volleyball (13). Early childhood and adolescence are critical times during which diversification of movement is necessary for comprehensive motor and coordination development. In this light, early sport specialization may stifle the development of critical motor skills during childhood (46). Sport diversification during childhood and adolescence may promote improved motor competence (22), leading to greater sport specific skill and technique acquisition later in adolescence. The lack of established criteria for "early" sport specialization, and lack of consensus on training volume and age criteria add greatly to the challenges when trying to establish future guidelines (47, 48). Biomechanical analysis of movement patterns that might increase injury risk may help to guide sports participation for young specialized athletes.

The results of this study should be interpreted in light of the following limitations. The definition of sport specialization used to differentiate single- and multi-sport athletes. Our definition differed slightly from previous work (17, 18) and may not have accurately represented true sport specialization (i.e., year-round, single-sport participation to the exclusion of others); thus, the year-round component was not clear in the present study. However, given our modified definition, biomechanical differences were still able to be detected through maturation in sport-specialized female athletes. Future studies examining injury risk biomechanics across puberty in sport-specialized athletes should establish this more fully. In addition, the present study used pubertal characteristics to establish maturational stages. This classification scheme has been used previously (34); however the authors acknowledge that the usage of discrete pubertal classifications may have participants at the beginning or end of stages that creates a mix of maturational levels in the chosen groupings. The authors acknowledge that other metrics of maturation may be more biomechanically relevant to refine this classification (e.g., timing of peak growth height velocity, etc.) and thus, future work should explore these potential relationships. Future work should also examine both male and female sport-specialized athletes; the present study examined female athletes exclusively. As females tend to be more at risk for knee injury than their male counterparts, it may be that early sport specialization does not have as a profound of an influence on risky knee biomechanics in males.

In the present study, sport specialized female athletes exhibited altered biomechanics during landing while performing the DVJ task compared to multi-sport athletes. The results of this study suggest that the biomechanical changes that occur during maturation in specialized female athletes may be combinatory in injury risk profile development. The current definition of sport specialization in youth emphasizes early and continual (i.e., year-round) involvement in sport (47, 48). However, no consensus exists on temporal characteristics (e.g., age, maturational level, etc.) and their potential use as a specifier of early specialization. The results of this study support consideration of maturation status in future efforts to educate athletes, parents, and coaches regarding sport specialization. They may also provide guidance on the inclusion of integrative neuromuscular training programs for young females who chose to specialize early.

ETHICS STATEMENT

Prior to data collection in both sessions, the study protocol was approved by the Cincinnati Children's Hospital Medical Center Institutional Review Board, and informed written consent, along with child assent, in accordance with the Declaration of Helsinki, was obtained from participants and their parents or legal guardians if under 18 years of age.

AUTHOR CONTRIBUTIONS

CD was responsible for the overall study design, analysis, preparation, and writing of the manuscript. AM was responsible for the preparation and writing of the manuscript. KB, ST, KF, GM, and TH were responsible for data collection and oversight, and preparation and writing of the manuscript. GM was also responsible for overall concept and study design. NJ, AS, and DB were responsible for preparation and writing of the manuscript.

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Motor Competence and Physical Activity in Early Childhood: Stability and Relationship

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Background: Normal motor development and adequate levels of physical activity engagement during the early years of life form the foundation of long-term psychological and physiological health. This is one of the very few studies that investigate the stability and relationships of motor competence and physical activity in preschool children.

Methods: Baseline and 12 month follow-up data of physical activity and motor competence of 550 preschool children aged 2–6 years from the Swiss Preschoolers' Health Study were used for this work. Physical activity data, expressed in counts per minute for total physical activity and minutes per day for time spent moderately-to-vigorously physically active, were collected over 1 week using accelerometers. Motor competence was assessed with the Zurich Neuromotor Assessment. Both motor competence and physical activity were age- and sex-adjusted. To examine the individual stability of physical activity and motor competence and reciprocal cross-sectional and longitudinal effects between these two domains, a latent variable cross-lagged panel model where motor competence was represented through a latent construct was examined using structural equation modeling.

Results: A weak cross-sectional correlation of motor competence with total physical activity ($r = 0.24$) and moderate-to-vigorous physical activity ($r = 0.23$) was found. Motor competence exhibited high stability ($\beta = 0.82$) in the preschool years and physical activity was moderately stable with estimates ranging from $\beta = 0.37$ for total physical activity to $\beta = 0.48$ for moderate-to-vigorous physical activity. In contrast to the autoregressive coefficients denoting individual stability, both cross-lagged effects were negligible indicating that physical activity was not a determinant of motor competence or vice versa.

Conclusions: Motor competence and physical activity developed independently of each other in early childhood. Although measures of quantity and intensity of physical activity were not related to motor development, specific movement experiences and practice—which are not reflected by accelerometry—may be needed for skill development. Future research should focus on examining what type of physical activity is important for motor development and how to assess it, and also whether the relationship between physical activity and motor competence evolves over time.

Clinical Trial Registration: Current Controlled Trials ISRCTN41045021 (date of registration: 21.03.14)

Keywords: motor competence, fundamental movement skills, physical activity, children, preschool, longitudinal, splashy

INTRODUCTION

Both physical activity (PA) and motor competence (MC) have been linked to improved health indicators including increased cardiorespiratory fitness and decreased adiposity (1–3). MC is a global term used to describe goal-directed gross movements that involve large muscle groups or the whole body (e.g., running, jumping, balancing) (3). In early childhood, children begin to learn how to move their body through space by developing so called fundamental movement skills, which form the foundation for future more complex movement skills. Motor development is an iterative learning process driven by changes in the structure or function of the body as well as the environment (4, 5). There is increasing agreement about the existence of a continuous interplay of nature and nurture in defining motor development. Theories have moved away from neuro-maturational approaches claiming a predetermined sequence of motor skill acquisition (6) to a more holistic view involving contextual and biological factors (5, 7). From the dynamic systems perspective motor skills develop in a perpetual interplay between the organism, environment and task constraints, which may vary across stages of development. PA, an important element of this complex system, is a behavior that is needed to attain or improve MC. At the same time it can be seen as a product of motor development. This chicken-and-egg dilemma has been feeding the debate about how MC and PA are related over decades (8, 9).

Since evidence suggests that behavioral capabilities and lifestyle habits establish in childhood and track over time (10, 11), appropriate development of MC and levels of PA are important not only for child health, but also to sustain health throughout life. Numerous researchers have investigated underlying pathways including inter- and intra-individual variation and relationships. While cross-sectional evidence indicates a positive association between MC and PA in children and youth (12–14), only a few longitudinal studies investigating the suspected causal pathways between MC and PA have been published (15–19). Studies in older children found MC and self-reported PA to be unrelated (20), MC to be predictive of subsequent self-reported PA (16, 17), objectively measured PA to be predictive of subsequent MC (21) or a reciprocal longitudinal relationship between MC and self-reported (18) or objectively measured (19) PA. The only study focusing specifically on preschool children showed that objectively measured moderate-to-vigorous PA at 3.5 years, but not at 19 months, was predictive of locomotor skills at age 5 (15).

Thus, current evidence relies on predominantly cross-sectional studies that show overall small effects. Whether a real causal pathway exists, and if so, whether it is unidirectional or reciprocal is unclear. To better understand how PA and MC are related in early childhood, more longitudinal studies that allow for cause-effect pathways in both directions are needed. The concept of reciprocal influence was first described in 2008 by Stodden et al. (8). The authors developed a theoretical framework where the direction of causation was hypothesized to change from early to middle childhood. In young children, PA was suggested to drive the development of MC through a variety of exploratory and structured movement experiences that promote neuromotor development. As children transition to middle and late childhood, the relationship was hypothesized to become stronger and more reciprocal, driven by the child's ability to perceive its competence in various movement contexts.

To the best of our knowledge, no longitudinal study has investigated the stability and reciprocal relationship of objectively measured PA and MC focusing specifically on preschool children. Such studies are important not only from a public health perspective, enabling the design of more effective and properly timed preventive measures or interventions that ultimately inform guidelines and recommendations. Also on the individual level, a thorough understanding of the stability and interplay can help predict performance and identify children with mild to severe delay or impairment of motor development requiring specialized clinical intervention during this crucial window of early childhood. Thus, to move research forward we investigated (a) the cross-sectional association between MC and PA, (b) the individual stability over time and (c) the longitudinal reciprocal relationship of MC and PA in preschool children. Because some evidence suggests that besides quantity of PA the intensity may affect the relationship between PA and MC, we used two different constructs of PA [total PA (TPA) and moderate-to-vigorous PA (MVPA)] (2). We also examined a potential moderating effect of sex and age group (younger vs. older) on the aforementioned research questions.

Abbreviations: BMI, body mass index; CFA, confirmatory factor analysis; CFI, comparative fit index; cpm, counts per minute; FIML, full information maximum likelihood; ISEI, international socio-economic index; MAR, missing at random; MC, motor competence; MCAR, missing completely at random; min, minute; MVPA, moderate-to-vigorous physical activity; PA, physical activity; RMSEA, rfoot mean square error of approximation; SD, standard deviation; SES, socio-economic status; SRMR, standardized root mean square residual; TPA, total physical activity.

MATERIALS AND METHODS

Study Population

Data presented in this work are drawn from the Swiss Preschoolers' Health Study (SPLASHY; ISRCTN41045021), a multi-site prospective cohort study including 555 2- to 6 year-old preschool-aged children from 84 childcare centers located in five cantons of Switzerland (covering 50% of the Swiss population in 2013). Sampling of childcare centers was stratified according to one stratum with four levels: urban community and rural community with high socio-economic status (SES; above-average) and low SES (below-average), each based on the prevalence of child care centers in the respective communities. In total, 639 child care centers were contacted between January 2013 and October 2014, of which 126 child care centers agreed to participate and to inform the parents. Forty-two centers were excluded after the preparation of testing dates due to too few (less than two) participating children (78%) or for other reasons (12%). Data collection in childcare centers was conducted in 2014 and 1 year later by the same study team in parallel at all study sites. Children recruited in 2014 ($n = 476$) had a follow-up assessment 1 year later. Those recruited in 2015 ($n = 79$) had a baseline assessment only. Both baseline (T0) and follow-up (T1) data are used in the current study. Ethical approval is in accordance with the Declaration of Helsinki and has been obtained from all local ethical committees (No 338/13 for the Ethical Committee of the Canton of Vaud as the main approving authority). Children and parents provided oral and written informed consent. A detailed description of the study design has been published elsewhere (22).

Measures

Physical Activity

PA was objectively monitored on seven consecutive days using a hip-worn accelerometer (wGT3X-BT, ActiGraph, Pensacola, FL, USA). Participants were instructed to wear the monitor 24 h/day except during water-based activities. A sampling frequency of 30 Hz was used. Accelerometer data were downloaded in 3-s epochs and aggregated to 15 s epochs. Nighttime hours (9 pm to 7 am) and non-wear periods, defined as $\geq$20 min of consecutive zero counts on all axes (23), were excluded. A monitoring day was considered valid if at least 10 h of activity were recorded. PA outcome data were expressed as counts per minute [cpm] for TPA and min/day for MVPA (defined as $\geq$420 counts per 15 s) (24). Since at both time points TPA and MVPA did not differ between participants who provided at least 3 valid days including 1 weekend day (baseline: 91 %, follow-up: 89 %), and those with less days of recording, all participants were included in analysis.

Motor Competence

After measuring height and body weight by standard procedures, MC was assessed using the Zurich Neuromotor Assessment 3–5 (ZNA 3-5) (25, 26), which is based on the original ZNA for children older than 5 years (ZNA 5–18) (27, 28). The ZNA 3-5 is a well-standardized motor test instrument with good intra-observer (0.56–1.00) and inter-observer (0.42–0.99) reliability, while test-retest reliability is lower in some tasks (0.35–0.84) (25). Five components were used to capture gross motor proficiency: static balance, walking on a straight line, sideward jumping, hopping on one leg and running. All tasks were videotaped, which allowed offline rating. The examiner explained and demonstrated each task. If children did not understand the task or did something different, the demonstration was repeated. In case of a second failure, the examiner scored the task as "failed" and continued the assessment. Instructions for the tasks were as follows: (1) Static balance: Children were asked to do a one-leg stand for as long as possible. Time counting started as soon as the child lifted one foot off the floor and stopped when the child touched the floor with the lifted foot or shifted the foot of the standing leg more than 2 cm. The same procedure was repeated for the other leg. A qualitative score from 0 to 4 was given: 0 = one-leg stand more than 5 s on both legs; 1 = one-leg stand more than 5 s on only one leg; 2 = one-leg stand between 2 and 5 s on both legs; 3 = one-leg stand between 2 and 5 s on only one leg; 4 = not able to stand on either leg for more than 2 s. (2) Walking on a straight line: Children were asked to walk on a straight line consisting of an elastic band placed on the floor putting one foot in front of the other such that the heel of the front foot touched the toes of the back one. Rating included a qualitative score from 0 to 4: 0 = perfect performance, heel touches toes; 1 = feet straight on the line but gap between the feet; 2 = feet not straight and/or off the line up to 3 times; 3 = feet perpendicular and/or feet off the line more than 3 times; 4 = not able to walk on the line. (3) Jumping sideways: Children were asked to jump sideways over the elastic band back and forth keeping the feet together. Rating included a qualitative score from 0 to 4: 0 = perfect performance, very smooth jumping; 1 = jumping performed correctly but not very smoothly; 2 = touchdown with both feet at the same time, stiff movements; 3 = total body involvement, poor coordination in relation to the band direction; 4 = Jumping over the elastic band but not in relation to the band direction. (4) Hopping on one leg: Children were asked to hop as many times as possible on one leg. Two trials per leg were given. Rating included a qualitative score from 0 to 4: 0 = hopping on both legs more than 7 times; 1 = hopping on only one leg more than 3 times; 2 = hopping on both legs up to 3 times; 3 = hopping on only one leg 1–3 times; 4 = cannot hop on either leg. (5) Running: Children were asked to run around the cord (at least 20 meters). Rating included a qualitative score from 0 to 4: 0 = rolling motion of feet with adjustment of upper body; 1 = rolling motion of feet, stiff upper body; 2 = running with partial rolling motion of feet; 3 = running without rolling motion of feet; 4 = cannot run (no flight phase).

Statistical Analyses

Statistical analyses were performed using R version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria). Descriptive statistics are presented as mean [standard deviation [SD]] and ranges for continuous variables and percentages for categorical variables, unless stated otherwise. Participants without PA and MC data were excluded from the analysis ($n = 5$), resulting in a sample of 550 individuals. Q-Q plots and frequency distributions were used to check for normal distribution and potential outliers. MC measures were standardized and expressed as standard deviation scores calculated from age- and sex-adjusted normative values to receive identical metrics across tasks. PA was also age- and sex-standardized to account for known age and sex effects. Thus, positive values correspond to above average performance or PA, respectively, and negative values indicate below average measurements within the same sex and age group. To investigate the hypothesized reciprocal longitudinal relationship between MC and PA, a latent variable cross-lagged panel model using structural equation modeling was created, where MC was represented through a latent construct (29). The latent constructs were first verified as separate measurement models with confirmatory factor analysis (CFA). The CFA and latent variable cross-lagged panel model were performed using the package lavaan (30). Full information maximum likelihood (FIML) was used to handle missing data and results were compared to a complete case analysis ($n = 218$). FIML is known to lead to unbiased estimates if the data are either missing completely at random (MCAR) or missing at random (MAR) whereas complete case analysis requires MCAR for unbiased estimates and suffers from reduced power due to reduction in sample size. In line with previous recommendations, good model-data fit was characterized by a non-significant $\chi 2$-test statistic, a standardized root mean square residual (SRMR) <0.08, a root mean square error of approximation (RMSEA) <0.06, and a comparative fit index (CFI) >0.90 (31). Bootstrapping was used to ensure robustness of model fit indices (500 bootstrap replications) (32, 33). Estimated paths were adjusted for accelerometer wear time. Additional analyses were conducted to further evaluate the robustness of our findings: (1) Multigroup structural equation modeling was applied to investigate whether sex or age group (younger vs. older children by using the sample median) moderated the relationship between PA and MC, (2) Estimated paths were additionally controlled for SES and excess body weight to exclude potential confounding. SES was assessed using the International Socio-Economic Index of occupational status (ISEI) (34, 35), which assigns values between 16 (manual labor in agricultural sector) and 90 (judge) to job titles with respect to education and income. BMI z-scores, calculated based on the World Health Organization growth charts were used as an indicator for body fatness. The statistical significance level alpha was set at 0.05.

TABLE 1 | Characteristics of participants at baseline and follow-up ($n = 550$).

	Baseline		Follow-up	
	Mean (SD)	**Range**	**Mean (SD)**	**Range**
Age (years)	3.9 (0.7)	2.2–6.6	4.9 (0.7)	3.2–7.6
BMI z-score[a]	0.4 (1.0)	−4.0–4.7	0.3 (0.9)	−3.3–5.4
SES	62.9 (15.5)	17.0–89.0	62.5 (15.5)	17.0–89.0
Monitor wear time [h/day]	12.8 (0.7)	10.2–14.0	13.0 (0.9)	10.2–14.0
TPA [cpm]	623 (153)	243–1,331	643 (154)	260–1,797
MVPA [min/day]	92 (29)	26–206	97 (28)	19–201
Walking[b]	2.2 (0.8)	0–4	1.8 (0.8)	0–4
Jumping[b]	2.6 (1.0)	0–4	2.0 (1.2)	0–4
Hopping[b]	2.4 (1.4)	0–4	1.2 (1.3)	0–4
Running[b]	2.4 (0.8)	0–4	1.9 (0.6)	0–4
Static balance[c] [sec]	8.0 (8.0)	2–75	12.4 (10.4)	2–88

[a]Based on WHO growth standards (36). [b]Measured on an ordinal scale, lower scores indicate better performance; [c]based on dominant leg, longer duration indicates better performance; BMI, Body mass index; SES, Socioeconomic status; TPA, Total physical activity; cpm, counts per minute; MVPA, moderate-to-vigorous physical activity.

RESULTS

Descriptive statistics are shown in **Table 1**. The sample comprised 550 preschool children (47% boys) aged 3.9 (0.7) years at baseline and 4.9 (0.7) at follow-up. Comparisons between baseline and follow-up measurements demonstrated that on average children performed better in MC tests and were more physically active at follow-up (all $p < 0.05$, paired t-tests). All children met the guidelines of at least 180 min of any PA per day at both time points (37–39). There were no differences in baseline demographic characteristics (age, SES, BMI) between children with complete and incomplete data (data not shown). Both MC measurement models (baseline and follow-up) showed a good fit; $\chi 2(5) = 0.59$, $p = 0.99$; SRMR = 0.01; RMSEA = 0.00; CFI = 1.00 and $\chi 2(5) = 1.16$, $p = 0.76$; SRMR = 0.01; RMSEA = 0.00; CFI = 1.00. Similarly, the latent variable cross-lagged panel models with TPA [$\chi 2(45) = 41.05$, $p = 0.47$; SRMR = 0.02; RMSEA = 0.00; CFI = 0.99] and MVPA [$\chi 2(45) = 39.11$, $p = 0.46$; SRMR = 0.03; RMSEA = 0.00; CFI = 0.99] demonstrated good overall fit. No *post-hoc* modifications were conducted.

Figure 1 depicts the latent variable cross-lagged panel models for TPA (A) and MVPA (B), respectively, for the whole group. MC was highly stable over time with an autoregressive coefficient of $\beta = 0.82$ ($p < 0.001$). Both TPA and MVPA showed moderate stability, autoregressive coefficients were $\beta = 0.37$ ($p < 0.001$) and $\beta = 0.48$ ($p < 0.001$), respectively. Cross-lagged coefficients between PA and MC were very small and not significant [standardized coefficients for the effect of TPA at baseline on MC at follow-up: $\beta = 0.02$ ($p = 0.77$), for the effect of MC at baseline on TPA at follow-up $\beta = 0.10$ ($p = 0.25$)]. A significant but weak cross-sectional association of MC with TPA and MVPA was found at baseline [$r = 0.24$ ($p < 0.001$) and $r = 0.23$ ($p = 0.001$), respectively]. Multigroup analyses revealed that neither age group nor sex had a moderating effect on the relationships between MC and PA in the model. Furthermore, adjusting for SES and BMI z-score did not change the observed effects.

DISCUSSION

To the best of our knowledge, this is the first study to examine both the stability and reciprocal relationship of MC and PA within a relatively large cohort of preschoolers using objective measures. We found that at this young age, children demonstrated diverse levels of MC and PA that were unrelated. Individual stability, i.e., the tendency to maintain the same relative position within a cohort, was relatively high for MC and moderate for PA over a 1 year period. Our findings suggest that

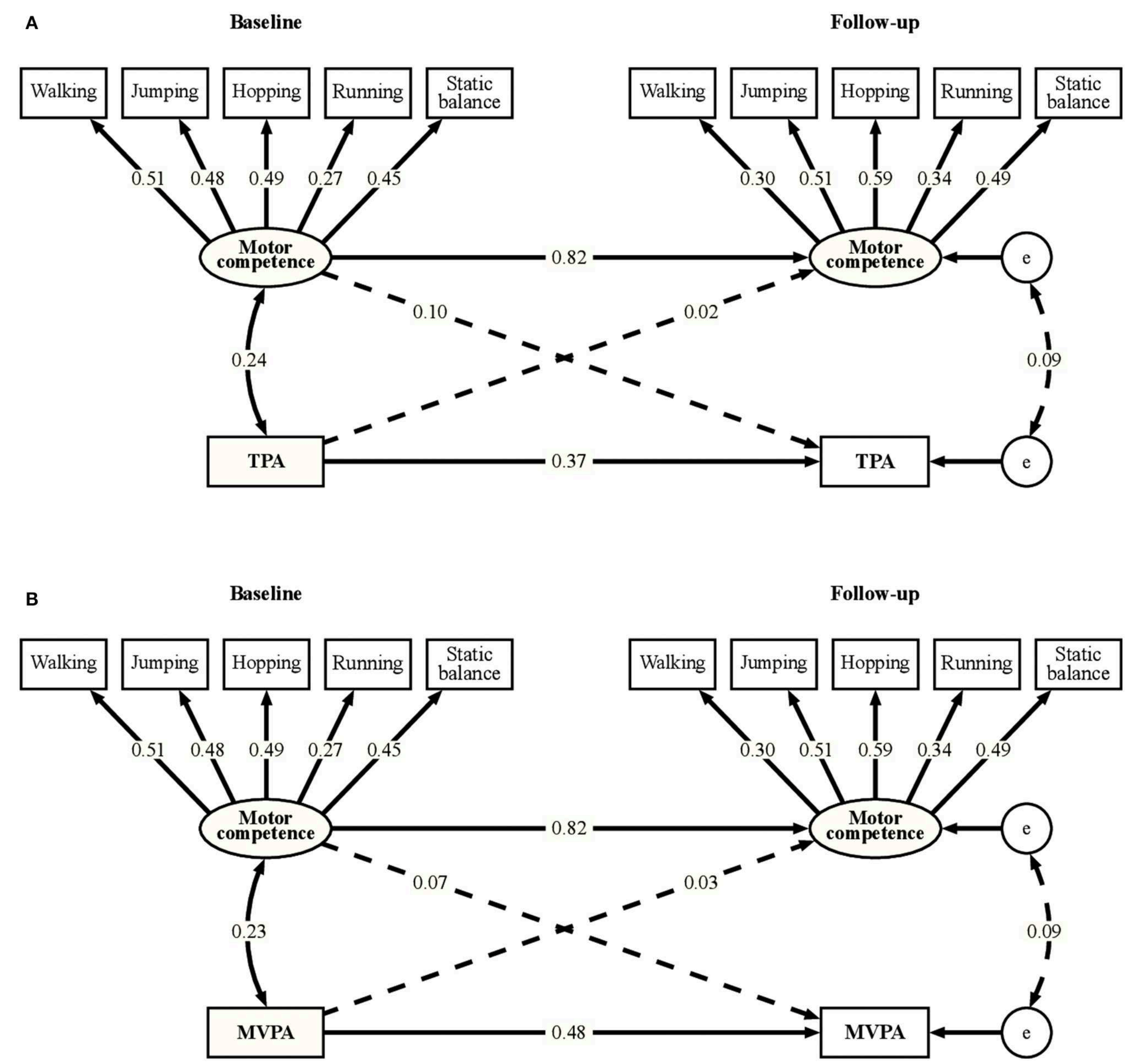

FIGURE 1 | Latent variable cross-lagged panel models for total physical activity **(A)** and moderate-to-vigorous physical activity **(B)**. TPA, Total physical activity; MVPA, moderate-to-vigorous physical activity; e, error term. Solid lines indicate paths significant at $p < 0.05$, non-significant paths are presented as dashed lines. Numbers are standardized coefficients. Correlations between residuals of indicator variables are not shown for simplicity.

MC and PA develop independently of each other and track over time during the period of early childhood.

Although we found a significant but weak cross-sectional association between PA and MC, analysis of cross-lagged effects indicated that PA was not predictive of MC in early childhood or vice versa. Previous cross-sectional studies in preschoolers found similar results (21, 40, 41). A study of 394 3–5 year-old children (40) reported slightly lower but significant positive correlations of TPA ($r = 0.10$) and percent time in MVPA ($r = 0.18$) with total movement skills. Others found similar correlations with total movement skills (MVPA, $r = 0.20$; VPA, $r = 0.26$) (41) and dynamic balance skills (TPA, $r = 0.20$; MVPA, $r = 0.22$) (21). The only study examining the longitudinal relationship in young children ($n = 185$) found that MVPA at 3.5 years predicted locomotor skills, but not object control skills or total skill competence, at age 5 (15). Investigations in older children reported mixed results (16–20), which further illustrates that the nature and strength of the relationship may not be straightforward. A possible explanation for our null result is the way through which

PA was operationalized. Although habitual PA *per se* may be important for some health-related outcomes, it may not promote MC. Specific types or quality of movement experiences may be required rather than overall movement quantity or intensity. High participation in balancing activities for example would not be represented by high levels of total or moderate-to-vigorous PA, yet would likely be associated with better balancing competence. This idea has previously been confirmed by a study investigating participation in different physical education activities in preschool aged children (42). Similarly, the implementation of planned movement programs was found to be effective at improving MC as compared to "free play" (43, 44). Along the same lines, it is important to consider how MC has been operationalized when analyzing the relationship with PA and comparing results. A systematic review of motor skill correlates found that only some aspects of MC were related to PA (14). While skill composite and motor coordination had a positive association with PA, evidence was indeterminate for object control and locomotor skills. Lastly, the use of different PA assessment tools (self-report, direct observation, or accelerometry) and MC instruments (quantitative vs. qualitative assessment batteries) as well as analysis approaches of PA [choice of epoch length and intensity cut-points (45)] can greatly impact the results.

We further hypothesized that the relationship between MC and PA strengthens as children age. As children transition to middle childhood, the sum of all influences is thought to lead to a positive or negative spiral of engagement that compounds over time (8) and affects health-related risk factors. Individuals with low actual and perceived MC for example will be drawn into a negative spiral of disengagement resulting in reduced sport involvement, low levels of PA or even obesity (8). While 70% of the children in our sample were below the age of 4 at baseline and potentially primarily constrained by endogenous developmental steps of maturation (14), we hypothesized that additional physiological or psychological factors, such as children's perceptions of their own MC, may develop at 5–6 years and influence the relationship. Yet, we did not find the relationship to strengthen as children aged. We assume that a longer time span beyond the fundamental movement skills development period would be required to capture the expected increase in strength of association (8).

Our findings indicated that MC was stable over time during the preschool period whereas PA exhibited moderate stability. Somewhat lower stability coefficients were found for MC in a longitudinal study from 4 to 5 and 6 years (boys: 0.58–0.69, girls: 0.31–0.47; $N = 205$) (11) and similar coefficients were found for PA (10, 46). It is plausible that the lower stability coefficients of PA compared to MC in early childhood are due to different etiological pathways and adaptability to internal and external factors. Habitual PA as a behavior may entail more flexibility and thus greater variation than a construct that at this stage is, at least in part, influenced by biological maturation (7).

Previous literature has not offered a clear answer as to whether the stability and relationship of PA and MC differed by sex (13). Some authors found different developmental trajectories between the two sexes, particularly in later childhood and adolescence, such that girls were more proficient in locomotion components whereas boys scored better in object control tasks (47–50). The MC assessment battery we used did not assess object control/manipulation skills, which could be a possible explanation of why we did not find a moderating effect of sex. However, this difference has often been found in middle childhood and adolescence and basic patterns were shown to be similar in boys and girls during the preschool period (11, 14). This suggests that various opportunities for practice may impact the development of specific skills (14, 43) and that opportunities and motivation for engagement in different context- or skill-specific activities may vary for boys and girls.

Important strengths of this study include (a) the longitudinal panel design, which allowed drawing some conclusions on change over time and direction of association, (b) the relatively large cohort of children from 2 to 6 years covering the whole preschool range, (c) the fact that PA was objectively assessed and MC was videotaped and rated offline by experts and (d) the use of state-of-the-art statistical methods to model latent constructs and test complex reciprocal relationships. Limitations that need to be addressed when interpreting our results include the short follow up time, the fact that not the entire range of motor skills was assessed (e.g., no object control) and that accelerometers likely underestimate PA in preschoolers as water-based and rolling activities are insufficiently reflected (23). Another potential weakness is that MVPA was defined using fixed cut-offs, which has a high probability of misclassification of MVPA because individual variation in such cut-offs. We are confident that taking another cutoff for MVPA would not change the result of the paper as we have also presented data with similar results on total PA that provides a safer way. Although we do not know whether children who do not attend childcare behave differently, the generalizability of our findings may be limited by the fact that our sample included only children who attended childcare at least twice a week.

This is the first longitudinal study that provides evidence on the stability and reciprocal relationship of PA and MC in young children. Based on our findings MC is a stable construct that is not influenced by the quantity or intensity of habitual PA at this early age. To inform the design of effective interventions, future longitudinal studies should examine what type of physical activity is important for motor skill development, how to assess it, and whether the (reciprocal) relationship between PA and MC evolves as children age.

ETHICS STATEMENT

Ethical approval is in accordance with the Declaration of Helsinki and has been obtained from all local ethical committees (No 338/13 for the Ethical Committee of the Canton of Vaud as the main approving authority). Children and parents provided oral and written informed consent.

AUTHOR CONTRIBUTIONS

Conceived and designed the Splashy study: JP, SK, SM, and OJ. Performed data collection: ES, CL-A, AZ, TK, KS, NM-B, and AA. Designed the research, had full access to all data, and take responsibility for the integrity of data and accuracy of data analysis: ES and SK. Assisted in statistical data analysis: AM. Performed data analysis and wrote, reviewed, and edited the manuscript: ES. All authors reviewed, edited, and approved the manuscript.

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