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Physical activity and exercise among children: Health implications

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Physical activity and exercise among children: Health implications

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Effects of Extreme Weight Loss on Cardiometabolic Health in Children With Metabolic Syndrome: A Metabolomic Study

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Objectives: To evaluate the effect of extreme weight loss programs on circulating metabolites and their relationship with cardiometabolic health in children with metabolic syndrome.

Methods: This study was a quasi-experimental design with a pretest and post-test. Thirty children with metabolic syndrome and aged 10–17 years were recruited to an extreme weight loss program (i.e., exercise combined with diet control). The primary outcomes included plasma metabolites, body composition, and cardiometabolic risk factors. A total of 324 metabolites were quantitatively detected by an ultra-performance liquid chromatography coupled to tandem mass spectrometry system, and the variable importance in the projection (VIP) value of each metabolite was calculated by the orthogonal projection to latent structures discriminant analysis. The fold change (FC) and *p* value of each metabolite were used to screen differential metabolites with the following values: VIP > 1, *p* value < 0.05, and |log2FC| > 0.25. Pathway enrichment and correlation analyses between metabolites and cardiometabolic risk factors were also performed.

Result: A large effect size was observed, presenting a weight loss of –8.9 kg (Cohen's $d = 1.00$, $p < 0.001$), body mass index reduction of –3.3 kg/m^2 (Cohen's $d = 1.47$, $p < 0.001$), and body fat percent reduction of –4.1 (%) (Cohen's $d = 1.22$, $p < 0.001$) after the intervention. Similar improvements were found in total cholesterol (Cohen's $d = 2.65$, $p < 0.001$), triglycerides (Cohen's $d = 2.59$, $p < 0.001$), low-density lipoprotein cholesterol (Cohen's $d = 2.81$, $p < 0.001$), glucose metabolism, and blood pressure. A total of 59 metabolites were changed after the intervention (e.g., aminoacyl-tRNA biosynthesis, glycine, serine, and threonine metabolism; nitrogen metabolism, tricarboxylic acid cycle, and phenylalanine, tyrosine, and tryptophan biosynthesis). The changes in metabolites (e.g., amino acids, fatty acids, organic acids, and carnitine) were related to lipid metabolism improvement ($p < 0.05$). Organic acids and carnitines were associated with changes in the body composition ($p < 0.05$).

Conclusion: Exercise combined with dietary control improved the body composition and cardiometabolic health in children with metabolic syndrome, and these changes may be related to plasma metabolites.

Keywords: children with obesity, metabolic syndrome, metabolomics, exercise, cardiometabolic health

INTRODUCTION

Childhood obesity is closely related to the clustering of cardiometabolic risk factors, such as dyslipidemia, hypertension, and insulin resistance, which contribute to the development of metabolic syndrome and an increased risk of developing co-morbidities, including type 2 diabetes and cardiovascular disease in adulthood (Juonala et al., 2011; Buscot et al., 2018). Weight loss is an effective strategy for reducing cardiometabolic risk in children with metabolic syndrome. Physical activity, which has attracted increasing amount of attention, can not only effectively reduce weight but also improve cardiometabolic health and increase cardiovascular fitness (Dias et al., 2018; Hansen et al., 2018; Labayen et al., 2020; Fridolfsson et al., 2021). A randomized controlled trial by Davis et al. also showed that moderate-intensity aerobic exercise (heart rate approximately 150 beats/min) reduced body composition and the risk of diabetes effectively and improved glucose metabolism in overweight and obese children (Davis et al., 2012). Moreover, a recent meta-analysis showed that high-intensity and moderate-intensity exercises can reduce body weight and improve cardiometabolic health in obese children (Liu et al., 2020). These findings suggest that moderate- or high-intensity exercises benefit the reduction of weight and promotion of cardiometabolic health in obese children. Furthermore, emerging evidence has shown that extreme weight loss programs that combine exercise with diet control can lead to a great weight loss in a short period of time. Hutchesson et al. discovered that an 8-week Biggest Loser Club with −500 kcal/day less than the estimated energy expenditure resulted from an exercise combined with diet intervention can reduce weight by −4.5 kg (Hutchesson et al., 2013). Kerns et al. (2017) observed that diet restriction and vigorous physical activity intervention in the Biggest Loser Competition can achieve rapid weight change. However, the effects of extreme weight loss programs on cardiometabolic health have been inconsistent between studies (Liu et al., 2015; Xu et al., 2018; Yang et al., 2018), and most of the research to date has focused on the effects of extreme weight loss programs on weight loss and cardiometabolic health; furthermore, discussion on the underlying mechanisms is still lacking.

Metabolomics is defined as an "omics" technology characterized by the high-throughput identification and quantification of small-molecule (<1,500 Da) metabolites in a cell, tissue, blood, or organism (Nicholson et al., 1999; Johnson et al., 2016). Plasma metabolites were early diagnostic markers for obesity-related type 2 diabetes and cardiovascular disease (Meyer et al., 2018; Short et al., 2019; Perng et al., 2020), plasma branched-chain amino acids (BCAAs), aromatic amino acids (AAAs), acylcarnitine, and incomplete oxidized lipid metabolites, which are associated with metabolic abnormalities in children with obesity (Newgard, 2012; Wahl et al., 2012; McCormack et al., 2013; Zhou et al., 2019). However, whether extreme weight loss programs can cause changes in small-molecule metabolites, and whether changes in small-molecule metabolites are associated with weight loss and cardiometabolic health improvement in children with metabolic syndrome remain unclear. Thus, this study aimed to evaluate the effects of extreme weight loss programs on circulating metabolites and their relationship with cardiometabolic health in children with metabolic syndrome.

MATERIALS AND METHODS

Study Design and Participants

From June 2019 to August 2019, 30 children with metabolic syndrome were screened and recruited from 103 obese children aged 10–17 years who participated in the Biggest Loser Training Camp (Shenzhen, China). Metabolic syndrome was defined under the definition and prevention and treatment of metabolic syndrome in Chinese children and adolescents (Liang Li and Fu Junfen, 2012); children with central obesity were defined to have a waist circumference (WC) higher than the 90th percentile for age and sex, and they should meet any two of the following criteria: fasting plasma glucose (FPG) ≥ 5.6 mmol/L; high-density lipoprotein-cholesterol (HDL-c) < 1.03 mmol/L or non-HDL-c ≥ 3.76 mmol/L; hypertension defined as systolic blood pressure (SBP) or diastolic blood pressure (DBP) in the 95th percentile or higher for age and sex; triglyceride (TG) ≥ 1.47 mmol/L. All children and their parents were notified of the benefits and potential risks in this study before the intervention. A written informed consent was obtained from all children and their parents, and the study protocol was approved by the Ethical Committee of the Guangzhou Sport University (No. 2018LCLL-008).

The present study was a quasi-experimental design with pretest and post-test. The participants performed a standardized exercise combined with diet control under an extreme weight loss intervention for 30 days. To ensure then-effective implementation of the intervention, experienced coaches and researchers were tasked to manage the participants and monitor and record the exercise and diet intake. Anthropometric data, body composition, and cardiometabolic risk factors (i.e., blood glucose, blood lipid, and blood pressure) were measured at pre- and post-intervention. The pretest was performed before the beginning of the extreme weight loss intervention, whereas the post-test was conducted 12 h after the last exercise training.

Standardized Exercise Combined With Diet Control

Diet Control

The participants were instructed to follow a regular diet habit, with breakfast from 8:00 to 8:30, lunch from 11:30 to 12:00, and dinner from 17:30 to 18:00. The diet control of each participant was designed based on the resting energy expenditure (REE). The REE was measured for each participant before the intervention using indirect calorimetry methods. The concentrations of O_2 and CO_2 were measured by a gas metabolizer (Cortex Meta Max 3B, Germany) for 15 min. Weir's equation was used to calculate the REE and resting metabolic rate (RMR): $REE(kcal/min) = 3.9 * VO_2(L/min) + 1.1 * VCO_2(L/min)$; $RMR(kcal/day) = REE * 1440$. To match the dietary intake with RMR, nutrition experts designed the diet in accordance with the Chinese Food Composition Table compiled by the Chinese Center for Disease and Prevention. The types of food included fruits, vegetables, grains, legumes, eggs, meat, and dairy products. The ratios of energy intake for breakfast, lunch, and dinner were 30, 40, and 30%, respectively.

Exercise Intervention

The exercise intervention was the main part of the extreme weight loss intervention, and it lasted for 240 min per day from 09:30 to 11:30 am and 15:30 to 17:30 pm. To ensure that all participants performed the exercise intervention effectively, we confirmed that the design of the exercise intervention program followed the principles of individuation, gradualism, interest, and safety. Considering the results of current studies mentioning that moderate- or high-intensity exercise can effectively improve the cardiometabolic health of obese children, the exercise intensity of the extreme weight loss intervention was mainly that of a moderate-intensity aerobic exercise combined with a short period of high-intensity exercise. The exercise types were mainly outdoor hiking, fast walking, jogging, sports games, aerobic exercises, recreational ball games, etc. The exercise intensity was monitored by heart rate, and the participant's heart rate during exercise was kept in the range of 50–80% HR_{max}. During the exercise intervention, researchers observed the participants' response to the exercise intervention and recorded and adjusted the exercise intensity based on the conditions of each participant. Each training session started with a 30-min warm-up, followed by an 80-min training session, and ended with a 10-min cooldown session. All exercise sessions were supervised by a qualified conditioning coach. **Supplementary Table S1** shows the detail of diet control.

Data Collection and Procedure

Anthropometric Measurements and Body Composition

Anthropometric measurements, including weight, height, WC, hip circumference (HC), waist-to-hip ratio (WHR), and waist-to-height ratio (WHtR), were performed for all children at pretest and post-test. Height was measured to the nearest 0.1 cm using a standard height meter, and weight was measured to the nearest 0.1 kg on a digital scale. Body mass index (BMI) was calculated by weight in kilograms divided by the square height in meters. Waist circumference was measured to the nearest 0.1 cm using a plastic tape while maintaining the measuring tape level. WHR was calculated by WC (cm) divided by HC (cm), and WHtR was calculated as WC (cm) divided by height (cm). Whole-body composition measurements, including fat-free mass (FFM), fat mass (FM), skeletal muscle mass (SMM), and body fat percentage (BFP), were measured using a body composition analyzer (T-SCAN PLUS, Korea). Anthropometric measurements and body composition assessment were performed by an expert with 2 years of background experience following the standard measurement methods. The body composition measurements were obtained in the morning (08:00–09:00 am) without eating.

Cardiometabolic Risk Factor Measurement

Blood pressure was measured thrice by an electronic blood pressure monitor (OMRON HEM-1020, China) in the morning after sitting for 10–15 min. The mean of the closest two tests was used to record the SBP and DBP. Mean arterial pressure (MAP) was calculated from the SBP and DBP with the following formula: MAP = DBP + (SBP-DBP)/3. With heparin sodium as an anticoagulant, the fasting plasma samples were acquired *via* the antecubital vein at baseline and again at 12 h after the last intervention at 30 days. After standing for 30 min, the plasma was separated by centrifugation at 4°C (10 min at 1000 g), frozen in liquid nitrogen, and stored at −80°C. The concentrations of HDL-c, low-density lipoprotein cholesterol (LDL-c), TG, and total cholesterol (TC) were measured by enzymatic assay. The FPG was measured using the glucose oxidase method. Fasting insulin (FIN) was measured using the enzyme-linked immunosorbent assay. Homeostatic model assessment for insulin resistance (HOMA-IR) was performed using the following formula.

$$HOMA - IR = \frac{FINs(\mu U/L) * FPG(mmol/L)}{22.5}$$

Metabolomic Analysis

An ultra-performance liquid chromatography coupled to tandem mass spectrometry (UPLC-MS/MS) system (ACQUITY UPLC-Xevo TQ-S, Waters Corp., Milford, MA, United States) was used to quantitatively determine 324 metabolites, including carbohydrates, amino acids, fatty acids, organic acids, and bile acids (Xie et al., 2021).

The standard compounds of 324 metabolites and stable isotope-labeled internal standards were obtained from Sigma-Aldrich (St. Louis, MO, United States), Steraloids Inc. (Newport, RI, United States) and TRC Chemicals (Toronto, ON, Canada). **Supplementary Table S2** shows the details of all metabolites. Methanol (Optima LC-MS), acetonitrile (Optima LC-MS), and isopropanol (Optima LC-MS) were commercially purchased from Thermo-Fisher Scientific (Fairlawn, NJ, United States). Formic acid was analytically pure and obtained from Sigma-Aldrich (St. Louis, Mo, United States). The ultrapure water was produced by a Mill-Q reference system equipped with a LC-MS Pak filter (Millipore, Billerica, MA, United States). All standard components were weighed and dissolved in water, methanol, sodium hydroxide solution, or hydrochloric acid solution to obtain a single, standard component reserve solution with a concentration of 5.0 mg/mL. An appropriate amount of each standard component reserve solution was used to prepare a mixed standard component reserve solution.

To diminish sample degradation, we thawed the plasma sample on an ice bath and added 25 µl of it to a 96-well plate. Then, 100 µl ice-cold methanol with a partial internal standard was automatically added to each sample at Biomek 4,000 workstation (Biomek 4,000, Beckman Coulter, Inc., Brea, California, United States) and mixed for 5 min after intense vortexing. Next, the samples were centrifuged for 30 min at 4000 g/min (Allegra X-15R, Beckman Coulter, Inc., Indianapolis, IN, United States).

A total of 30 μl supernatant was transferred to a clean 96-well plate, and 20 μl freshly prepared derivative reagents were added to each well in the workstation. The 96-well plate was sealed and followed by derivatization, which was carried out at 30°C for 60 min. After derivatization, the sample was diluted with ice-cold 50% methanol solution in 350 μl. The plates were placed at −20°C for 20 min and then centrifuged at 4°C (4,000 g, 30 min). The supernatant (135 μl) was transferred to a new 96-well plate with 15 μl internal standard to each well. Finally, the serial dilutions of derivatized stock standards were added to the left of the 96-well plate and sealed for analysis.

ACQUITY UPLC BEH C18 1.7 μm VanGuard pre-column ($2.1 \times 5\,mm^2$) and ACQUITY UPLC BEH C18 1.7 μm analytical column ($2.1 \times 100\,mm^2$) were used for separation with the column temperature set at 40°C and the sample manager temperature at 10°C. The mobile phases were water with 0.1% formic acid (A) and acetonitrile/IPA (90:10, B). The initial gradient was 5% B and kept for 1 min, increased to 80% B at 12 min, increased to 95% B at 15 min, increased to 100% B at 16 min, kept at 100% B until 18 min, switched back to the initial condition at 18.1 min, and held until 20 min. The flow rate was 0.40 ml/min, and the injection volume was 5.0 μl. The capillary voltages were 1.5 (ESI+) and 2.0 Kv (ESI−), and the source temperature was set at 150°C. The desolvation temperature was set at 550°C with a desolvation gas flow rate of 1,000 L nitrogen per hour.

QuanMET software (v2.0, Metabo-Profile, Shanghai, China), which can perform peak integration, calibration, and quantitation for each metabolite, was used to process the raw data generated by UPLC-MS/MS.

Quantification and Statistical Analysis

The Shapiro–Wilk and Kolmogorov–Smirnov tests were used to determine the normality of data distribution. The continuous variables were reported as means ± standard deviation (*SD*) with normal distribution, whereas the median and interquartile range (IQR) were applied to denote the non-normally distributed data. The baseline characteristics between boys and girls were compared with an independent sample t test for normally distributed continuous variables. Paired sample t test and Mann–Whitney test were used for comparison before and after intervention depending on data normality. For each outcome, the effect size (Cohen's *d*) was calculated as $\text{Cohen s}\, d = (pre\_test - \text{post\_test}) / pooled\,SD$ and defined as trivial (<0.2), small (≥ 0.2, < 0.5), moderate (≥ 0.5, < 0.8), and large (≥ 0.8). Statistical analysis was performed with SPSS version 20.0 (SPSS, Inc., Chicago, IL, United States), and the statistical significance level was set at 0.05.

Multivariate statistical analyses, including principal component analysis (PCA), orthogonal projection to latent structures discriminant analysis (OPLS-DA), and univariate statistical analyses including t test and Mann–Whitney Wilcoxon test (U test), were performed to obtain the differential metabolites. First, PCA was conducted to examine the cluster of samples and identify outliers before and after the intervention. Second, OPLS-DA was performed to visualize the changes between the baseline and post-intervention. A seven-round cross-validation was carried out to validate the model against over-fitting of the OPLS-DA models, and Q2Y, R2X, and R2Y were used to quantify the interpretation of models. Q2Y suggests the model's predictive accuracy, whereas R2X and R2Y represent the fraction of the variance of the X and Y matrixes, respectively. Cumulative values of R2X, R2Y, and Q2Y close to 1.0 indicate an excellent model with a reliable predictive capability. The variable importance in the projection (VIP) value of each metabolite was used as the criterion for metabolite screening. The fold change (FC) was displayed, and the *p* value of each metabolite was used to screen differential metabolites. To reduce the error rate, the *p* value of each differential metabolite was adjusted by a false discovery rate (FDR) method in pretest and post-test comparisons. The selection of differential metabolites was based on the following criteria: VIP > 1, p value <0.05, and $|\log2FC| > 0.25$.

Metabolic pathway analysis was performed for differential metabolites to determine which metabolic pathway changed after the intervention, and the metabolic pathway analysis used the HSA sets by Kyoto Encyclopedia of Genes and Genomes (KEGG). Pathway impact was derived from the centrality normalization of the differential metabolite nodes and their sum. The pathway impact score was used to assess the importance of differential metabolites in the metabolic pathway before and after intervention. The greater the pathway impact, the more important the differential metabolites were in the metabolic pathway. To verify whether the differential metabolites were associated with improvements in the body composition and cardiometabolic health, we further performed the Spearman correlation analysis. Statistical algorithms were adapted from the widely used statistical analysis software packages in R studio.[1]

RESULTS

General Characteristics and Changes in Cardiometabolic Risk Factors After Intervention

A total of 103 obese children were recruited from the Biggest Loser Train Camp program, and 30 children, including 18 boys and 12 girls, were selected for metabolic syndrome (**Table 1**). A large effect size was observed in the body composition following intervention, including a weight loss of −8.9 ± 3.42 kg (Cohen's $d = 1.00$, $p < 0.001$), BMI reduction of $-3.3 \pm 1.16\,kg/m^2$ (Cohen's $d = 1.47$, $p < 0.001$), FM reduction of −6.1 ± 2.7 kg (Cohen's $d = 1.33$, $p < 0.001$), and BFP reduction of −4.1% ± 2.1% (Cohen's $d = 1.22$, $p < 0.001$) after the intervention (**Table 2**). Our results also revealed a decrease in body circumference, including $a - 8.6 \pm 4.1$ cm (Cohen's $d = 1.39$, $p < 0.001$) reduction in WC and $a - 7.3 \pm 3.4$ cm (Cohen's $d = 1.32$, $p < 0.001$) reduction in HC (**Table 2**). Our results also showed an improvement in cardiometabolic health and body composition after the intervention. In terms of lipid metabolism, our results showed that TC, TG, and LDL-c decreased by −1.14 ± 0.75 (Cohen's $d = 2.65$, $p < 0.001$), −1.20 ± 0.64 (Cohen's $d = 2.59$,

[1]http://cran.r-project.org/

TABLE 1 | Baseline participant characteristics.

Characteristics	Boys (*n* =18)	Girls (*n* =12)	Total (*n* =30)	Value of *p*
Age (years)	12.6 ± 1.9	13.3 ± 1.5	12.9 ± 1.8	0.318
Height (cm)	167.4 ± 10.7	158.4 ± 8.2	163.8 ± 10.6	0.020
Weight (kg)	87.7 ± 18.0	80.5 ± 12.3	84.8 ± 16.1	0.239
Body mass index (BMI; kg/m^2)	31.0 ± 4.0	32.02 ± 4.1	31.4 ± 4.0	0.502
RMR (kcal/day)	2445.23 ± 468.35	2129.51 ± 427.51	2318.97 ± 471.86	0.072

Data are expressed as means ± SD; independent sample t test was used for comparison.

TABLE 2 | Changes in clinical characteristics and cardiometabolic risk factors in children with metabolic syndrome.

Outcomes	Pre-intervention	Post-intervention	Changes	Cohen's *d*	Value of *p*
Weight (kg)	84.8 ± 16.1	75.9 ± 14.4	−8.9 ± 3.4	1.00	1.10E-14
BMI (kg/m^2)	31.4 ± 4.0	28.1 ± 3.8	−3.3 ± 1.2	1.47	1.36E-15
FM (kg)	28.8 ± 8.2	22.7 ± 7.4	−6.1 ± 2.7	1.33	3.41E-13
Fat-free mass (kg)	56.0 ± 10.0	53.2 ± 9.4	−2.9 ± 1.5	0.51	2.66E-11
Skeletal muscle mass (kg)	51.2 ± 9.2	48.8 ± 8.6	−2.4 ± 1.4	0.46	2.14E-10
Body fat percentage (%)	33.6 ± 5.4	29.5 ± 6.1	−4.1 ± 2.1	1.22	7.82E-12
WC (cm)	104.9 ± 10.7	96.3 ± 10.4	−8.6 ± 4.14	1.41	3.19E-12
HC (cm)	109.0 ± 9.7	101.7 ± 9.0	−7.3 ± 3.4	1.34	1.33E-12
WHR	0.96 ± 0.08	0.95 ± 0.09	−0.01 ± 0.02	0.20	0.001
WHtR	0.64 ± 0.08	0.59 ± 0.07	−0.05 ± 0.3	1.13	1.08E-11
TC (mmol/L)	4.52 ± 0.78	3.38 ± 0.64	−1.14 ± 0.75	2.65	3.25E-09
TG (mmol/L)	1.91 ± 0.65	0.71 ± 0.25	−1.20 ± 0.64	2.59	3.27E-11
High-density lipoprotein-cholesterol (HDL-c; mmol/L)	1.01 ± 0.21	1.08 ± 0.21	0.07 ± 0.19	0.58	8.60E-02
Low-density lipoprotein cholesterol (mmol/L)	2.75 ± 0.62	1.78 ± 0.56	−0.97 ± 0.60	2.81	8.48E-10
non-HDL-c (mmol/L)	3.51 ± 0.69	2.30 ± 0.56	−1.21 ± 0.64	3.17	2.94E-11
fasting plasma glucose (mmol/L)	5.86 ± 1.01	5.15 ± 0.75	−0.71 ± 1.18	1.26	0.003
FINs	10.80 (5.02)	8.97 (7.75)	−2.26 (6.99)	-	0.006
HOMA-IR	2.69 (1.70)	2.00 (1.99)	−0.58 (1.71)	-	0.002
SBP (mmHg)	113 ± 10	105 ± 10	−7 ± 9	1.39	9.70E-05
DBP (mmHg)	71 ± 8	64 ± 11	−7 ± 6	1.13	4.19E-07
MAP (mmHg)	85 ± 8	78 ± 10	−7 ± 5	1.27	1.54E-08

Continuous variables were reported as means ± (SD) with normal distribution, and the paired sample t test was used to test the differences. FINs and HOMA-IR were reported as median (IQR), and Mann–Whitney test was used to test the differences.

$p < 0.001$), and − 0.97 ± 0.60 mmol/L (Cohen's $d = 2.81$, $p < 0.001$), respectively. Similar to the improvement of lipid metabolism, glucose metabolism, and blood pressure improved after the intervention, whereas FPG, FINs, HOMA-IR, SBP, DBP, and MAP decreased (**Table 2**).

Selection and Identification of Discriminatory Metabolites Related to Metabolic Improvement

All plasma samples were processed and analyzed through UPLC-MS/MS following the standardized protocol, and 204 metabolites were successfully determined in each sample. The relative abundance of each metabolite class (**Supplementary Figure S1**) and the separation of metabolites were evident from the PCA and OPLS-DA results (**Figures 1A,B**).

The scoring plot generated from a cross-validated OPLS-DA model using one predictive component and three orthogonal components further showed a distinct separation (R2Y = 0.921, Q2Y = 0.78; **Figure 1E**), indicating that the OPLS-DA model was stable and effective for fitness and prediction. Compared with the pre-intervention, the volcano plots showed that 64 metabolites were screened based on OPLS-DA with a VIP > 1 (**Figure 1C**). The *t* test or Mann–Whitney test with the *p* value < 0.05 and |log2FC| > 0.25 was also carried out to validate the differential metabolites. The volcano plots showed that 30 metabolites increased, and 54 metabolites decreased after the intervention (**Figure 1D**). With the VIP > 1, *p* value < 0.05, and |log2FC| > 0.25 as screening criteria, 59 differential metabolites were screened (**Figure 1F, Table 3**). The p value of the metabolite in **Table 3** was adjusted by FDR methods, and the results showed that the pFDR of each metabolite was less than 0.05, indicating that the screened differential metabolites were more reliable (**Table 3**).

Pathway and Correlation Analyses for Cardiometabolic Health Improvement

Pathway Analysis

To further explore the changes in the differential metabolites after the intervention, we performed the pathway analysis

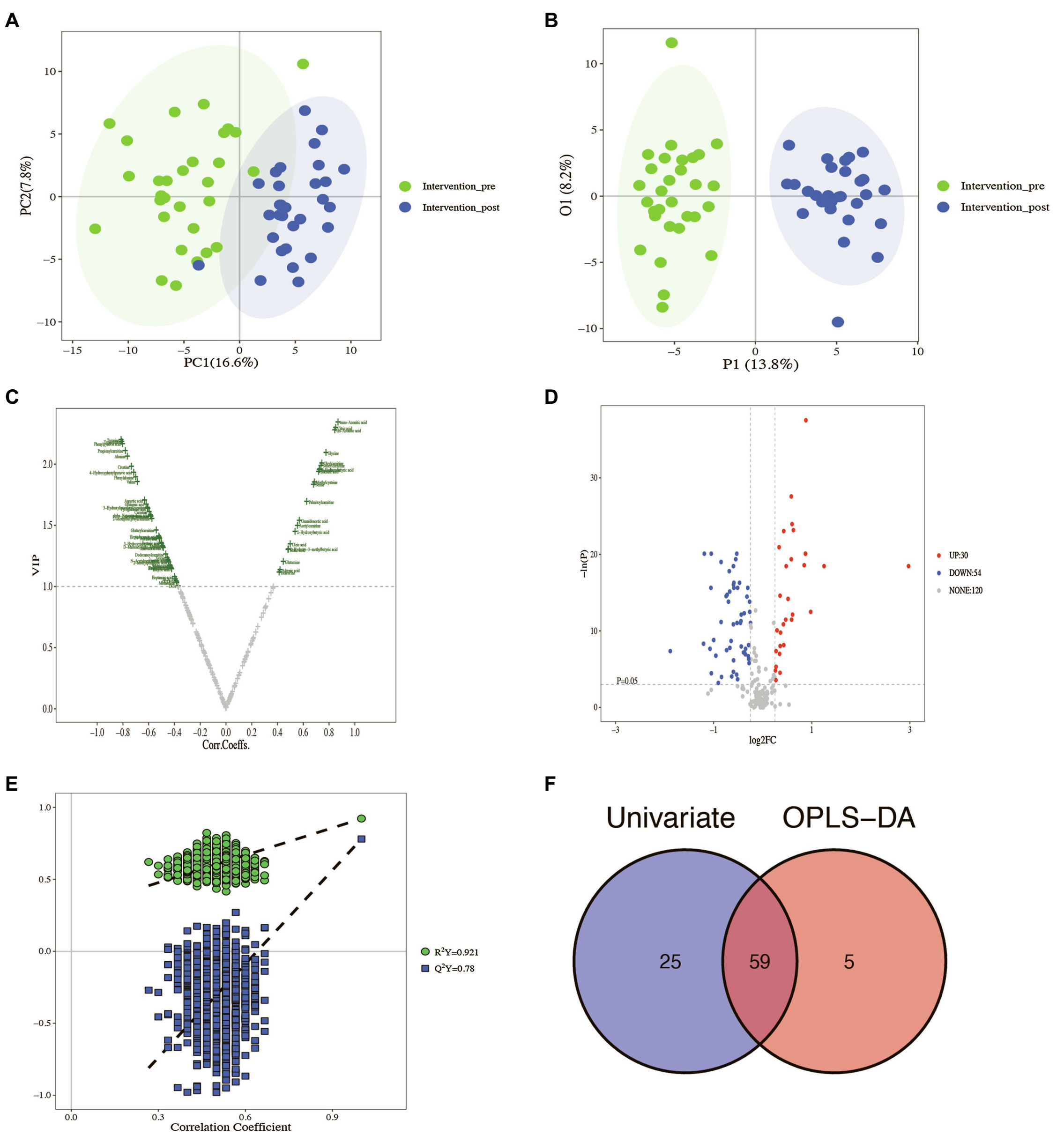

FIGURE 1 | Identification of the potential metabolites between baseline and post-intervention. **(A)** PCA plot; **(B)** OPLS-DA plot; **(C)** volcano plot of OPLS-DA model; **(D)** volcano plot of univariate statistics; **(E)** OPLS-DA permutation plot; **(F)** Venn plot of differential metabolites.

by the KEGG database. A total of 48 pathways were enriched when the 59 differential metabolites were introduced into KEGG (**Figure 2**), and based on ln(p value) and pathway impact scores, the 10 most important pathways, including aminoacyl-tRNA biosynthesis, glycine, serine, and threonine metabolism; nitrogen metabolism, citrate cycle [tricarboxylic acid (TCA) cycle], phenylalanine, tyrosine, and tryptophan biosynthesis; valine, leucine, and isoleucine biosynthesis; glyoxylate and dicarboxylate metabolism; alanine, aspartate, and glutamate metabolism; pantothenate and CoA biosynthesis, and cyanoamino acid metabolism, were enriched (**Supplementary Table S3**).

Correlation Analysis Between Changes in Plasma Differential Metabolites and Cardiometabolic Health

To further explore the changes in differential metabolites association with body composition and cardiometabolic health improvement, we conducted a correlation analysis between 59 potential metabolites and cardiometabolic risk factors; the correlation analysis heat map is shown in **Figure 3**. In our results, a range of different metabolites correlated with the improvements in body composition. The changes in 3-hydroxybutyric acid, isocitric acid, citric acid, trans-aconitic acid, 2-hydroxybutyric acid, pipecolic acid, acetylcarnitine, palmitoyl carnitine, and oleylcarnitine were negatively correlated

TABLE 3 | Changes in potential metabolites in children with metabolic syndrome following the intervention.

Class	Metabolite	Value of *p*	pFDR	FC	log2FC
Amino Acids	Alanine	9.31E-09	1.01E-07	0.6596	−0.6004
Amino Acids	Aspartic acid	1.64E-07	1.24E-06	0.4813	−1.0549
Amino Acids	Creatine	1.86E-09	3.45E-08	0.4381	−1.1908
Amino Acids	Glutamic acid	1.64E-07	1.24E-06	0.6658	−0.5868
Amino Acids	Glycine	3.73E-09	5.85E-08	1.4961	0.5812
Amino Acids	Homocitrulline	1.82E-05	7.35E-05	0.6599	−0.5997
Amino Acids	Isoleucine	1.04E-05	4.92E-05	1.3842	0.4691
Amino Acids	Leucine	4.60E-04	1.42E-03	0.7844	−0.3504
Amino Acids	Methylcysteine	9.31E-09	1.01E-07	2.3801	1.251
Amino Acids	N-Acetylserine	3.79E-06	2.03E-05	0.8329	−0.2637
Amino Acids	Phenylalanine	1.86E-08	1.90E-07	0.6225	−0.6839
Amino Acids	Pipecolic acid	8.56E-09	1.01E-07	1.7982	0.8465
Amino Acids	Pyroglutamic acid	1.02E-07	9.09E-07	0.6617	−0.5958
Amino Acids	Serine	9.44E-11	3.85E-09	1.3458	0.4285
Amino Acids	Tryptophan	1.86E-09	3.45E-08	0.6943	−0.5265
Amino Acids	Tyrosine	3.73E-09	5.85E-08	0.6829	−0.5502
Amino Acids	Valine	5.09E-07	3.25E-06	0.8015	−0.3192
Benzenoids	Phenylpyruvic acid	5.59E-09	8.14E-08	0.5555	−0.8481
Bile Acids	DCA	6.08E-04	1.80E-03	0.2707	−1.885
Carbohydrates	Gluconolactone	9.98E-07	5.82E-06	0.8304	−0.2681
Carbohydrates	Glyceric acid	1.64E-07	1.24E-06	0.8096	−0.3047
Carbohydrates	Maltotriose	4.60E-04	1.42E-03	0.4748	−1.0746
Carbohydrates	Xylose	2.99E-03	7.34E-03	0.8239	−0.2795
Carboxylic acids	2-Methylbutyroylcarnitine	8.01E-08	7.43E-07	0.6657	−0.5869
Carnitines	Acetylcarnitine	1.01E-05	4.90E-05	1.5007	0.5856
Carnitines	Carnitine	1.64E-07	1.24E-06	0.6998	−0.515
Carnitines	Dodecanoylcarnitine	1.60E-05	6.65E-05	0.7302	−0.4537
Carnitines	Glutarylcarnitine	8.01E-08	7.43E-07	0.722	−0.4698
Carnitines	Isovalerylcarnitine	4.71E-07	3.10E-06	0.5972	−0.7437
Carnitines	Oleylcarnitine	1.01E-12	1.03E-10	1.4978	0.5828
Carnitines	Palmitoylcarnitine	7.72E-10	2.62E-08	1.258	0.3311
Carnitines	Propionylcarnitine	1.86E-09	3.45E-08	0.4825	−1.0515
Carnitines	Stearylcarnitine	8.35E-11	3.85E-09	1.5441	0.6268
Carnitines	2-Hydroxy-3-methyl butyric acid	5.14E-06	2.56E-05	1.5201	0.6042
Fatty Acids	Adrenic acid	1.84E-05	7.35E-05	1.3389	0.421
Fatty Acids	Azelaic acid	9.98E-07	5.82E-06	0.6165	−0.6979
Fatty Acids	Heptadecanoic acid	3.86E-07	2.71E-06	0.6052	−0.7244
Fatty Acids	Heptanoic acid	2.02E-03	5.15E-03	0.6635	−0.5918
Fatty Acids	Oleic acid	4.16E-05	1.57E-04	1.2232	0.2906
Fatty Acids	AMP	1.24E-05	5.76E-05	0.7345	−0.4452
Nucleotides	2-Hydroxybutyric acid	3.79E-06	2.03E-05	1.9684	0.977
Organic Acids	trans-Aconitic acid	4.81E-17	9.82E-15	1.8366	0.877
Organic Acids	3-Hydroxybutyric acid	9.31E-09	1.01E-07	7.8566	2.9739
Organic Acids	alpha-Ketoisovaleric acid	1.57E-05	6.65E-05	0.8407	−0.2503
Organic Acids	cis-Aconitic acid	1.86E-09	3.45E-08	1.8296	0.8715
Organic Acids	Citric acid	1.86E-09	3.45E-08	1.8301	0.872
Organic Acids	Guanidoacetic acid	9.42E-09	1.01E-07	1.3953	0.4806
Organic Acids	Isocitric acid	3.95E-11	2.69E-09	1.5129	0.5973
Organic Acids	Malic acid	4.40E-07	2.99E-06	1.2751	0.3506
Organic Acids	Pyruvic acid	1.60E-05	6.65E-05	0.696	−0.5229
Phenols	4-Hydroxyphenylpyruvic acid	2.55E-07	1.86E-06	0.6265	−0.6747
Primary BAs	GCDCA	1.13E-03	3.07E-03	0.5158	−0.955
SCFAs	2-Methylpentanoic acid	5.55E-04	1.69E-03	0.6013	−0.7339
SCFAs	3-Hydroxyisovaleric acid	2.83E-04	9.63E-04	0.8201	−0.2861
SCFAs	Caproic acid	1.72E-03	4.49E-03	0.8195	−0.2871
SCFAs	Propionic acid	4.42E-06	2.31E-05	0.7692	−0.3786
SCFAs	Valeric acid	5.14E-06	2.56E-05	0.7388	−0.4367
Unknown	D-Maltose/Alpha-Lactose	3.45E-04	1.14E-03	0.7389	−0.4365
Unknown	GCA_1	2.32E-04	8.15E-04	0.4336	−1.2056

with the changes in body composition, whereas the changes in valeric acid, glyceric acid, and 2-methylbutyroylcarnitine showed a positive correlation. Correlation analysis of differential metabolites with glucose metabolic outcomes showed that the levels of D-maltose/alpha-lactose were negatively correlated with HOMA-IR and FIN changes. The changes in GCA_1 was positively correlated

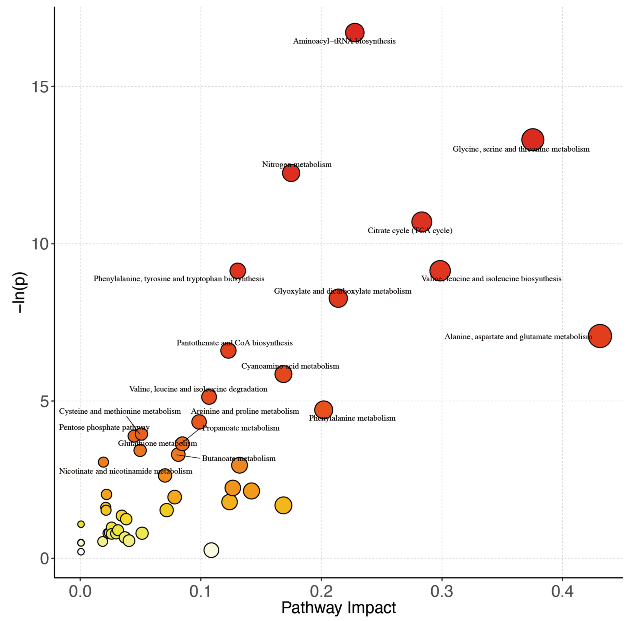

FIGURE 2 | Pathway analysis bubble plot by the HSA set in KEGG. On the horizontal axis is the pathway impact, which represents the importance of differential metabolites in metabolic pathways. The vertical axis is the negative logarithm of *p* value obtained from pathway enrichment analysis. The size of pathway symbols represents the statistical significance level of pathway analysis. The color of pathway symbols represents the impact factor; large sizes and dark colors represent central pathway enrichment and high pathway impact values, respectively.

with the changes in HOMA-IR and FPG, whereas changes in AMP, pyruvic, and alanine were positively correlated with the change in FPG. For the outcomes of lipid metabolism, a positive correlation existed between the changes in TG and a large number of differential metabolites, including GCA_1, tryptophan, alanine, 2-methybutyroycarntine, propionyl carnitine, propionic acid, creatine, isovalerylcarnitine, DCA, pyruvic acid, malic acid, et al. The changes in HDL-c and TC were negatively correlated with leucine. The changes in pyruvic acid, DCA, were positively correlated with the improvement of blood pressure, as observed in our study (**Figure 3**).

DISCUSSION

Obesity is a risk factor for metabolic syndrome, and metabolic syndrome in childhood increases the risk of metabolic diseases in adulthood. Metabolites, as biomarkers for the early diagnosis of diseases, play an important role in revealing the early changes in diseases. Changes in plasma metabolites are closely related to metabolic abnormalities in obese children (Newgard et al., 2009; Wahl et al., 2012; Butte et al., 2015). Although extensive research has been carried out to analyze the effects of extreme weight loss programs, no study evaluated the effect of extreme weight loss programs on circulating metabolites and their relationship with cardiometabolic health in children with metabolic syndrome. To our knowledge, this research is the first study to investigate the effects of an extreme weight loss intervention based on exercise combined with diet control on plasma metabolite profile in children with metabolic syndrome. In our study, the dietary control was designed in reference to RMR. Thus, exercise may play an important role in improving body composition. Our results showed that the body composition and cardiometabolic risk factors improved, and 59 metabolites, including amino acids, fatty acids, carnitine, carbohydrates, and organic acids, were changed after intervention.

Effects of Extreme Weight Loss Intervention on Body Composition and Cardiometabolic Health

In our study, the body composition outcomes, including body weight, BMI, BFP, and FM, decreased after the intervention, with Cohen's *d* greater than 0.8, indicating that the extreme weight loss intervention can cause substantial improvement in body composition. Although moderate-intensity exercise without diet control can reduce the weight of obese children, the effect size is small. Mendelson et al. (2015) observed that a 12-week exercise program consisting of 60–80% VO_{2peak} exercise intensity, 60–120 min train session, and three times/week frequency had a limited effect on weight loss and lipid metabolism. In our study, a large improvement in the body composition might have played an important role in weight maintenance. A great weight loss at the beginning of treatment has been identified as a predictor of long-term weight loss success and maintenance (Nackers et al., 2010). In addition to the improved body composition, our intervention showed an enhancement in glucose metabolism, lipid metabolism, and blood pressure. This finding is consistent with that of Kerns et al. (2017), who reported that diet restriction and vigorous physical activity intervention in the Biggest Loser Competition can achieve the rapid loss of massive weight and that the maintenance of weight loss depends on physical activity changes rather than dietary intake changes during the 6-year follow-up. Liu et al. (2015) discovered that after 4 weeks of aerobic exercise combined with dietary intervention, glucose metabolism parameters, such as FINs, HOMA-IR, and HOMA-β, decreased in obese children, indicating that insulin sensitivity in obese children was effectively improved. Given these results, the extreme weight loss intervention based on exercise combined with dietary control may be a more effective intervention for improving body composition and metabolic health in children with metabolic syndrome.

Effects of Extreme Weight Loss Intervention on Amino Acid Metabolism and Potential Metabolite Pathway

Obesity can cause changes in amino acid metabolism, which is closely related to glucose and lipid metabolism in individuals with obesity (Newgard, 2012; McCormack et al., 2013; Lee et al., 2015). Perng et al. (2014) observed that the concentration of plasma BCAAs in children with obesity was higher than that in children with normal weight, and each unit increase in BCAAs resulted in a corresponding 6% increase in HOMA-IR. BCAAs and AAAs (phenylalanine and tyrosine) together constitute PC6, which is closely related to the occurrence of

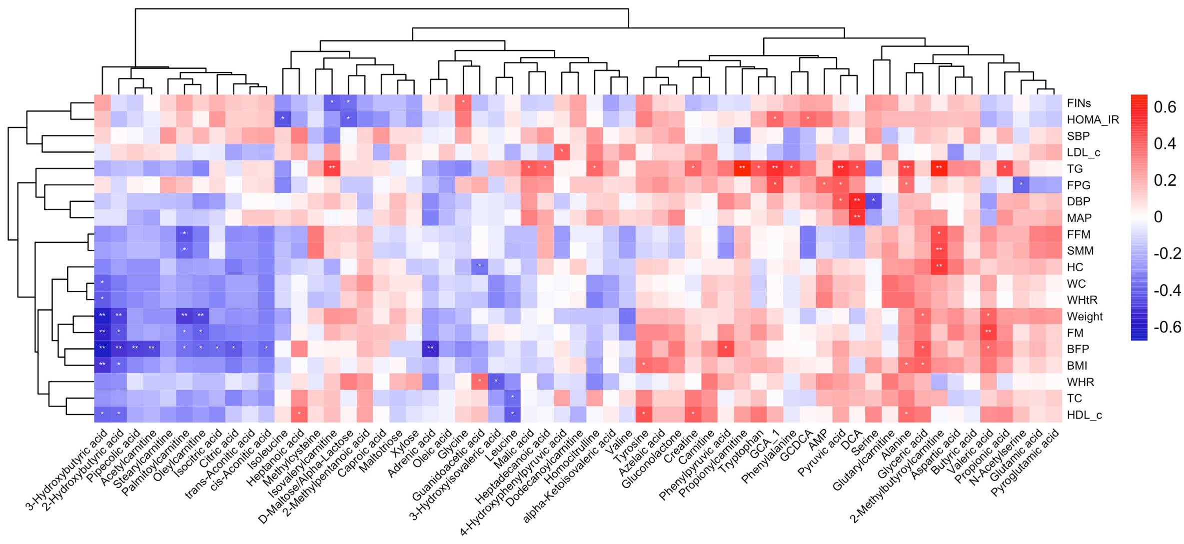

FIGURE 3 | Heat map of the correlations between different metabolites and metabolic improvement. Each square represents the Spearman's correlation coefficient with the statistical significance threshold set at *$p < 0.05$, **$p < 0.01$. Red and blue colors represent positive and negative correlations, respectively.

insulin resistance (Butte et al., 2015). In this study, we observed that BCAAs, including leucine and valine, and AAAs, including tyrosine, phenylalanine, and tryptophan, decreased after the intervention. Given their critical role in insulin resistance, the changes in BCAAs and AAAs may play an important role in maintaining metabolic health. Metabolic pathway analysis further supported this hypothesis and revealed that aminoacyl-tRNA biosynthesis, nitrogen metabolism, phenylalanine, tyrosine, and tryptophan biosynthesis; and valine-leucine and isoleucine biosynthesis were enriched as the most critical metabolic pathways, and BCAAs and AAAs are important metabolites of these metabolic pathways. This finding is consistent with that of Chen et al. (2015), who observed that weight loss was associated with the decrease in BCAAs (leucine and isoleucine) and AAAs (tyrosine and phenylalanine); the decrease in tyrosine and phenylalanine was associated with the improvement of insulin resistance, and this effect was independent of weight change. In our study, we also observed that changes in amino acid metabolites were strongly associated with improved body composition and cardiometabolic risk factors. Aspartic acid and alanine are amino acid metabolites in the aminoacyl-tRNA biosynthesis and alanine, aspartate, and glutamate metabolism, which decreased after the intervention; the change in alanine was positively correlated with the changes in TG, non-HDL-c, TC, BMI, and FPG. This result was consistent with that of Brennan et al. (2018a), who reported that the change in alanine is positively associated with the change in BMI after a regular exercise. A low plasma glycine level is closely correlated with the occurrence of obesity, type 2 diabetes, and non-alcoholic fatty liver disease (Guasch-Ferré et al., 2016; Gaggini et al., 2018), and the level of plasma glycine is positively correlated with insulin sensitivity (Takashina et al., 2016); precursors of glycine, such as trimethylglycine and dimethylglycine, can reduce the risk of diabetes (Svingen et al., 2016). Our results showed that the levels of glycine and serine increased after the intervention, and the change in glycine is positively correlated with HOMA-IR and FIN improvement, suggesting that elevated plasma glycine levels may play an important role in insulin resistance improvement. This finding was also reported by Palmnäs et al. (2018), who observed that low serum serine and glycine levels in adult males were associated with increased body fat and risk of metabolic syndrome, whereas an increased physical activity energy expenditure was positively correlated with increased serum serine and glycine levels.

Effects of Extreme Weight Loss Intervention on Fatty Acid Metabolism

Fatty acid composition can provide valuable information on the diagnosis of diseases and can be used as a biomarker to evaluate disease status (Bogie et al., 2020; Schjødt et al., 2020; Huang et al., 2021). Based on the carbon chain length, fatty acids can be divided into short-chain fatty acids (SCFAs), medium-chain fatty acids, and long-chain fatty acids. SCFAs are vital energy and signaling molecules produced by microbial fermentation (Koh et al., 2016). SCFAs are increasingly being accepted to play an important role in human health. Riva et al. (2017) observed that childhood obesity is associated with altered gut microbiota, and that the levels of SCFAs produced by gut bacteria are higher than those of normal-weight children. The results of Goffredo et al. are consistent with those of Riva's; the plasma concentrations of SCFAs, such as acetate, propionate, and butyrate, were positively correlated with the degree of adiposity in children independent of age, gender, and ethnicity (Goffredo et al., 2016). These results suggest that the increased plasma SCFA concentrations were associated with obesity; several research showed that the association between SCFAs and obesity may be bidirectional, and obesity may have an effect on SCFA metabolism (Sowah et al., 2019). In this study, we observed that five SCFAs, including

3-hydroxyisovaleric acid, propionic acid, valeric acid, 2-methylvaleric acid, and caproic acid, were reduced after the intervention. The changes in propionic acid, valeric acid, and caproic acid were associated with the improvements in TG, weight and FM, and SBP, respectively. The decrease in SCFA after weight loss was similar to that of previous systematic review. Sowah et al. conducted a systematic review and discovered that the decreases in SCFA concentrations may accompany the weight loss induced by bariatric surgery or dietary restriction among overweight and obese adults (Sowah et al., 2019). The decreased in SCFA concentrations in our study may be related to the diet control, because SCFAs are the major products of the anaerobic fermentation of primarily nondigestible carbohydrates by the gut microbiome. In addition, a relatively limited number of studies reported the effects of exercise on intestinal flora and SCFAs. The role of exercise in the reduction of SCFA concentration still needs further study. Furthermore, our results revealed that azelaic acid, heptanoic acid, and heptadecanoic acid decreased, whereas 2-hydroxy-3-methyl butyric acid, adrenic acid, and oleic acid increased following the intervention, indicating that exercise plus diet improves the fatty acid metabolism. This finding is consistent with that of Guo et al., who observed that serum total fatty acids, unsaturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, and N-6 polyunsaturated fatty acids reduced after 16 weeks of exercise plus diet (Guo et al., 2014).

Effects of Extreme Weight Loss Intervention on Carnitine Metabolism

Acylcarnitine is a product of the incomplete oxidation of fatty acids. High levels of BCAAs interfere with the oxidation of fatty acids in muscles, leading to the accumulation of various acylcarnitines and insulin resistance (Olisja et al., 2015; White et al., 2016). Wahl et al. (2012) observed that the C12:1 and C16:1 acylcarnitine levels in children with obesity were higher than those in children with normal weight. Perng et al. (2014) also discovered a positive correlation between C3 and C5 acylcarnitine and insulin resistance in children with obesity. Our results showed that carnitine, propionyl carnitine, 2-methylbutyroylcarnitine, isovalerylcarnitine, glutaryl carnitine, and dodecanoyl carnitine decreased, whereas acetylcarnitine, palmitoyl carnitine, oleylcarnitine, and stearylcarnitine increased following the intervention. The changes in propionylcarnitine and isovalerylcarnitine were associated with the changes in TG, whereas those in acetylcarnitine, palmitoyl carnitine, and oleylcarnitine were associated with body composition improvement. This condition may be associated with a reduction in body weight and concentrations of energy fatty acids after the intervention, whereas the adaptive decrease in carnitine content may be the result of improved lipid metabolism.

Effects of Extreme Weight Loss Intervention on Carbohydrate and Organic Acid Metabolism

Carbohydrate metabolism showed a similar trend to fatty acid and carnitine metabolisms, which decreased following the intervention. Given that fatty acids and carbohydrate compounds are energy substances, the decrease in fatty acid and carbohydrate metabolites after the intervention suggests an increase in the energy metabolic pathway. The TCA cycle is a key link for the metabolism of carbohydrates, fatty acids, and amino acids. Previous studies have revealed damage to the TCA cycle in individuals with obesity and diabetes, which is manifested by the decrease in key metabolites, such as citric acid, α-ketoglutarate, malic acid, and oxaloacetic acid, in the TCA cycle pathway; the damage to the TCA cycle is closely related to insulin resistance (Schrauwen and Hesselink, 2008; Martins et al., 2018). Citric acid, isocitrate, cis-aconic acid, and malic acid are important metabolites in the TCA cycle; increases in these organic acids indicate an increase in the TCA cycle pathway. Similar to the results of this study, Menshikova et al. (2007) revealed that moderate-intensity aerobic exercise increased citrate synthase activity by 29% in adults with obesity. Brennan et al. (2018b) observed that the increase in TCA cycle metabolites was associated with the decreased visceral fat following 6 months of exercise. Furthermore, our results showed that 2-hydroxybutyric, cis-aconitic acid, citric acid, and isocitric acid were associated with body composition improvement, whereas malic acid was associated with TG reduction. Altogether, these results suggest that the TCA cycle and organic acid metabolism may play an important role following intervention and are correlated with obesity and its metabolic complications.

Strength and limitation: In accordance with the Convention on the Rights of the Child, we informed the children about the research, and in the implementation of our intervention program, we respected the children's appeals and rights and encouraged them to complete the intervention program. Compared with previous studies, the advantage of our study is that it can achieve a great weight loss effect in a short period and improve metabolic health. Our study may provide references for the development of effective intervention strategies for children with metabolic syndrome. In our study, we observed that the changes in plasma metabolites were closely associated with the improvement in body composition and cardiometabolic health, which may provide a new research perspective for further exploration of metabolic mechanisms. This study presents several limitations. First, the absence of a control group for diet intervention alone restricted the interpretation of the effects of exercise on metabolic responses. Second, given the lack of sample size, the metabolomic findings could not be further validated in our study. We will continue to carry out relevant verification work in the future. Third, although the body composition and cardiometabolic health improved in our study, the long-term outcomes of the intervention may be different, and further studies with a large sample size and long intervention duration should be carried out.

CONCLUSION

In conclusion, the most evident finding of this study is that extreme weight loss intervention can effectively improve body composition and cardiometabolic health in children with metabolic syndrome in a short intervention period. The metabolomic data provided a comprehensive view of circulating metabolite changes after exercise combined with diet control; these changes included amino acid, fatty acid, carnitine, and organic acid metabolism. The changes in plasma metabolites are closely associated with body and cardiometabolic health improvement, which provides a new perspective for the study of the mechanism of exercise combined with diet control to promote cardiometabolic health. Additional research is necessary to further validate the result and determine the key metabolism pathway related to cardiometabolic health improvement in children with metabolic syndrome.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethical Committee of the Guangzhou Sport University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

JLiu and LZ conceived and carried out experiments. JLiu and JLia conceived experiments and analyzed data. XL carried out experiments. All authors were involved in writing the paper and had final approval of the submitted and published versions.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphys.2021.731762/full#supplementary-material

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Reliability of Isokinetic Strength Assessments of Knee and Hip Using the Biodex System 4 Dynamometer and Associations With Functional Strength in Healthy Children

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Background: This study aimed to analyze the reliability of concentric isokinetic strength assessments (knee and hip) using the Biodex System 4 in healthy children and assess the association with functional strength tests (sit-to-stand [STS], lateral-step-up [LSU]).

Methods: 19 children (6–12 years) were included. Knee and hip flexion and extension, and hip abduction and adduction were tested at 60 and 90°/s.

Results: Relative and absolute reliability at 60°/s tended to show better results compared to those at 90°/s. Intra class correlations (ICCs) of knee flexion and extension at 60°/s were good (0.79–0.89). For hip flexion, extension, abduction and adduction at 60°/s ICCs were moderate to good (0.53–0.83). The smallest detectable change (SDC) values (expressed in %) were highly variable. The SDC% for knee flexion and extension and hip abduction at 60°/s were around 50%. Positive associations were found between hip extension and abduction isokinetic strength and the STS test.

Conclusion: Concentric isokinetic strength assessments in healthy children using the Biodex System 4 were found reliable for knee flexion and extension and hip abduction. Limited associations were found between concentric isokinetic strength tests and functional strength tests.

Keywords: isokinetic dynamometry, lower limbs, children, reliability, functional strength

INTRODUCTION

Muscle strength is crucial for many daily life activities such as walking or jumping (De Ste Croix et al., 2003; van der Krogt et al., 2012; Santos et al., 2013; Eliakim et al., 2019). Youngsters with inadequate muscular strength are less likely to gain competence and confidence in their motor skill abilities and will have limited participation in exercise, games, and sports activities (Faigenbaum et al., 2013). Caregivers should therefore recognize muscle strength as a prerequisite of global health (Faigenbaum et al., 2013; Eliakim et al., 2019).

Resistance training has shown to be safe, to improve muscular fitness and to reduce the risk of injury in children and adolescents (Faigenbaum et al., 2013). To analyze possible effects of resistance training, a valid and reliable tool for muscle strength assessment is indispensable. Currently, several options are available: manual tests, handheld dynamometry, the 1-repetition maximum test, functional strength tests and isokinetic dynamometry (Schwartz et al., 1992; van den Beld et al., 2006; Santos et al., 2013; Aertssen et al., 2016). Isokinetic dynamometry is considered the gold standard for objectifying strength (Ayalon et al., 2000; Wiggin et al., 2006; Tsiros et al., 2011).

In many functional activities, the knee extensors and flexors play an important role by stabilizing the knee joint (Mikesky et al., 2000; Fagher et al., 2016; Munoz-Bermejo et al., 2019). A recent review, including 10 studies, on the reliability of isokinetic strength measurements of the knee in children (healthy and with cerebral palsy) revealed poor to excellent (intra-class correlation [ICC], 0.31–0.99) levels of relative reliability for concentric movements (Munoz-Bermejo et al., 2019). Nevertheless, the heterogeneity of the included studies (e.g., isokinetic devices, populations, protocols) hamper general conclusions.

Weakness of the hip abductors and hip flexors affect a normal gait pattern by increasing total muscle cost (van der Krogt et al., 2012). Hip flexors are important during swing phase, and the gluteus medius is crucial for vertical support (Liu et al., 2008; Hall et al., 2011). To our knowledge, only two studies focused on the evaluation of isokinetic strength assessment of the hip joint in children (Molnar et al., 1979; Burnett et al., 1990). Burnett et al. (1990) reported poor to good relative reliability for concentric isokinetic measurements of the hip flexors, extensors, abductors and adductors with ICCs ranging from 0.49 to 0.75. Molnar and Alexander concluded, based on score deviations, that the isokinetic technique is reliable for muscle strength assessment of the hip flexors, extensors and abductors in children (Molnar et al., 1979).

Absolute reliability provides clinical guidance for assessing real changes (Dvir, 2003). Only few studies focusing on isokinetic assessment of the knee in children reported absolute reliability results. They found results for the standard error of measurement (SEM%) results ranging from 5.2 to 13.9% and for the smallest detectable change (SDC%) ranging from 14.4 to 38.5% (Munoz-Bermejo et al., 2019). However, no conclusions can be drawn due to several discrepancies between these studies. No data are available for the hip.

Pediatric physical therapy interventions ultimately aim to target activity and participation levels. Functional strength tests are often used to evaluate functional capacity in children. Overall, a low to moderate association ($r = 0.42–0.69$) has been previously shown between isometric strength measurements and functional strength tests of the lower limbs (Aertssen et al., 2016).

The main aim of the present study is to analyze the relative and absolute reliability of concentric isokinetic strength assessments of the knee and the hip using the Biodex System 4 in healthy children. Additionally, the possible relationship between isokinetic dynamometry of several relevant muscle groups and functional strength tests were explored.

Abbreviations: Cm, centimeters; ICC, intra class correlations; Kg, kilogram; LSU, lateral-step-up; MPT, mean peak torque; Nm, Newton meter; PT, peak torque; r, Pearson correlation coefficient; s, second; SEM, standard error of measurement; SDC, smallest detectable change; STS, sit-to-stand; y, years.

METHODS

Study Design

To investigate intra-tester reliability of the concentric isokinetic strength assessments of the knee and hip, children were tested twice by the same pediatric physical therapists and on the same time of the day with a minimum interval of 1 week and a maximum interval of 2 weeks in between testing. During the first session, children also performed functional strength tests after the isokinetic strength assessments to enable analysis of the possible relationships between functional strength and isokinetic strength.

The clinical trial registration date and number of this study are, respectively, 18/07/2019 and NCT04024592.

Participants

Healthy children were recruited from several primary schools in Flanders, Belgium and via acquaintances of the authors between February and March 2018. Children with chronic orthopedic, neurological, or cardiorespiratory problems were excluded. All parents and 12-year-old children signed an informed consent form. In this document they confirmed that they received sufficient oral and written information regarding the study. For all participants an adapted information form was given with easy to understand explanation of the testing protocol. This study was approved by the institutional ethics committee of Ghent University Hospital (EC/2017/1674).

Testing Protocol

All children were tested separately. Participants were asked to create the same conditions for both test occasions (e.g. physical activity and sleep) and to limit physical activity to their habitual activities before testing. Physical activity of the last 24 hours was questioned by means of a standardized interview. Before each session, a warm-up period of 2 min on a cycle ergometer at a low pre-set intensity of 25 Watt was performed, similar to warming ups provided in previous research (Wiggin et al., 2006; Fagher et al., 2016). Leg dominance was determined by asking the child to kick a ball three times.

A detailed description of the testing procedures of the concentric isokinetic strength assessments and functional strength tests is presented in **Figure 1**.

Concentric Isokinetic Strength Assessment

All concentric isokinetic measurements were performed using a Biodex System 4 (Model 850-230, Universal Pro Single Chair Assy, Biodex Medical Systems, Inc., Shirley, New York, USA). The measurements included knee flexion and extension, and hip flexion, extension, abduction, and adduction. Assessment protocols of the manufacturer were applied and dynamometer setup specifications during the first session (e.g., seat pan position, dynamometer height and leg cuff position) were noted

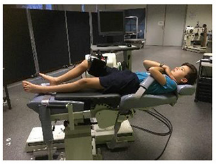
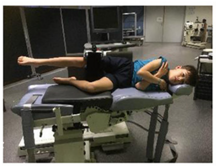
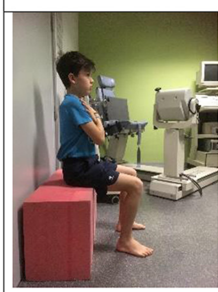
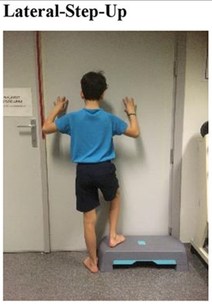
Concentric Isokinetic Strength Assessments		
Assessment	**Setup**	**Positioning**
Knee flexion – extension 	Dynamometer Orientation: 90˚ Dynamometer Tilt: 0˚ Seat Orientation: 90˚ Seatback Tilt: 85˚ Axis of Rotation: through the lateral femoral condyle on a sagittal plane. Knee attachment proximal to medial malleoli. Range of motion is set. Ready Position: Full Flexion	Comfortable sitting position. Good alignment upper body, pelvis and lower legs. Tested leg fixated above the knee. Straps around the chest and arms crossed to avoid compensatory movements.
Hip flexion – extension 	Dynamometer Orientation: 0° Dynamometer Tilt: 0° Seat Orientation: 0° Seatback Tilt: Fully Reclined Axis of Rotation: superior and anterior to greater trochanter when limb is in neutral position. Range of motion is set. Ready Positon: Neutral Extension	Comfortable position. Good alignment upper body, pelvis and lower legs. Non-tested leg fixated on chair. Straps around the chest and arms crossed to avoid compensatory movements.
Hip abduction – adduction 	Dynamometer Orientation: 0° Dynamometer Tilt: 0° Seat Orientation: 0° Seatback Tilt: Fully Reclined Axis of Rotation: superior and medial to greater trochanter. Hip attachment proximal to the knee. Range of motion is set. Ready Position: Full Adduction	Comfortable position. Good alignment upper body, pelvis and lower legs using a backrest. Non-tested leg fixated on chair. Arms crossed to avoid compensatory movements.
Functional Strength Tests		
Assessment	**Muscles function**	**Positioning**
Sit-To-Stand	Muscle endurance (number of repetitions within 30 seconds). Main muscles involved: knee and hip extensors and hip abductors.	Starting position: 90° flexion in knees and hips. Arms crossed over the chest.
		Ending position: maximum extension of knees and hips. Good alignment of upper body, trunk and lower legs. Each time the child goes up and down touching the seat with his pelvis, a repetition is counted.
Lateral-Step-Up 	Muscle endurance (number of repetitions within 30 seconds). Main muscles involved: knee and hip extensors and hip abductors.	Starting position: tested leg on a step of 16 cm. Child holds the wall, on shoulder level, with his fingertips. Good alignment of the upper body, pelvis and lower legs. Ending position: tested foot on the step with maximum extension of the knee and hip. Good alignment of upper body, trunk and lower legs. Each time the child goes up and down touching the floor with the foot of the non-tested leg, a repetition is counted. The child is not allowed to push with the toes of the non-tested leg to go upwards again.

FIGURE 1 | Description of concentric isokinetic strength assessments and functional strength tests.

and repeated during the second session. For hip abduction and adduction, a standardized test setup based on the study of Meyer et al. (2013) was used. Participants laid in side-lying, using a backrest to provide stability and to avoid compensatory movements. In the current study, no pediatric attachments were used (Fagher et al., 2016). The leg length of the included children was sufficiently long to allow standardized positioning, both for knee and hip assessments. Moreover, the pediatric hip attachment does only enable measurements in a standing position.

The dominant leg was always tested first and both legs were tested at a rate of 60° and 90° per second (/s), as these velocities seem to represent velocities used during activities of daily life (Li et al., 1996; Ayalon et al., 2000; Wiggin et al., 2006). Moreover, an angular velocity of 60°/s has been used in previous research (Ayalon et al., 2000; Wiggin et al., 2006; Santos et al., 2013) whereas 90°/s has not yet been explored in children. Lower (e.g. 30°/s) and higher (e.g. 180°/s) velocities were not selected since children seem to get discouraged or show difficulties in consistently generating torques at these velocities, respectively (Wiggin et al., 2006; Santos et al., 2013). Before each test, children were asked to perform three submaximal and one maximal repetition to become familiar with the test procedure. During the test procedure, children were asked to perform three consecutive maximal repetitions for each tested muscle group. There was no pause in between the repetitions of the practice session, neither in between the repetitions of the test session. The time between the practice moment and the actual test was 30 s. Between the two velocity conditions, children could rest for 1 min. Between each tested muscle group, participants were again allowed to rest for 2 min. The assessors gave standardized verbal feedback, encouraging the children to perform at maximal strength and to move through the total preset range of motion. Also, constant update regarding the remaining repetitions was provided. For each test, the values of three consecutive isokinetic contractions were used for statistical analyses. To ensure that best effort was obtained only assessments for which the coefficient of variance was $\leq$ 20% were included (Wiggin et al., 2006). Limb weight correction was not applied. The use of gravity correction in children is unclear. Literature suggests that in adult error levels in isokinetic measurements occur when gravity is uncorrected. Nevertheless, according to Jones and Stratton (2000), correction using adult procedures is thought to overestimate gravitational torque in children, as these do not account for the elastic components of the growing muscle-joint system. From our observations, it is very difficult for children to relax and obtain a correct limb weight. This is even more so when total limb weight has to be considered while measuring hip strength (Burnett et al., 1990). Furthermore, gravity correction was not essential to the aim of our study, which was to analyze the reliability of isokinetic strength assessments. The weight of the limb was assumed to be the same within the 2-week interval period, and the testing positions were standardized.

Peak torque (PT; expressed in Newton meter, Nm) and mean PT (MPT; Nm) were identified for each assessment. Peak torque was defined as the highest force output at any moment during a repetition. MPT was the average of the peak torque values obtained during a series of three repetitions. The MPT may be considered a better estimate of overall function than PT given that function is dependent on repetition of movement. PT and MPT values have been found to be reliable measures of muscle performance and are often used in previous research articles covering isokinetic strength assessments in children. Using those values, the data of the current study could be compared with those of previously published studies.

Functional Strength Tests

Participants performed the sit-to-stand (STS) test and lateral step-up (LSU) test. Those functional tests are frequently used for assessment of functional strength in children, both in research and clinical practice. Test-retest reliability of these tests range from 0.70 to 0.79 in children aged from seven to 10 years (y) old (Aertssen et al., 2016).

Participants had three practice trials to ensure good understanding of the test. For all functional strength tests, the number of correct trials within 30 s were counted. Children were motivated verbally by the assessors. A 2-min rest period was implemented between the different functional tests. There was a 15-min rest period between the isokinetic strength assessments and the functional strength tests.

Only the most related muscles to each functional strength test were used for analysis.

Statistical Analysis

Descriptive Statistics

Agreement between both test occasions and potential differences between the dominant and the non-dominant side and between the two velocities (60°/s and 90°/s) were assessed with a paired t-test.

Intra-Tester Reliability

The relative reliability was assessed by means of the 2-way $ICC_{2.1}$ for agreement to determine the test–retest reliability of the isokinetic strength assessments. The ICC values were interpreted based on the classification of Portney and Watkins (2009): $<$ 0.5 = poor reliability, 0.5–0.75 = moderate (poor to moderate) reliability, 0.75–0.9 = good reliability, and $>$ 0.90 = excellent reliability. For ICC, a 95% confidence interval was calculated.

Absolute reliability was assessed with the SEM. The SEM agreement was defined by the formula: $\sqrt{(\sigma^2_{1-2} + \sigma^2_{\text{residual}})}$ (de Vet et al., 2006). The SEM% was defined as: SEM/mean of all measurements from both test sessions $\times$ 100. The SDC is the minimum difference to be considered clinically important and was determined using following formula: $1.96 \times \sqrt{2} \times SEM_{\text{agreement}}$. The SDC was also expressed as a percentage value (Copay et al., 2007; Weir, 2009).

Associations Between Functional Strength Tests and Concentric Isokinetic Dynamometry

Associations were determined by calculating the Pearson correlation coefficients (r-value), relating the outcomes of the isokinetic strength assessments of the first test occasion with the functional strength tests scores. The interpretation of the r-value was done based on following distribution: $r < 0.3$: very weak, $r = 0.3$–0.5: weak, $r = 0.5$–0.7: moderate, $r = 0.7$–0.85: strong, $r = 0.85$–0.95: very strong, and $r > 0.95$: excellent correlation (Van Maele et al., 2014).

All statistical analysis were performed with IBM SPSS Version 23.0 (SPSS Inc., Chicago, IL).

RESULTS

Participants

A total of 19 healthy children (8 girls, 11 boys) aged 6–12 y (mean 10.0, standard deviation [SD] 1.6) were included in this study. Height of the children ranged from 132 to 161 cm (mean 146, SD 10.1) and weight from 26.8 to 45.9 kg (mean 35.1, SD 7.2).

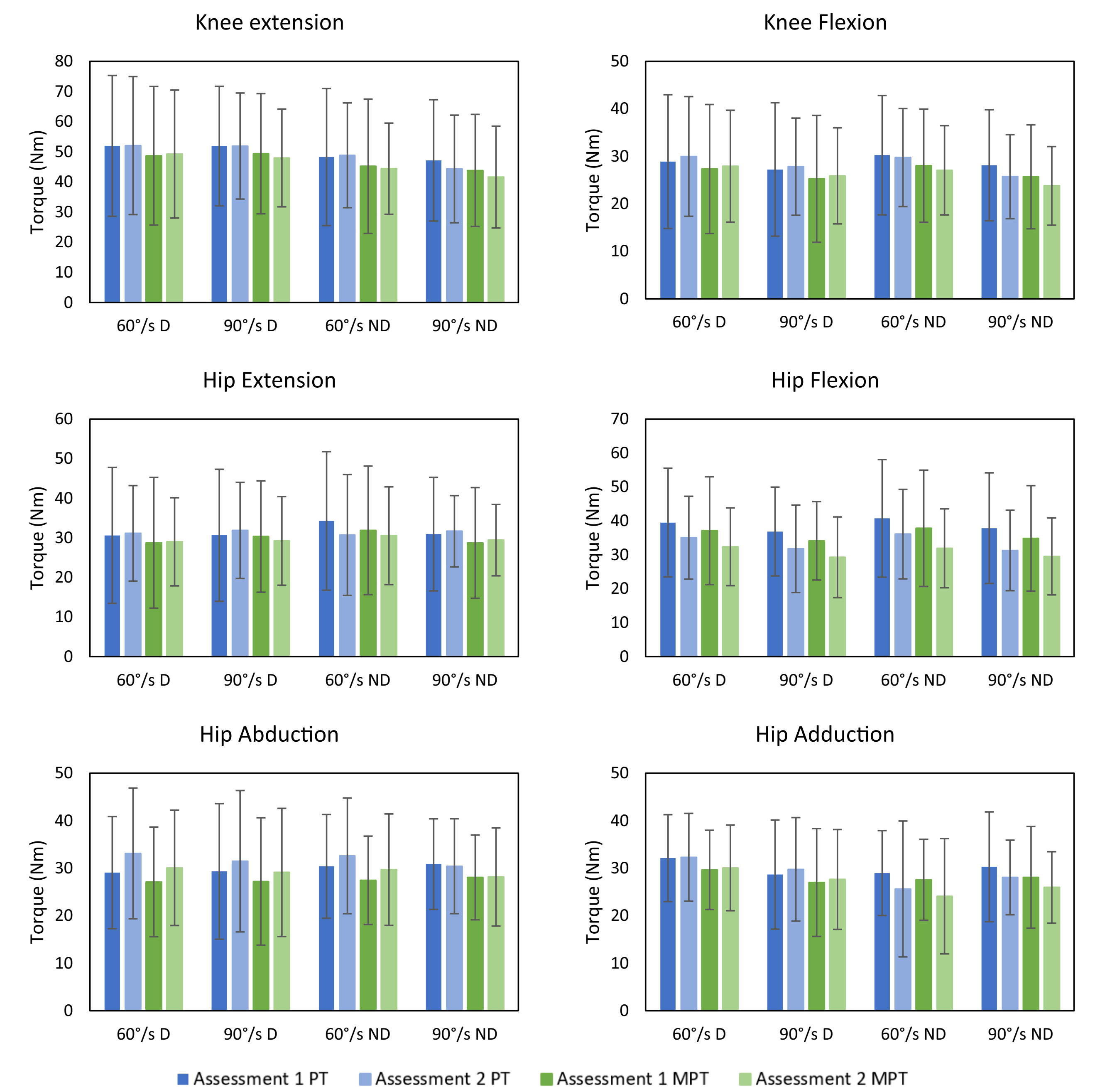


FIGURE 2 | Depiction of the means and standard deviations of the repeated assessments for each joint movement, velocity and dominant and non-dominant leg. D: dominant; MPT: Mean Peak Torque; ND: Non-dominant; Nm: Newton meter; PT: Peak Torque; /s: per second.

Torques

The tables of the mean and standard deviation of PT and mean MPT for each assessment can be found in the **Appendix Tables A1–A3**. Graphical representation of the torques can be found in **Figure 2**.

There were no significant differences between both test occasions. The torques of the dominant side and the non-dominant side did not show significant differences. Torques performed at 60°/s and 90°/s did not differ significantly from each other, except for hip extension PT and MPT, hip flexion MPT and knee flexion PT of the non-dominant side.

Intra-Tester Reliability

Reliability results are reported in **Tables 1–4**. Relative reliability of PT and MPT assessments for knee flexion, knee extension, and hip abduction were good. Moderate relative reliability was found

TABLE 1 | Relative reliability (ICC) of the concentric isokinetic strength assessments at 60°/s.

	Peak torque				Mean peak torque			
	Dominant		Non-dominant		Dominant		Non-dominant	
	ICC	CI (95%)	ICC	CI (95%)	ICC	CI (95%)	ICC	CI (95%)
Knee extension	**0.87**	0.64–0.96	**0.81**	0.51–0.97	**0.88**	0.65–0.96	**0.79**	0.47–0.93
Knee flexion	**0.84**	0.50–0.95	**0.89**	0.69–0.96	**0.85**	0.53–0.96	**0.88**	0.67–0.96
Hip extension	0.56	0.10–0.81	**0.75**	0.43–0.90	0.53	0.07–0.80	**0.76**	0.44–0.91
Hip flexion	0.62	0.18–0.86	0.69	0.36–0.87	0.71	0.33–0.90	0.73	0.35–0.89
Hip abduction	**0.81**	0.50–0.93	**0.77**	0.45–0.91	**0.83**	0.57–0.94	0.71	0.34–0.89
Hip adduction	**0.75**	0.37–0.91	0.60	0.14–0.85	0.73	0.34–0.91	0.66	0.25–0.93

Reliability indices classified as good (ICC, 0.75 – 0.90) are shown in bold type. /s, per second; CI, confidence interval; ICC, intra-class correlation coefficient.

TABLE 2 | Relative reliability (ICC) of the concentric isokinetic strength assessments at 90°/s.

	Peak torque				Mean peak torque			
	Dominant		Non-dominant		Dominant		Non-dominant	
	ICC	CI (95%)	ICC	CI (95%)	ICC	CI (95%)	ICC	CI (95%)
Knee extension	0.59	0.11–0.84	**0.83**	0.61–0.93	0.58	0.11–0.84	**0.80**	0.55–0.92
Knee flexion	**0.75**	0.39–0.92	0.67	0.26–0.88	**0.80**	0.53–0.92	0.62	0.17–0.86
Hip extension	0.52	0.03–0.80	0.67	0.22–0.88	0.50	0.01–0.79	0.64	0.18–0.87
Hip flexion	0.55	0.11–0.82	0.69	0.27–0.87	0.50	0.04–0.79	0.69	0.33–0.87
Hip abduction	**0.83**	0.56–0.94	**0.88**	0.66–0.96	**0.85**	0.61–0.95	**0.88**	0.68–0.96
Hip adduction	0.72	0.34–0.89	0.72	0.32–0.90	0.69	0.28–0.88	0.71	0.30–0.90

Reliability indices classified as good (ICC, 0.75 – 0.90) are shown in bold type. /s, per second; CI, confidence interval; ICC, intra-class correlation coefficient.

TABLE 3 | Absolute reliability (SEM%, SDC%) of the concentric isokinetic strength assessments at 60°/s.

	Peak torque				Mean peak torque			
	Dominant		Non-dominant		Dominant		Non-dominant	
	SEM%	SDC%	SEM%	SDC%	SEM%	SDC%	SEM%	SDC%
Knee extension	15.65	**43.26**	18.17	50.21	15.71	**43.40**	19.60	54.17
Knee flexion	18.63	51.47	12.64	**34.94**	18.02	**49.81**	21.61	59.71
Hip extension	31.57	87.26	25.38	70.15	32.89	90.91	46.22	127.73
Hip flexion	23.85	65.90	22.56	62.35	21.69	59.96	22.57	62.37
Hip abduction	18.34	50.68	17.69	**48.88**	17.06	**47.16**	19.95	55.14
Hip adduction	29.68	82.02	27.83	76.93	14.94	**41.28**	23.92	66.12

Acceptable values (≤ 50.00%) are shown in bold type. /s, per second; SDC%, smallest detectable change; SEM%, standard error of measurement.

for PT and MPT of hip extension, hip flexion, and hip adduction. Overall, relative reliability at 60°/s tended to show slightly better results than at 90°/s. Absolute reliability, expressed in SEM% and SDC%, tended to show the same pattern as the relative reliability.

Relative Reliability

Assessments of knee flexion and knee extension at 60°/s showed good relative reliability for the PT values, with ICCs of 0.84 and 0.87 (dominant leg) and 0.89 and 0.81 (non-dominant leg), respectively. MPT results at 60°/s showed good relative reliability for knee flexion and knee extension, both for dominant (ICCs of 0.85 and 0.88, respectively), and non-dominant side (ICCs of 0.88 and 0.79, respectively). Assessments at 90°/s showed good relative reliability for knee flexion of the dominant leg for PT and MPT values (ICC 0.75 and 0.80, respectively). Further, the PT and MPT for knee extension of the non-dominant leg (ICC 0.83 and 0.80, respectively), showed good reproducibility. Knee extension of the dominant leg and knee flexion of the non-dominant leg showed moderate relative reliability (PT and MPT values) of 0.58–0.67.

Isokinetic assessment of hip extension at 60°/s for the non-dominant leg (PT and MPT value) showed good relative

TABLE 4 | Absolute reliability (SEM%, SDC%) of the concentric isokinetic strength assessments at 90°/s.

	Peak torque				Mean peak torque			
	Dominant		Non-dominant		Dominant		Non-dominant	
	SEM%	SDC%	SEM%	SDC%	SEM%	SDC%	SEM%	SDC%
Knee extension	22.84	63.11	17.10	**47.26**	23.80	65.78	18.55	51.25
Knee flexion	45.91	126.89	22.15	61.21	20.61	56.96	24.01	66.38
Hip extension	30.09	83.16	21.83	60.35	29.71	82.10	23.87	65.98
Hip flexion	25.93	71.67	24.15	66.75	26.84	74.19	24.25	67.01
Hip abduction	19.02	52.57	11.16	**30.85**	18.06	**49.91**	11.49	**31.77**
Hip adduction	20.27	56.03	18.07	**49.93**	22.15	61.22	18.62	51.46

Acceptable values (≤ 50.00%) are shown in bold type. /s, per second; SDC%, smallest detectable change; SEM%, standard error of measurement.

TABLE 5 | Associations between concentric isokinetic strength assessments (mean peak torque) and the functional strength tests.

	Knee extension				Hip extension				Hip abduction			
	60		90		60		90		60		90	
	D	ND	D	ND	D	ND	D	ND	D	ND	D	ND
STS	**0.51**	0.12	0.42	0.19	0.22	–0.13	0.05	–0.39	**0.52**	0.25	**0.53**	0.25
LSU_D	0.39	/	0.03	/	0.14	/	0.12	/	0.33	/	0.30	/
LSU_ND	/	0.14	/	0.18	/	0.13	/	0.15	/	0.32	/	0.28

Significant values are shown in bold type. D, dominant; LSU, lateral-step-up; ND, non dominant; STS, sit-to-stand.

reliability (ICC 0.75 and 0.76, respectively), while poor to moderate results were recorded for all other assessments of both hip extension and flexion (0.50–0.73). Assessments of PT values of hip abduction showed good relative reliability for hip abduction for both sides and velocity conditions (0.77–0.88). The same results were observed for MPT values except for hip abduction at 60°/s of the non-dominant leg. Hip adduction showed overall moderate reproducibility (0.60–0.75).

Absolute Reliability

The SEM% values for knee flexion and extension were highly variable, with the lowest for knee flexion of the non-dominant leg at 60°/s (PT; 12.6%) and the highest for knee flexion of the dominant leg at 90°/s (PT; 45.9%). This variability is also reflected in the relatively large standard deviations. With exception of the knee flexion of the dominant leg at 90°/s (PT), the SDC% values ranged from 34.9% for knee flexion of the non-dominant leg at 60°/s (PT) to 66.4% for knee flexion of the non-dominant leg at 90°/s (MPT).

The SEM% values for the hip assessments showed the same patterns as the relative reliability results. For hip flexion and extension SDC% values were above 50%. The SDC% were ≤ 50% for hip abduction except for PT value of the dominant leg at 60°/s and 90°/s (50.7% and 52.6%, respectively) and the MPT value of the non-dominant leg at 60°/s (55.1%). For hip adduction, only the PT value of the non-dominant leg at 90°/s (49.9%) and MPT value of the dominant leg at 60°/s (41.3%) were ≤ 50%.

Associations

Table 5 shows the associations between the MPT values of the concentric isokinetic strength assessments and the functional strength tests.

Moderate significant positive correlations were found between the concentric isokinetic strength assessment of the knee extensors at 60°/s, hip abductors at 60°/s and 90°/s (dominant leg) and the STS ($r = 0.51$–0.53). All other correlations were weak to very weak.

DISCUSSION

The main purpose of the present study was to analyze the relative and absolute reliability of concentric isokinetic strength assessments of the knee and hip in healthy children. This study tended to highlight the importance of reliable strength assessments of the lower limbs in healthy children. Both relative and absolute reliability were analyzed to emphasize the usability of concentric isokinetic strength assessments in clinical practice. Besides, the relationship between concentric isokinetic strength assessments and functional strength tests was analyzed.

Torques

Torque values for knee and hip found in this study were rather similar to results found in previous literature (Burnett et al., 1990; Fagher et al., 2016). However, in the present study, the standard deviations appeared to be larger, which might be partially explained by the larger age range compared to other studies.

Intra-Tester Reliability

In comparison with the results of Fagher et al. (2016), reporting an ICC of 0.62 for knee flexion and 0.81 for knee extension at 60°/s using the Biodex System 4, better results for knee flexion and for knee extension were found in current study. The better results might be partially explained by the larger variation in age of the participants (10 ± 1.6 y) compared to Fagher et al. (2016) (8.8 ± 0.5 y). Another parameter that could have influenced the results is the use of gravity correction in the study of Fagher et al. (2016). Knowing that limb weight is difficult to assess in children, variations in those values might have influenced their results resulting in lower reliability indices (ICC).

Burnett et al. (1990) reported good relative reliability for PT values at 90°/s for hip flexion (ICC 0.75) and extension (ICC 0.84), and reported poor to moderate relative reliability results for hip adduction (0.49) and abduction (0.59) using the Cybex II dynamometer. The current study showed better results for hip adduction and abduction which might be related to a better standardization of the testing procedure with a positioning of the children (with backrest) that allowed less compensatory movements.

The clinical value of a measurement device can be derived from the magnitude of the absolute reliability, as reflected by the SEM% and the SDC%. Hereby, changes over time and thus effectiveness of interventions can be determined. In current study highly variable SEM% values were found and those values tended to be smaller at 60°/s. This tendency for better results at lower velocity conditions was also reported by Fagher et al. (2016) and is in line with the results for relative reliability. It is known children have reduced ability to recruit a greater percentage of motor units, compared to adults (Amstrong, 2017). An immature neuromuscular activation pattern in children could explain why they have more difficulties being consistent at higher velocities (De Ste Croix et al., 2003; Fagher et al., 2016). The SDC% reflects the threshold to define a real change in a single subject. Youth strength training interventions often result in benefits of up to 50% strength gain (Dahab and McCambridge, 2009). For knee flexion and extension, and hip abduction SDC% values were around 50%. Fagher et al. (2016) reported better results for knee flexion and extension of the dominant leg at 60°/s (30.9% and 36.5%, respectively).

Regarding the hip, Burnett et al. (1990) did not report absolute reliability results, so no comparison can be made.

Overall, the better results for knee flexion and extension and hip abduction might be influenced by the fact that a more standardized testing procedure could be adopted, e.g., the backrest in side-lying position when testing hip abduction, allowing more isolated movements. In opposition, compensatory movements of the pelvis and of the shank segment during hip flexion and hip extension might have influenced the moderate reliability results. Also, knee flexion and extension in a seated position are movements that children are familiar with in daily life, easier to understand and to execute in a selective way, which may also have contributed to these good results. Hip adduction and hip extension, respectively in side-lying and supine position, might be more difficult to understand and perform.

Associations

In the current study, few associations between concentric isokinetic strength and the functional strength tests were found. Only knee extension and hip abduction at 60°/s and hip abduction at 90°/s of the dominant side correlated significantly with the STS test. Those results suggest that the strength of the dominant leg would have a greater influence on the performance of the STS compared to the non-dominant leg. The STS also tended to show more associations to strength generated at a lower velocity (60°/s). The assessments at 60°/s tend to show better reliability results and it is easier to generate maximum strength at lower velocities, which might explain the better associations of the functional strength tests with torques generated at a lower angular velocity. No associations were found with isokinetic strength of the hip extensors. This could be due to the weaker reliability of the isokinetic assessment of the hip extensors in the current study. Concentric activity of the hip extensors might also be less important during the STS movement compared to the activity of the knee extensors and hip abductors. Regarding the LSU, no associations were found with the isokinetic assessments. This might be due to some confounding factors that are more difficult to objectify during the LSU, such as the amount of support children took on the wall in front of them, the way they touched the ground with the non-tested leg or the amount of lateral dipping of the hip. Besides, the range of motion (ROM) of the knee and the hip during the LSU is smaller compared to the STS, which could make it more difficult to associate it with muscular strength. Future research is needed to provide more solid conclusions. In general, the results of the associations in the current study are not very consistent and associations are scarce. These findings are in accordance with the results reported by Duncan et al. (2018), suggesting that concentric isokinetic muscle strength might not fully represent the muscular and motor performance demands of functional strength tests, which also involve components such as balance and coordination and are more likely to be considered as endurance tests. Dynamometers test the performance of one joint at a time in an open kinetic chain, whereas functional strength tests may give a more accurate view of overall limb function in closed kinetic chain activities. This is in line with the concept of specificity of training, in which the carry-over of gains made in strength in the open chain into the closed chain function is questioned (Palmitier et al., 1991; Worrell et al., 1993). Also in adults, the relationship between isokinetic strength and functional tests has been studied previously. Nevertheless, results are inconclusive varying from small to large correlations (Vassis et al., 2020). Differences in associations might be due to the variety in population (different pathological conditions e.g. total knee replacement or patellofemoral problems) and methodologies (selected functional strength tests, angular velocities, isokinetic outcomes) (Wilk et al., 1994; Yoshida et al., 2008; Guney et al., 2016). A study conducted in healthy adults evaluated the effects of a lateral-step-up exercise protocol on isokinetic peak torque of the knee extensors (Worrell et al., 1993).

They concluded that an isokinetic dynamometer was unable to detect the strength gains that resulted from increases in lower extremity performance. Isokinetic strength assessments and functional strength seem to represent different aspects of the ability to perform functional tasks and might be seen as complementary.

Limitations and Recommendations for Future Research

The present study has some limitations that could be addressed in further research. Firstly, the sample size of this study was rather small. The minimum required number of participants to obtain a correct estimate of the reliability (at least 15) was recruited (Fleiss, 2011). To express usable SDC%, a greater sample of 30–50 participants is recommended (Hopkins, 2000). Secondly, the age range of the participants included in this study was large (6 to 12 y). Differences in performance of strength assessments could be expected in younger children compared to older children. A study conducted in young boys (6 to 8 y; $n = 12$) using a Lido Active dynamometer reported good relative reliability for knee flexion and knee extension (ICC, 0.85 and 0.95, respectively) at 100°/s (Merlini et al., 1995). Nevertheless, future studies should be able to define the reliability in different age groups and compare the outcomes, using the same testing protocol. Although Tsiros et al. (2011) showed that there is no need for a separate familiarization session for concentric isokinetic strength testing of the knee in children, this might not be the case for the assessments of the hip joint. Future research should investigate the impact of a separate familiarization session for isokinetic strength assessment of the hip. To enhance standardization and avoid compensatory movements during hip abduction and adduction, a backrest was used. In order to improve reliability of concentric isokinetic strength assessments of the hip flexors and extensors, future research could implement the use of a brace to avoid movements of the shank (Meyer et al., 2013). Another limitation is the fact that only PT and MPT values were taken for analyses. Isokinetic dynamometers offer a wide range of data that can be examined and give information about the quality of performance. Other variables (e.g. total work, average power, time to peak torque) could be taken for analysis in future research. To study associations with the timed functional strength tests, endurance protocols could be used. At last, given the knowledge that eccentric muscle strength plays an important role in functional activities, it could be valuable to study associations of eccentric strength assessments with functional tests. Nevertheless, more research is needed to give an insight on the reliability of eccentric isokinetic strength assessments of the knee and hip in children.

Conclusion and Clinical Implications

Concentric isokinetic strength assessments with the Biodex System 4 device in healthy children show moderate to good reproducibility with good relative reliability for knee flexion, knee extension and hip abduction and moderate to good relative reliability for hip extension, hip flexion, and hip adduction. To measure changes in time, knee flexion, knee extension, and hip abduction had acceptable absolute reliability. Both relative and absolute reliability at 60°/s tended to show slightly better results compared to reliability at 90°/s. Since no differences were found between outcome values of different velocities and between the dominant and non-dominant side, as well as no substantial differences in reliability indices, we would recommend to limit the assessments to one velocity (60°/s) and one side (dominant side) in order to be able to optimize the testing protocol. Because MPT may be considered as a better estimate for overall function compared to PT, we would suggest to use MPT values.

Few correlations were found between concentric isokinetic strength and the functional strength tests which means other variables such as muscle endurance, balance and coordination are to be taken into consideration if functional performance is targeted. Isokinetic strength assessments and functional strength seem to represent different aspects of the ability to perform functional tasks and might be seen as complementary.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Ghent University Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

VvT: study conception and design, data collection, analysis and interpretation of the data, and drafting the manuscript. IA-G, PC: analysis and interpretation of the data, drafting the manuscript. BH, LH, HF, and KD: interpretation of the data and drafting the manuscript. CV: study conception and design, analysis and interpretation of the data, and drafting the manuscript. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fspor.2022.817216/full#supplementary-material

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Use of Frame Running for Adolescent Athletes With Movement Challenges: Study of Feasibility to Support Health and Participation

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Children and adolescents with movement challenges have lower instances of physical activity and longer time spent in sedentary behaviors compared to children with typical development. The purpose of this study was to investigate the feasibility of a sport-based youth development running program modified for accessibility using a running frame and to evaluate initial evidence for its efficacy on endurance and functional strength. We completed four 8-week seasons (2–3 times per week) in a combination of 3 different formats by season: online remote (winter and spring), in person in a community park (winter, spring, and summer), and in person in an afterschool setting (autumn). Participants included 13 athletes (average age 14.46 years, range 8–18 years, 4 females), who collectively completed 22 season blocks. Diagnoses included cerebral palsy ($n = 10$), arthrogryposis ($n = 1$), Dandy-Walker malformation ($n = 1$), and transverse myelitis ($n = 1$). In all settings, participants engaged in activities of social emotional learning, cardiovascular endurance, and muscle strengthening in a progressive manner. We found that each season format was feasible to administer with high attendance rates (76–97%) and positive qualitative feedback from athletes. In addition, promising average improvements in motor performance across a season (6 min frame running test, 170 m; timed up and go test, 8.44 s; five times sit to stand, 14.1 s; and Goal Attainment Scale, $t = 65.01$) were identified in the pilot data of this non-randomized cohort. Training in any of the proposed settings with an overall goal of completing a community race in a running frame is feasible and warrants further study.

Keywords: participation, childhood disability, fitness, frame running, sport based youth development

INTRODUCTION

There are widely established benefits to exercise in children and adolescents including cardiovascular and musculoskeletal as well as academic and mental health benefits (Herting and Chu, 2017) for children of all ability levels. These benefits are also clear in regards to physical activity for persons with disabilities (Carroll et al., 2014) and the American Academy of Pediatrics has recently released a policy related to this (Carbone et al., 2021) where they emphasize the importance of exercise for all patients, regardless of ability level. For conditions such as cerebral palsy (CP), an initial and non-progressive injury to the developing brain may still cause secondary cardiovascular consequences due to lack of movement and physical activity. These co-occurring conditions occur in adulthood at a higher rate and earlier onset than the population of adults without CP (Ryan et al., 2019; Peterson et al., 2020; Thorpe et al., 2021). Although data are limited, there is reason to believe that a lack of moderate to vigorous physical activity and high levels of sedentary time (Verschuren et al., 2016) during the course of a day may be at least partially responsible for these conditions seen in adulthood.

CP has an emerging field of evidence associated with activity and participation, but children with other diagnoses that impact movement would also likely benefit from increased access to participation in activities that encourage movement and elevate heart rate. However, children with disabilities and movement challenges have difficulty accessing programs targeted at improving physical fitness (Martin Ginis et al., 2016). In addition, they have 38% higher rates of obesity in childhood (Grondhuis and Aman, 2014), which may be linked to a greater risk of cardiovascular comorbidities (Peterson et al., 2015; Edwards, 2018), pain (Jahnsen et al., 2004), and fatigue (Malone and Vogtle, 2010) in adulthood.

Youth are significantly influenced by environmental factors including relationships with peers and mentors. Sport-based youth development is a strategy that aims to promote healthy behaviors in conjunction with social confidence (Curran and Wexler, 2017) through athletic games, team building, and emotional learning opportunities. Running is an appealing option for sport-based youth development as it requires virtually no equipment, can have both individual and team aspects, and accommodate children of various skill levels. Importantly, it is also an activity that can be maintained over a lifetime, particularly if a strong foundation and interest is built early in life.

The translation of a skill such as running can be difficult for those with motor challenges especially when they typically use more restrictive orthoses or equipment for ambulation. With community locations such as fitness centers often less accessible (Martin Ginis et al., 2016), fitness opportunities need to be sought elsewhere.

A running frame is a 3-wheeled device with a seat and frame and no pedals (**Figures 1A–C**). It was created to allow for participation in running for people who have disabilities that affect their movement. The first running frame (initially called a RaceRunner) was constructed in Denmark in 1991, and they have extended their reach across Europe. There is an international competitive association for frame running (http://www.racerunning.org). Although limited, the data for using these devices for therapeutic indications are encouraging. Preliminary evidence is positive for changes in bone mineral density (Bryant et al., 2015; Van Schie et al., 2016) and muscle thickness (Hjalmarsson et al., 2020), but formal evaluation of running programs performed using these tools is limited, particularly in the American context.

The purpose of this study was to pilot an intervention of a sport-based youth development program modified for accessibility for children and adolescents with movement challenges, with the goal of community-based running participation using running frames. In addition, we sought to investigate the feasibility of offering such a program using a variety of formats, and to evaluate initial evidence for its efficacy on endurance and functional strength.

MATERIALS AND METHODS

This non-registered feasibility study had a non-randomized design with a sample of convenience that occurred in the City of Chicago, Illinois, USA. Athletes were invited to participate if they were between 6 and 18 years of age (covering both childhood and adolescent phases of development), if they had a diagnosis that made running difficult for them, and no medical concerns that made participation unsafe for them (for e.g., poorly controlled seizures, bone fracture risk, or orthopedic surgery within the previous year). Potential candidates were selected from the caseloads of the physical therapists in the trial; parents were sent details about the team, goals of the program, and logistic details. Parents and participants were given the opportunity to ask questions, and they completed an informed consent and assent, respectively. In addition to the informed consent document, parents/guardians completed the Chicago Run participation waiver. They also needed access to a reliable internet connection for remote sessions; there were several government programs in the city at the time to support students learning remotely, which reduced the barrier of this requirement. At the time of enrollment, the interest/need for transportation was assessed and athletes were provided or offered a para-transit bus to attend practice. To assess general community resources, participant zip code was found on the US Census American Community Survey (US Government, 2021), and the number of unrelated adults living below the poverty line within participant zip codes was extracted as a proxy for relative level of resources available within a local community.

Our study was set to begin in the winter of 2020. Consistent with previous studies by other investigators (Hjalmarsson et al., 2020), the initial strategy was to have all sessions conducted in person after school. However, fully remote school education for much of the 2020–2021 school year meant that an alternative strategy was required (Egan et al., 2021). Guided by the local gathering restrictions in place at the time, we evaluated whether each season should include virtual components or be entirely in person. The first season began in January of 2021, and was entirely virtual until the weather was suitable for outdoor practices to commence in city parks in late February of 2021. By summer, when vaccination rates were improving and cases of COVID were decreasing locally, we hosted the practices entirely in person outdoors with masking and distancing procedures in place. In fall, school returned for in person learning and we launched the after-school format. The school location was also safe and felt familiar to the athletes where they were co-located with students who do not have disabilities. The summary of each season can be found in **Table 1**.

FIGURE 1 | (A) Running frame example. There are 3 wheels, a seat (styles of seat vary in shape and dimension), and a chest plate for additional trunk support. The front wheel is held steady with the use of a damper. Bicycle style breaks on the front wheel allow athletes to stop and wheel locks on one or both back wheels secure the frame for mounting and dismounting. The model shown here is by Petra (Peterson et al., 2015). **(B)** Front view of athletes using a running frame during a social and emotional learning (SEL) teamwork activity at practice. Both frames are by RAD (Black, 2021). **(C)** Back view of running frames in use during an endurance portion of practice by three athletes on a track to show relative width of the back wheels; they are wide enough for stability and fit through ADA-compliant doorways. The frames on right and left are RAD (Black, 2021), and middle is Eagle Sportschairs (Ewing, 2021). **(D)** Rate of perceived exertion (RPE) scale image used by athletes to report their perceived level of effort. This image was shown on shared screen during virtual sessions, and on a laminated index card during in-person sessions.

To support the in-person components of the training, running frames were fit individually for each athlete. There were a number of frames available [Petra (Hansen, 2021), Eagle (Ewing, 2021), and RAD (Black, 2021)], and the sizes were selected by approximate inseam length and lateral stability offered by the frame. The seat height and depth were adjusted for distance to the ground, and seat styles were chosen for comfort by each athlete. Handlebars were generally kept in stock condition (as seen in **Figure 1**), but the height/angle were occasionally adjusted to be closer to the participant using either the rotation ability of the device, or through the addition of a stem extender. Frames were stored for athletes between sessions.

Chicago Run is a non-profit organization that provides young people from Pre-K through high school with inclusive running and physical activity programs. Chicago Run's *Running Mates* program utilizes running and physical activity to improve the social and emotional wellbeing of young people in middle school and high school. This program provides an inclusive and non-competitive environment in which young people work toward completing a community race, while developing a positive self-image, promoting goal setting and building relationships with peers. It is highly tailored to the needs of the athletes and settings in which it is administered, but generally includes elements of team building/emotional growth, and building endurance for running activities. The Chicago Run curriculum was adapted for the online format and to accommodate running frames when in person.

Each practice was generally formatted to include a focused social emotional learning (SEL) element, activities aimed at cardiovascular fitness (to elevate heart rate), and strengthening activities. SEL activities were designed to help athletes learn more about themselves (such as goal setting or identifying their own strengths) and their teammates. Cardiovascular activities were graded to increase duration and intensity over time, aiming to meet at least 20 min of continual activity completed at a moderate to vigorous intensity level (Verschuren et al., 2016). Athletes were educated in the Rating of Perceived Exertion (RPE) scale (Fragala-Pinkham et al., 2015). This tool was used to promote body awareness and help monitor the intensity of activity. The scale was set between 1 and 10, with both numeric values and emoticon representations, shown in **Figure 1D**. The aim was to obtain the RPE two to three times during the cardiovascular endurance section of the practice, and once during or at the conclusion of strength training. Online training was completed

TABLE 1 | Example training session schedule.

	Online	In person
Social emotional learning (10–15 min)	Check in with how everyone is feeling Two truths and a lie: athletes take turn sharing 3 statements, 2 of them are truthful and one is made up. The team attempts to distinguish the untrue one	Check in with how everyone is feeling "Sole mates" activity: athletes move their running frames to pair up based on a physical similarity called by coach (example, both wearing same color shoes), and then share with each other something about themselves (example, what do you like to eat for breakfast?)
Strength focused activities (10–15 min)	Sit to stands or squats (chosen by coach or athlete based on ability/safety): 3 × 15 reps Seated leg extensions using a resistance band: 3 × 15 reps	Frame running with resistance provided by coach using resistance band: 4 ×100 m Hill navigation in running frame: 4 × 30 m
Endurance focused activities (20–30 min)	Circuit of the following exercises x2–3 min each (options chosen by coach or athlete based on ability/safety): - Step ups or marching in place - Seated punches with water bottles for resistance or jumping jacks - Side steps or jumping jacks - Running in place or speedbag punches	Pacing activity rotating between frame running for 1 min at slow speed ("turtle"), 3 min at medium speed ("dog"), 30 s at fast speed ("cheetah"), repeated 5 times, ending with 5 min on medium speed. Completed on a loop so athletes are near one another even though they may move at different speeds.

at a set time during the day when coaches and athletes all joined a video conference together (Zoom). This format was conducive to many of the SEL activities as they involved speaking and sharing; some athletes preferred to use the chat box feature, while others preferred to use verbal participation. Examples of strength-based activities included sit to stands or squats, step ups to a small folding step provided to athletes, resisted lower extremity activities using a provided resistance band, and standing hip abduction exercises. We attempted floor-based activities for safety, but it was more challenging to coordinate the camera and appropriate spaces for these activities for athletes in their home environments. Cardiovascular endurance activities varied by athlete ability and safety. Some athletes completed standing activities such as repetitive step ups, side shuffles, or jogging in place, while others elevated heart rate using activities such as seated arm punches to various directions with or without water bottles for resistance or arm cycles at various speeds. As the season progressed, some athletes also completed full body activities such as jumping jacks. We utilized a demonstration of activities by coaches, teammates, or animated movies, and we often used a screen-share of a timer to show progression in the activity. When in person we met as a group at an outdoor community park or the indoors in school hallways or the gymnasium. Almost all endurance-based activities were completed on the running frame with an increasing time goal for movement (at any speed) each week. Strength activities in person were also completed using the running frames with a focus on high speed, using resistance (resistance bands applied by a coach to make it more challenging for the athlete to move forward), or incorporating hills or ramps. The SEL activities in person presented the opportunity for kinetic problem solving such as connecting partners by pool noodles to navigate an obstacle course as a team or playing a card game while collecting cards from different areas of the gym. An example of each session type is shown in **Table 1**. Four seasons were completed with 4–8 athletes participating each season. The format of each is specified in **Table 2**. For all seasons, athletes competed in a community run at or toward the end of the training. They could chose to complete either a 1-mile or 5-km distance with other runners in our local community at a city park usually in proximity to their neighborhood (Chicago Area Runners Association, 2021). This season-long goal is consistent with Chicago Run teams at other schools and sites that do not use running frames and was timed in conjunction with other Chicago Run teams as possible; family members of the athletes were invited to join them in the run. Head coaches in our program included 2 physical therapists (authors TS-M and TE), each with more than a decade of clinical experience in pediatrics and knowledge of a variety of equipment types and extensive experience in adjusting equipment and titrating exercise for individual needs. Neither has been certified in frame running coaching, but both obtained experience through research, consultation with manufacturers, discussions with local adaptive sports organizations, and trial and error. Assistant coaches varied by season, but included 1 physical therapist, and 2 paraprofessionals with experience in working with children with movement challenges in a school setting.

We used the 500 m distance of the Functional Mobility Scale (FMS-500) (Graham et al., 2004; Harvey et al., 2010) to describe how the participants typically maneuvered around their community. Attendance rate percentage was calculated for each athlete each season as the number of sessions attended divided by the number of sessions offered that season. The following outcome measures were collected at the beginning and end of each season: 6 min RaceRunning test (Bolster et al., 2017), or 6 min frame running test (6MFRT), as a measure of endurance while in the running frame; Timed Up and Go (TUG) test (Carey et al., 2016) as a measure of functional mobility; and five times sit to stand test (5xSTS) (Kumban et al., 2013) as a measure of functional strength. Each participant contributed to their own goals using the Goal Attainment Scale (Steenbeek et al., 2007), a tool designed to standardize the setting and scaling of goals in a way that allows for both improvement and regression as a result of intervention. GAS has been used to show meaningful change across a range of diagnoses and intervention types in pediatric rehabilitation (Harpster et al., 2019). Goals were collaboratively identified starting with what

TABLE 2 | Season formats.

	Format	Coaching support
Season 1: Winter (4 athletes)	4 weeks of 2 times per week online (45 min per session) remote 4 weeks of 2 times per week online (45 min per session) plus 1×/week (60 min per session) in person	2 DPT head coaches Chicago Run program staff*
Season 2: Spring (8 athletes)	8 weeks of 2 times per week online (45 min per session) plus 1×/week (60 min per session) in person at pubic park location	2 DPT head coaches 1 Chicago Run Junior Coach Chicago Run program staff* Intermittent parent assistance
Season 3: Summer (6 athletes)	8 weeks of 2 times per week in person (60–90 min per session) at public park location	2 DPT head coaches 1 Chicago Run Junior Coach 1 DPT, 2 paraprofessional assistant coaches Chicago Run program staff*
Season 4: Autumn (4 athletes)	8 weeks of 2 times per week in person (90 min per session) after school in hallways and gymnasium	2 DPT head coaches 1 DPT, 2 paraprofessional assistant coaches Chicago Run program staff*

Consistent with other Chicago Run program sites, staff provided curriculum content, access to resources, and attended practice ∼1 session per week.

was important to the participant ("I want to be go from the 1 mile distance to the 5K distance in the race, but it is a big jump and I am not sure I can do it"). The investigator and participant worked together to determine current level ("I can finish the mile like last season," GAS = −1), regression ("I have to stop before completing the mile," GAS = −2), expected level ("I will complete 2 miles," GAS = 0), greater than expected ("I will complete 2.5 miles," GAS = 1), and much greater than expected ("I will complete the full 5K," GAS = 2). All athletes were encouraged to have at least 1 participation-based goal in a process consistent with the framework proposed by Krasny-Pacini et al. (2016). The results were converted to a T-score for overall goal attainment within a season for comparison across participants. Non-blinded physical therapists completed the assessments using standardized protocols for each. In addition, we asked for feedback from participants using a semi-structured interview about the season and their self-perception and enjoyment as an athlete (starting with the broad question of "what are your thoughts about this program?" with follow-up questions based on their responses). We asked other stakeholders (parents and teachers) if they noted any differences during the athlete's participation in the program. Data collected from interviews through written notes, audio recordings and field notes from throughout the season were evaluated by authors using thematic analysis. The study was approved by the institutional review board of Northwestern University and the research review board of Chicago Public Schools. Participants were able to withdraw from the study at any time and still participate in the curriculum as long as they maintained the waiver to participate with Chicago Run.

Study data were collected and managed using REDCap (Research Electronic Data Capture) tools hosted at Northwestern University (Harris et al., 2009, 2019). To evaluate the feasibility of the program we summarized the percentage of sessions attended, comments made by parents, athletes and coaches, and the pilot results of outcome measure differences. Descriptive statistics were used to evaluate differences between pre and post outcome measures, as well as comparison to thresholds of detectable or meaningful difference. The reported RPE and attendance each day were evaluated using a Kruskal–Wallis test to examine the impact of location (3 levels: online, park, and school). A $p < 0.05$ was considered to be significant, and software used was IBM SPSS statistics, Version 27.

RESULTS

A total of 13 athletes participated in the program, with 22 season blocks in total. Some athletes participated in a single season ($n = 8$), and others appeared in 2 seasons ($n = 1$) or 3 seasons ($n = 4$). Diagnoses included cerebral palsy (CP, $n = 10$), arthrogryposis ($n = 1$), Dandy Walker malformation ($n = 1$), and transverse myelitis ($n = 1$). The FMS-500 of participants included those who walked without assistive devices, but had difficulty in crowds (FMS-500 = 5, $n = 4$), one who used bilateral forearm crutches (FMS-500 = 3), one who used a reverse walker (FMS-500 = 2), and several who used a manual or power-assist wheelchair (FMS-500 = 5, $n = 6$). Average age of the participants was 14.46 years on the first day of their participation, and ranged between 8 and 18 years. There were 4 athletes with biological sex of female, and 9 who were male. The zip codes where athletes lived had an average of 26.4% of adults with an annual income below the poverty line (range 17.4–34.7%). Two athletes used the bus transportation in winter, spring, and summer; and 1 athlete used the bus in the summer only.

Starting in the spring season one of the athletes served as a Junior Coach for the team (author LJ), taking a role in planning ∼1 activity per session, encouraging teammates, and leading through example within the group. In addition, we had one participant that was the sibling of an athlete and did not have a disability. She initially joined as a volunteer, and eventually was engaging in most aspects of team activities. Consistent with our plans, there was always at least one head coach/licensed physical therapist at practice, with additional support as shown in **Table 1**.

Our overall attendance average across all seasons and participants was 79% of offered sessions. Two athletes (15% of cohort) chose to stop attending sessions early in the program due to scheduling constraints and not enjoying the program enough to continue. Both athletes who stopped attending were diagnosed with CP (ages 15 and 17 years), and had an FMS-500 score of 5. To assess feasibility in terms of barriers to ongoing participation we removed them from subsequent descriptive results. The remaining 11 participants demonstrated an 86%

attendance rate across all seasons combined. In the winter season, we had an average attendance rate of 97%; spring season was 87%; summer season was 82%; and autumn season was 78%. Among the athletes that were provided transportation ($n = 7$ season blocks) the rate was 89%. Attendance divided by location showed 83% of online sessions were attended, 85% of the sessions offered at a community park, and 78% of those hosted after school. The Kruskal–Wallis test did not reveal differences of attendance based on practice locations ($H = 1.42$, $p = 0.49$). Reasons for non-attendance included vacations during times that school was not in session, COVID-19 exposures or illness, death in the family, and medical procedures/appointments.

Our secondary goal was to evaluate the initial efficacy of the intervention. We did receive reports of minor muscle soreness or fatigue after practice (<2 reports per week across all athletes), particularly early in the season. Ongoing tweaks to running frame settings were made as needed to improve comfort or running form. There were no injuries requiring physician follow-up, and no complaints outside of the musculoskeletal system. Athletes reported RPE ($n = 412$ total data points) at a range of levels (from 1 to 10) that were generally reflective of outward signs of exertion such as heavier breathing or sweating (mean RPE = 4.52, standard deviation, SD = 2.36; median RPE = 4.00, interquartile range = 3). The Kruskal-Wallis test revealed a main effect of location ($H = 42.38$, $p < 0.001$). Athletes reported significantly higher RPE in person (either park or school) compared *post-hoc* to RPE reported online (mean, SD for school = 5.36, 3.11; park = 4.81, 2.38; online = 4.03, 1.87), seen in **Figure 2A**. There was inconsistent collection of the RPE in certain seasons, especially when athletes were further spread apart in distance.

With respect to outcome measures, we did have some gaps in research-quality data; longitudinal data is shown in **Figure 2**. Considering the data available, the 6 min frame running test improved by 170.4 m over a season ($n = 16$ pre-posttest pairs, SD = 135.6 m). Using the most conservative minimal detectable change (MDC) according to Bolster et al. (2017) of 172 m, 6 athletes surpassed the threshold of change. The TUG improved by 8.44 s ($n = 15$ pre-post-test pairs, SD = 10.07 s), with 8 athletes surpassing the minimal clinically important difference (MCID) of 5.31 s (Carey et al., 2016) during a single season. The 5xSTS improved by an average 14.1 s ($n = 15$ pre-post-test pairs, SD = 20.74 s), with 6 athletes surpassing the MDC of 0.11 reps/s (Wang et al., 2012) in a single season. The GAS T-score average was 65.01 ($n = 20$ season end assessments, SD = 8.92), with 14 athletes achieving a "successful" season using the criteria of Desloovere et al. (2012) (T-score > 60). We completed community-based runs at distances of 1 mile ($n = 20$; completed at Garfield Park, Humboldt Park, Jackson Park, Columbus Park and River Park in Chicago, IL; the number of participants in each race was limited to 150 registered runners due to COVID-19 policies of Chicago Area Runners Association) and 5 km ($n = 3$; completed at Humboldt Park with ∼75 runners and the Great Lakes Adaptive Sports Association Twilight 5K with ∼150 runners and para-athletes), as well as an in-school celebration run completed at multiple distances (0.6, 1, 1.2, and 1.7 miles, $n = 1$ athlete running each distance). At every race, each athlete had at least 1 family member attend to cheer for them or to run with them. One athlete in the winter season decided to not participate in the run due to concerns about COVID-19 precautions and potential exposures, but was able to complete the 1-mile distance during a practice at the end of the season.

Qualitatively, we completed 21 interviews (18 for athletes at the end of their season, 1 paraprofessional, and 2 teachers), and 6 coaches/Chicago Run staff contributed to field notes. We found a few themes in our data. The most common sentiment was an enjoyment of physical activity and happiness to be moving and active after the time spent in isolation during COVID-related quarantine. Within this overall theme, athletes noted that they liked using the running frames to move, and also enjoyed interacting with peers in a team setting. Athletes expressed opinions such as "exercising is winning," and "it is been a while since I have been outside and it was so nice to see everyone." One athlete's paraprofessional noted that he was more positive throughout the day during the running program, and that he expressed sadness about it coming to an end. In addition, our field notes detailed several instances of informal leadership and strong team behaviors, including verbal encouragement for elevated performance between athletes, providing clear instructions to one another during a tethered obstacle course, and a younger athlete sharing with coaches that they looked up to one of the older athletes and their abilities.

A second theme identified was pride for goal accomplishment and noticing results related to effort put into the running program. Specifically, there was a lot of positive expressions related to the community run. One participant was asked what the best part of their summer had been on the day of their community run, and their response was "today." Another athlete noted, "We are a family of runners now," in reference to the participant's father and mother being runners who also completed community races. In addition to goals documented with GAS, some athletes said they could move more easily (stairs, walking were examples shared by athletes). Following the autumn season, one teacher shared her impression that an athlete in her class was sitting with better posture in his wheelchair throughout the day while participating in the program.

A third theme identified in field notes and interviews was the impact of the community environment on the athletes' efforts and pride in participating. In winter, spring and summer, our celebration race was held at a community race where we had the opportunity to raise awareness about athletes with movement disabilities within our local community. Fellow runners and spectators demonstrated support and encouragement that athletes said increased their enjoyment and pride of accomplishment. Our autumn season celebration race was held in the school, and was attended by parents of the athletes as well as other students attending a different afterschool program. Notably, we observed non-disabled peers of the athletes spontaneously voiced words of support, made signs of encouragement, and cheered for the duration of the race, with some spectators noting, "I am so proud of them."

Finally, there was a theme related to a lack of reliable access to fitness outside of the program. A minority of participants discussed other structured activities they were

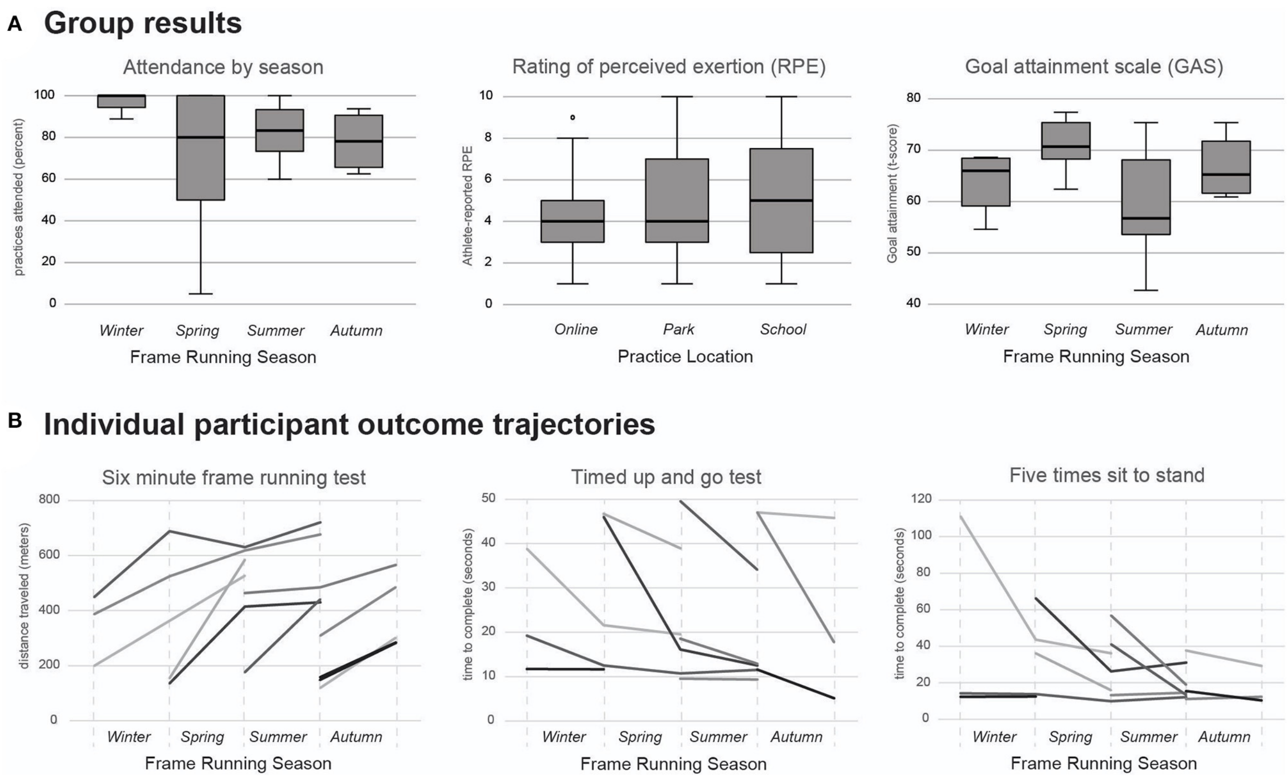

FIGURE 2 | (A) Group summary box and whisker plots. The practice attendance percentage is calculated by dividing the number of practices attended by the total number for a season. This panel includes all 8 athletes that began the spring season. There was a significant main effect of location found in the Kruskal–Wallis test of RPE ($H = 42.38$, $p < 0.001$), where park and school were both significantly higher than online; the median (shown in thick black in plot) of home was four, park was four, and school was five. GAS *t*-scores are calculated to combine each athlete's overall goal attainment within a season; with coaching and support from researchers, athletes set 2–4 goals each season. **(B)** Individual data trajectories shown for performance-based outcome measures. Each line represents a different participant. For reference, the normative TUG for 5–13 year old youth ranges from 6.20 to 7.12 s (Itzkowitz et al., 2016), and the 5xSTS for 14–19 year old youth is 6.5 s, with a standard deviation of 1.2 s (Bohannon et al., 2010).

involved in, and many shared they were otherwise engaged in predominantly sedentary activities during their day. When accessing our program, barriers to attendance included technology difficulties (online sessions), transportation (in person), or competing events (both formats). Those that used the provided transportation ($n = 2$ in winter and spring and $n = 3$ in summer) stated they would have been otherwise unable to participate due to limitations in transportation access. Everyone who completed a season said they would sign up for another one.

We did not find any consistent themes related to location of practices, and no clear preference between session type for athletes experiencing both online and in person; both were deemed acceptable and generally easy to attend. However it was noted that being in person was "not the same as a computer or iPad." In addition, we did not complete interviews with the athletes who decided after a limited number of sessions that they were not interested in continuing. One cited that they felt the program was too juvenile in the activities and the other was hesitant to try the running frames at enrollment and did not find them comfortable.

DISCUSSION

This preliminary study provides evidence for the feasibility of the use sport-based youth development and running frames to support fitness and participation goals for athletes who have movement and/or balance challenges. We found a number of useful lessons for future seasons by trialing a variety of formats, providing for flexibility and opportunities as the uncertainty of the pandemic continues.

The program in this study addressed many of the common barriers and facilitators noted by the American Academy of Pediatrics (Carbone et al., 2021), including access to transportation, supervision, a focus on social learning, physical literacy, and individual goals at activity plans. It also is consistent with the recommendations of a recent international clinical practice guide (Jackman et al., 2021) and there is a demonstrated interest for programs aimed at participation-based exercise for youth with disabilities (Shields et al., 2018). Our cohort confirmed that they liked to exercise, and needed appropriate outlets to do so. Supportive relationships and service availability are key factors in community participation (Willis et al., 2017).

The use of online programming was safe and well-attended, including by families who were extra cautious about the spread of COVID-19. An advantage of the virtual format was the use of features such as screen sharing, chat box, and polls to facilitate activities and communication. It was feasible for one coach to lead several athletes. In addition, we were not limited by the physical distances of where athletes and coaches were located and athletes could participate from their own home, which lead to high convenience as has been shown in other studies (Rowland et al., 2016; Astley et al., 2021; Calcaterra et al., 2021; Weiss et al., 2021). However, it was difficult at times to fully engage remote athletes in a way that was both safe and challenging without anyone close by to supervise for their specific movement challenges.

While in person, athletes appeared more likely to fully engage in an activity, able to push themselves a further with guidance and supervision of coaches and teammates and perhaps through the use of the running frame to support movement, as evidenced by the RPE differences. In-person practices were overall safe, as some musculoskeletal discomfort was an anticipated potential side effect of engaging in a new activity. These reports were few, minor, and diminished as the season progressed, indicating a training effect and/or finding optimally comfortable settings. Being outdoors was a further advantage because it offered more safety related to spread of COVID-19 in combination with other precautions such as cleaning protocols and temperature monitoring. The less desirable aspects of in-person included potential impact of the weather and added cost for additional coaches and transportation.

The afterschool format was more like programming aimed at children without disabilities and took advantage of multiple athletes already being in one location. Joint activities where students with and without disabilities work together have a positive impact on the attitude toward students with disabilities, highlighting the advantage of peer interactions and support (Alnahdi et al., 2021). This demonstrates the value and importance of active participation by all students in their community and peer group. It was anticipated that attendance would be higher given the convenience of programming at school, but we found there were higher rates of schedule conflicts during this season. Missed practices appeared to be at least partially attributable to pandemic related precautions and circumstances such as exposure to someone infected with COVID-19. In addition, following a pause in certain medical care for the year prior (Sutter et al., 2021) families may have been catching up on medical appointments for routine care such as eye exams or physiatry visits. Children with movement challenges have higher healthcare needs in general, and future expectations for attendance may need to take some of these factors into consideration. Like other programs in a school setting (Cleary et al., 2017), our data from the autumn season suggest improvements in endurance (6MFRT).

Each of the three modes of intervention was found to be feasible and with different benefits and challenges. In combination with in-person programming, the use of remote practices ongoing would be a feasible way to increase dosage without the added cost of transportation or time constraint for travel. When in person, we found that athletes engaged in higher perceived intensity of exercise, potentially due to the combination of balance support and freedom of movement provided by the running frame. This mode of delivery also provided for specificity of practice for the team goal of community race participation. The option for transportation was critical for equitable access to the program by all who could benefit (Aviram et al., 2021). The locations where most of our participants live and attend school are within 26 areas of high economic hardship in the city of Chicago and in areas of low childhood opportunity (Health, 2021). This highlights a need for additional supports to ensure equitable access to physical activity.

Provision of a program such as the one introduced in this study fills an important gap in options for physical activity. A study of almost 2,000 children with CP in Sweden (Degerstedt et al., 2021) found that while most (87%) participated in physical education class at school, barely half (58%) had physical leisure activity. International guidelines highlight the importance of exercise and muscle strengthening for CP (Damiano et al., 2021). In addition to a focus on reducing sedentary behaviors and increasing physical activity in general, Verschuren et al. recommend that cardiorespiratory exercise be completed 2–3 times per week for a minimum of 20 min, at more that 60% peak heart rate, or more than 40% of the heart rate reserve (Verschuren et al., 2016). We achieved the time target in all seasons in the current study, and based on the RPE and observation, the intensity level was at least moderate, although this will require future study. We are exploring ways to record RPE and heart rate more consistently, including with athletes who have challenges in communication or for all athletes as they are still learning to connect physiologic signals with reported numbers. Although 8 successive weeks of training are recommended, a lifestyle practice is most likely to result in optimal health benefits (Verschuren et al., 2016). In our athletes who completed more than one season, we also found continued improvements in their running times and outcome measures. When administered in higher dosages, other running interventions have shown improved running abilities, particularly those with CP who could walk unaided at the onset of the program (Gibson et al., 2018). Programs shaped in an individual's personal goals added to their enjoyment of the program (Kahlon et al., 2019). Consistent with these studies, we found changes in physical performance for athletes participating in our frame running focused fitness group.

We also found strong community support for the athletes as well as strong parental support previously shown to be important in youth physical activity (Ku and Rhodes, 2020). In mainstream media, there is emerging coverage of talents and abilities that individuals with mobility impairments possess. For examples, the professional sponsorship of Justin Gallegos (Cash, 2018), coverage of Paralympic events and documentaries (Ferrara et al., 2015; Coates and Vickerman, 2016) of multi-medal athletes such as Tatyana McFadden (Bonhôte and Ettedgui, 2020; Committee, 2021b) and Ryley Batt (Committee, 2021a), and the inclusion of dancers with disabilities in professional performances (Caldwell, 2019; Chicago, 2021; Dubon et al., 2021) are becoming more common. The positive messaging associated with this type of accomplishment lays the foundation for young children with similar physical challenges to envision themselves also achieving fitness and athletic goals. Similar to the qualitative experience of adults participating in adaptive sports (Lape et al., 2018), the cohort of athletes in our study already had general social interactions during practices at baseline, but continued to grow through the use of social-emotional learning and goal acquisition. This is an area of opportunity to explore more deeply in future work.

Although our study was not adequately powered to evaluate outcomes in the body structure and function domain, pilot findings in the activity domain (TUG, 5xSTS, 6MFRT) are encouraging and warrant further investigations. The study does demonstrate that several modes of intervention administration are feasible and can be tailored to individuals, teams, or communities for maximal impact. If targeted and engaging intervention makes an impact during adolescence, there's promise of shifting behaviors toward more physical activity and fitness across the lifespan.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the data set is limited due to pilot nature. Requests to access the datasets should be directed to Theresa Sukal-Moulton, theresa-moulton@northwestern.edu.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Northwestern University Institutional Review Board and Chicago Public School Research Review Board. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

TS-M, TE, LJ, CL, and DG-S designed the program and study. TS-M, TE, LJ, and CL administered the program, collected data, and summarized results. TS-M, TE, and DG-S drafted the manuscript. All authors have reviewed and edited the manuscript. All authors contributed to the article and approved the submitted version.

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Physical Activity Levels, Perceived Body Appearance, and Body Functioning in Relation to Perceived Wellbeing Among Adolescents

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This study aimed to investigate self-reported physical activity levels, perceived body appearance, and body functioning in relation to perceived wellbeing among adolescents. A cross-sectional survey was performed in four upper secondary schools in one municipality in southern Sweden. Data were obtained from questionnaires completed by 1,491 adolescents (55.4% females; median age 16; range 15–17 years) during school hours. The participation rate was 71.4%. Logistic regression analyses were carried out with wellbeing as the dependent variable. The independent variables included gender, perceived family financial situation, perceived body appearance, perceived body function, and physical activity level. Perceived positive wellbeing was associated with being satisfied with their body's appearance (OR 3.4; CI 2.6–4.4) and function (OR 3.1; CI 2.2–4.2), being physically active three or more times per week (OR 1.5; CI 1.1–2.0), and a good perceived family financial situation (OR 3.3; CI 1.6–6.7). Gender was not significantly associated with wellbeing. A positive body image, which include both body appearance and body function, and high physical activity levels were significantly associated with wellbeing in adolescents, corroborating the importance of promoting physical activity among younger populations.

Keywords: physical activity, body image, body appearance, body functioning, adolescents, wellbeing, health

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INTRODUCTION

According to the World Health Organization (WHO), mental health "is a state of wellbeing in which the individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to his or her community" (World Health Organization, 2018). Adolescent mental health problems are a global public health concern accompanied by a growing disease burden (Whiteford et al., 2013). Mental disorders are estimated to affect 10–20% of children and adolescents worldwide, resulting in short- and long-term consequences that include school disengagement and poor quality of life (Kieling et al., 2011). One in five adolescents are reported to have a mental illness that will persist into adulthood (Kessler et al., 2005) that imposes high costs for society (Suhrcke et al., 2008). Emerging evidence suggests that primary prevention can address some mental health problems and improve the overall mental wellbeing of children and adolescents (Kieling et al., 2011). Given the pervasiveness of mental health disorders in adolescents, importance must be placed on promoting good mental health in this population.

Adolescence is an important period for the development of good health and wellbeing in adulthood (Bluth et al., 2017). Physical activity (PA) is often suggested as a method to improve wellbeing in young people (Biddle and Asare, 2011; Ekkekakis, 2013). Although the physical and psychological benefits of PA are well-established, PA decreases during adolescence (Kemper et al., 2001) and large numbers of adolescents are physically inactive or sedentary (de Moraes et al., 2013). In addition low levels of PA are shown to be independently associated with diminished psychological wellbeing among adolescents (Ussher et al., 2007). Furthermore, cognitive functioning, depression, and self-esteem were found to be associated with PA (Biddle et al., 2019). Self-esteem is considered a key indicator of mental health and as a construct includes emotional stability and subjective wellbeing (Lindwall et al., 2014). Adolescents are recommended to engage in moderate to vigorous physical activity (MVPA) for at least 60 min every day (World Health Organization, 2020); however, 81% of the world's adolescents fail to reach this target (World Health Organization, 2018). Similar results are seen in Sweden, where 87% of adolescent males and 91% of adolescent females do not reach the WHO's recommendations (Public Health Agency of Sweden, 2019). Approximately 10–15% of adolescents were shown to be engaging in MVPA on a regular basis, with females being less active than males (Ekelund et al., 2012; Khan et al., 2015; Chzhen et al., 2018). Over the past decades, PA levels have decreased, and sedentary behavior has increased among adolescents (Tremblay et al., 2011; Nyström et al., 2018). Further, at the age of 15, ∼75% of waking time is spent as inactive and sedentary (Public Health Agency of Sweden, 2019).

The 2017–2018 Health Behavior in School-aged Children (HBSC) study found that 66% of adolescent females and 85% of adolescent males aged 15 years in Sweden rated their wellbeing as high or very high (Public Health Agency of Sweden, 2019). This result indicates that there are more adolescent males than adolescent females who report positive wellbeing in Sweden. This discrepancy is also seen in HBSC contributions from other countries (Inchley et al., 2020). In Norway, France, and Italy, adolescent females rated their wellbeing lower than that of adolescent males (Bonsergent et al., 2012; Petracci and Cavrini, 2013; Bjørnsen et al., 2019). Additionally, wellbeing tends to decrease with increasing age (Inchley et al., 2020). In France, a study was conducted with 5,226 adolescents aged 14–18 years in which the results showed less wellbeing in adolescent females and adolescent males in late adolescence as compared to early adolescence (Bonsergent et al., 2012).

Good wellbeing was significantly associated with regular PA (Petracci and Cavrini, 2013; McMahon et al., 2017) and with several health benefits (Janssen and LeBlanc, 2010; Warburton and Bredin, 2017; Rodriguez-Ayllon et al., 2019) and a positive body image (Griffiths et al., 2017; Ra and Cho, 2017). Body image includes the feelings that an individual experiences about his or her body (Slade, 1988; Hosseini and Padhy, 2021). Body image is defined as the internal, subjective representations of physical appearance and bodily experience that encompasses perception of both body appearance and body functioning (Cash and Pruzinsky, 1990). It also includes an attitudinal component that reflects the degree to which individuals are satisfied with body appearance and functioning, and involves how one sees themselves (Grogan, 2021). Body image can be deconstructed into three components: the body's objective features (weight, size, body shape), how the individual experiences his or her body based on its appearance (satisfied, dissatisfied), and how the body functions in daily life (movement, fitness) (Hosseini and Padhy, 2021). However, previous studies do often not take into consideration the different dimensions of body image (Fenton et al., 2010). There is therefore a need for studies that distinguish between body appearance and body function.

For many individuals, appearance reaches a new degree of importance during adolescence (Foley Davelaar, 2021). As the body develops with age, increased concerns about weight and body appearance may emerge (Ren et al., 2018). Generally, female and male adolescents tend to hold a more negative view of their bodies during adolescence than during childhood. According to the Swedish contribution of the HBSC study, the majority of adolescents in Sweden were quite satisfied with the appearance of their bodies (Public Health Agency of Sweden, 2019). More adolescent males than adolescent females thought they were at a normal weight weighed, while more females thought they were overweight (Public Health Agency of Sweden, 2019). Overall, more adolescent females reported holding a negative body image compared to adolescent males (Lawler and Nixon, 2011; Griffiths et al., 2017; Ren et al., 2018), and more females than males (80 vs. 55%, respectively) aged 16 years wanted to change a feature on their body (Lawler and Nixon, 2011). A negative body image was affected by a poor socioeconomic status (SES) (Mikkilä et al., 2003), pressure from friends, and being criticized for one's appearance (Lawler and Nixon, 2011). Furthermore, depression, low self-esteem, and a high body mass index (BMI) were significantly associated with a negative body image among female adolescents (Ganesan et al., 2018). Studies have found that physical self-concepts predict behaviors important for wellbeing, such as PA, dietary behavior and self-esteem (Crocker et al., 2006). Physical self-concepts have been shown to be an even better predictor of behavior than characteristics such as height and weight (Fox, 1997). A recent study among adolescents aged 13–15 in Sweden (Sollerhed et al., 2021) found that good subjective health was associated with good wellbeing in school, good family financial situation, positive body image, and high physical activity levels. Further studies on self-concepts such as body image and PA behavior in relation to wellbeing among adolescents in Sweden are warranted.

Given that previous studies show that many adolescents report poor wellbeing, low PA levels, and negative self-concepts such as poor body image and body anxiety, these observations lead to questions as to how these factors are associated in a population of adolescents in Sweden. Therefore, the purpose of this study is to investigate self-reported PA levels, perceived body appearance, and body functioning in relation to perceived wellbeing among male and female 16-year-old adolescents.

MATERIALS AND METHODS

This study used quantitative data from a larger research project (ISRCTN17006300). The study was approved by the Regional Ethical Review Board (EPN 2015/113) and conducted in accordance with the Declaration of Helsinki. Participation in the study was voluntary, and all participants and their parents or legal guardians received both oral and written information about the study. This cross-sectional study was performed in four upper secondary schools in a municipality in southern Sweden with approximately 100,000 inhabitants. Five schools were invited to participate, and one declined. The four participating schools were situated in urban areas, but the students who attended these schools came from both urban and rural areas. One was a private school and three were public schools. The study utilized online questionnaires that were completed during school hours in a classroom with a teacher present. Data collection took place between November 2017 and June 2019. The questionnaire used in our study was found to be reliable for our age group (Sollerhed, 2006).

All students in their first year at the four participating upper secondary schools were asked to participate in the study. The median age of the students was 16 years (range: 15–17 years). Of the 2,089 total respondents, 1,491 (43.7% males, 55.4% females) participated in the study and completed the entire questionnaire, representing a response rate of 71.4%. Participation was voluntary and could be withdrawn without question at any time; however, the age and gender of students who withdrew from the study did not significantly differ from those of participants.

Statistical Analysis

The online questionnaire included questions about PA, body image (perceived body appearance and body functioning), perceived wellbeing, and perceived family finances. SPSS Statistics v.25 software was used to produce both descriptive and analytical statistics. Data were first analyzed using descriptive statistics with frequencies and percentages. Chi-square tests were used to investigate the associations between perceived wellbeing and the independent variables of body appearance, body functioning, PA, gender, and family financial situation. Subjective health has been shown to be affected by gender and SES (Operario et al., 2004; Marmot and Wilkinson, 2005; Michel et al., 2009) and therefore, these variables were included in our analysis. The relationships between perceived wellbeing and the independent variables of sex, body appearance, body functioning, PA, and perceived family finances were investigated by bivariate analysis. Finally, multiple logistic regression was used to examine whether perceived body appearance, body functioning, PA, gender and perceived family finances had any significant effect on the likelihood of observing positive perceived wellbeing among adolescents. All independent variables were included in a single model, without any additional variable selection (method "enter" in SPSS). The rationale for using a logistic regression analysis is that it allows us to see the effects of variables after adjusting for other variables (e.g., perceived body appearance). This helps us verify that the associations seen in the bivariate analysis aren't due to the influence of other variables.

The response options were collapsed to facilitate data interpretation. For example, the question "How are you most of the time?," with its answer options "Very good" and "Quite good" have been recoded into one alternative answer (good wellbeing); likewise with the answer options "Neither good nor bad", "Pretty bad," and "Very bad" (poor wellbeing). The answer option "Do not know" to the question of family financial situation had no natural distribution to the other answer alternatives and was, therefore, not dichotomized. Coding of response options is shown in **Table 1**. The significance level was set at $p < 0.05$.

RESULTS

As shown in **Table 2**, the majority of the adolescents rated their wellbeing as good (68%), while 74% perceived their family financial situation as good. The majority of respondents were satisfied with their body appearance (68%) and their body functions (83%), and 52% of respondents reported engaging in PA for at least 30 min three or more times per week. A larger percentage of adolescent females in our sample rated their wellbeing as good relative to adolescent males (71 and 64%, respectively; $p = 0.003$). Furthermore, more adolescent females were satisfied with their body appearance (72%) and body function (85%) compared to adolescent males (63 and 80%, respectively; **Table 2**).

The results of the bivariate analysis showed a significant association between perceived positive wellbeing and being satisfied with one's body appearance and body function among both adolescent males and females ($p < 0.0001$). Perceived positive wellbeing was also associated with being physically active three or more times per week in both male and female adolescents ($p < 0.0001$). An association between perceived positive wellbeing and a perceived good financial situation was also found among adolescent males ($p < 0.0001$) and females ($p = 0.011$; **Table 3**).

The results from the multiple logistic regression analysis showed that perceived positive wellbeing was associated with being satisfied with one's body appearance (OR 3.4; CI 2.6–4.4) and body function (OR 3.1; CI 2.2–4.2), engaging in PA three or more times per week (OR 1.5; CI 1.1–2.0), and perceived good family financial situation (OR 3.3; CI 1.6–6.7). Gender was not significantly associated with wellbeing (**Table 4**).

DISCUSSION

The main findings of our study revealed that PA level, perceived body appearance, and perceived body function were each significantly associated with perceived wellbeing. A greater number of adolescents who were physically active three or more times per week perceived their wellbeing as positive relative to less active or inactive adolescents. Other studies have reported that lower PA levels are significantly associated with worse mental wellbeing (Kirkcaldy et al., 2002; Brodersen et al., 2005), which is in accordance with the results of our study. Given the salutogenic approach used in our study, we focused on positive wellbeing instead of poor wellbeing; however, the pathogenic side of the phenomenon is also shown: low PA levels were associated with poor wellbeing. Similar results were shown in previous studies (Ussher et al., 2007; Petracci and Cavrini, 2013; Ho et al., 2015; McMahon et al., 2017). High PA levels

TABLE 1 | Variables included in the logistic regression with wellbeing as the dependent variable.

Item	Response options in questions	Coding
Wellbeing	5 categories	Good wellbeing (1–2)
"How are you most of the time?"	Very good (1) → Very bad (5)	Poor wellbeing (3–5)
Body appearence	4 categories	Satisfied (1–2)
"How satisfied are you with your body appearance?"	Yes, completely satisfied (1) → No, not satisfied at all (4)	Not satisfied (3–4)
Body function	4 categories	Satisfied (1–2)
"How satisfied are you with how your body works?"	Yes, completely satisfied (1) → No, not satisfied at all (4)	Not satisfied (3–4)
Physical activity	7 categories	PA ≥3 times/week (6–7)
"How often do you exercise in your free time for at Least half an hour so that you become short of breath And sweaty?!"	Never (1) → Regularly 4 times or more/week (7)	PA 2 times/week (5)
		PA never, seldom, or once a week (1–4)
Perceived family financial situation	5 categories	Good (1–2)
"How well-off do you think your family is?"	Very good (1) → Very bad (5)	Average (3)
		Not so good (4–5)

reduced symptoms of depression and anxiety in adolescents (Bell et al., 2019). Thus, primary prevention such as PA can improve overall mental wellbeing of children and youth in different ways, which is generally considered a more appealing treatment than psychotropic medications.

Mental health difficulties affect 10–20% of children and adolescents worldwide (Kieling et al., 2011). At the same time a large proportion of adolescents have low PA levels or are sedentary (World Health Organization, 2018). Moreover, evidence shows that a substantial proportion of mental health problems in adults originate early in life (Kessler et al., 2007). Thus, efforts are urgently needed to reduce the burden of mental health difficulties in adults by detecting and treating these difficulties as early in life as possible. PA is an attractive intervention to this end, because it is a low-cost, non-pharmacological option with few deleterious effects or costs on society. A more resilient mindset appears to be developed among physically active children and adolescents, which may strengthen problem-solving skills that can further enhance their resilience (Edward, 2005).

A greater percentage of the physically active adolescents in our study rated their body functions as good relative to less active adolescents, which may indicate that physically fit adolescents rely more on their movement skills and fitness. They may interpret their high stamina and strength as sufficient to perform regular PA and to help them cope with daily stressors, which increase resilience, self-efficacy, and wellbeing (Edward, 2005). Improving cardiorespiratory fitness has been shown to be an important interventional strategy to promote psychological wellbeing in children (Chen et al., 2021).

In our study, the adolescents who were satisfied with their body functions appear to be in a positive development spiral. They perceive their body function positively, with ability to engage in PA, which in turn is related to wellbeing. Higher levels of regular PA were shown to be associated with better self-perceived health status and quality of life in both adults (Anokye et al., 2012), and youth (Marker et al., 2018). Furthermore, a high percentage of adolescents in our study who reported a positive body image (both body appearance and function) estimated their wellbeing as good, which is in accordance with results from previous studies (Griffiths et al., 2017; Ra and Cho, 2017). Body image, which is defined as the internal subjective perceptions of both body appearance and body functioning (Cash and Pruzinsky, 1990), also includes attitudinal components that involve how one perceives themselves (Grogan, 2021) and experiences appearance and body functions in daily life (Hosseini and Padhy, 2021), which are all vital to wellbeing. The relationship between body image and wellbeing (Gillen, 2015), between body image and PA (Kantanista et al., 2015), and between PA and wellbeing (Biddle and Asare, 2011; Ekkekakis, 2013; Chen et al., 2021) indicate that school and health care providers should encourage PA and positive body image among young persons to improve wellbeing and yield potential health benefits.

The results of the study showed that a perceived good family financial situation was significantly associated with good wellbeing, which has been shown in previous studies. Family financial status can influence the degree to which young people engage in PA (Kirby et al., 2013). SES and financial situation have been shown to provide more opportunities for organized PA in leisure time (Kirby et al., 2013) and is associated with wellbeing (Stalsberg and Pedersen, 2010; Plenty and Mood, 2016). Other studies showed that adolescent's PA was associated with their father's SES and education. However, these associations with SES were weaker than with the fathers' own PA level (Yang et al., 1996). Participation in PA by children and adolescents is greater in families with active parents than in families with less physically active parents (Moore et al., 1991; Yang et al., 1996; Trost et al., 2003; Ornelas et al., 2007). Parents play a large role in determining what type of PA their children engage in and which financial resources they have available, while parental support, modeling, and shared activities appear equally as important or

TABLE 2 | Description of wellbeing, body appearance, body function, physical activity, and family financial situation in male and female adolescents ($n = 1,491$).

	Total, *n* (%)	Males, *n* (%)	Females, *n* (%)	*P*[a]
Wellbeing	1,458 (97.8)	642 (98.5)	816 (98.8)	0.003
Very good	278 (19.0)	112 (17.4)	166 (20.3)	
Quite good	713 (48.9)	300 (46.7)	413 (50.6)	
Neither good nor bad	327 (22.5)	145 (22.6)	182 (22.3)	
Quite bad	114 (7.8)	70 (10.9)	44 (5.4)	
Very bad	26 (1.8)	15 (2.4)	11 (1.4)	
Missing data	33 (2.2)	10 (1.5)	10 (1.2)	
Body appearence	1,461 (98.0)	641 (98.3)	820 (99.3)	<0.0001
Yes, completly satisfied	184 (12.6)	78 (12.2)	106 (12.9)	
Yes, quite satisfied	812 (55.6)	328 (51.2)	484 (59.0)	
No, not that satisfied	340 (23.3)	155 (24.1)	185 (22.6)	
No, not satisfied at all	125 (8.5)	80 (12.5)	45 (5.5)	
Missing data	30 (2.0)	11 (1.7)	6 (0.7)	
Body function	1,453 (97.4)	639 (98.0)	814 (98.5)	0.015
Yes, completly satisfied	417 (28.7)	158 (24.7)	259 (31.8)	
Yes, quite satisfied	784 (54.0)	351 (54.9)	433 (53.2)	
No, not that satisfied	200 (13.7)	99 (15.5)	101 (12.4)	
No, not satisfied at all	52 (3.6)	31 (4.9)	21 (2.6)	
Missing data	38 (2.6)	13 (2.0)	12 (1.5)	
Physical activity	1,470 (98.6)	645 (98.9)	825 (99.9)	0.008
Regularly $\geq$4 times/week	456 (31.0)	190 (29.5)	266 (32.2)	
Regularly 3 times/week	307 (20.9)	132 (20.5)	175 (21.2)	
Regularly 2 times/week	243 (16.5)	87 (13.5)	156 (18.9)	
Regularly 1 time/week	198 (13.5)	98 (15.2)	100 (12.1)	
Sometime every month	171 (11.6)	88 (13.6)	83 (10.1)	
Sometime every year	55 (3.8)	28 (4.3)	27 (3.3)	
Never	40 (2.7)	22 (3.4)	18 (2.2)	
Missing data	21 (1.4)	7 (1.1)	1 (0.1)	
Perceived family financial situation	1,470 (98.6)	647 (99.2)	823 (99.6)	0.458
Very good	557 (37.9)	230 (35.5)	327 (39.7)	
Quite good	523 (35.6)	234 (36.2)	289 (35.1)	
Average	326 (22.1)	147 (22.7)	179 (21.7)	
Not so good	34 (2.3)	22 (3.4)	12 (1.5)	
Not good at all	7 (0.5)	3 (0.5)	4 (0.5)	
Do not know	23 (1.6)	11 (1.7)	12 (1.5)	
Missing data	21 (1.4)	5 (0.8)	3 (0.4)	

[a]*Chi-squared test.*

even more important as financial status in determining the type of PA in which their children engage (Gustafson and Rhodes, 2006).

Results from our logistic regression analysis showed that gender was not significantly associated with wellbeing. However, the results showed that more adolescent females than males rated their wellbeing as very good or quite good (71 vs. 64%, $p = 0.003$). This result differs from previous studies, where more adolescent males than females rate their wellbeing as good (Bonsergent et al., 2012; Petracci and Cavrini, 2013; Bjørnsen et al., 2019). Furthermore, more adolescent females than males in this study reported regularly engaging in PA three or more times per week and reported a positive body image, which contradicts the results of other studies (Public Health Agency of Sweden, 2019; Steene-Johannessen et al., 2020). The explanation for our finding that adolescent females were more physically active than adolescent males is unclear. The results may indicate a skewness in the sample of female adolescents, who were as physically active as their male counterparts—and at times slightly more physically active—and their PA level was associated with a high self-reported wellbeing. Furthermore, this sample of physically active females can be seen as a good example of non-specific gender behavior that can serve as a model for improved wellbeing, since PA is suggested to improve wellbeing in young people (Biddle and Asare, 2011; Ekkekakis, 2013) and to improve body image (Vocks et al., 2009).

TABLE 3 | Relationship between wellbeing, body appearance, body function, physical activity, and family financial situation in male and female adolescents ($n = 1{,}491$).

	Males, *n* (%)			Females, *n* (%)		
	Good wellbeing	**Poor wellbeing**	***p****	**Good wellbeing**	**Poor wellbeing**	***p****
Body appearence			<0.0001			<0.0001
Satisfied	311 (76.2)	91 (40.1)		469 (81.4)	116 (49.4)	
Not satisfied	97 (23.8)	136 (59.9)		107 (18.6)	119 (50.6)	
Body function			<0.0001			<0.0001
Satisfied	364 (88.8)	141 (62.9)		527 (92.1)	159 (67.4)	
Not satisfied	46 (11.2)	83 (37.1)		45 (7.9)	77 (32.6)	
Physical activity			<0.0001			<0.0001
Regularly ≥3 times/week	231 (56.3)	88 (38.4)		333 (57.6)	104 (43.9)	
Regularly 2 times/week	55 (13.4)	32 (14.0)		111 (19.2)	43 (18.1)	
Never, seldom, or once a week	124 (30.2)	109 (47.6)		134 (23.2)	90 (38.0)	
Perceived family financial situation			<0.0001			0.011
Good	329 (81.4)	132 (58.9)		449 (78.5)	159 (69.4)	
Average	68 (16.8)	75 (33.5)		115 (20.1)	62 (27.1)	
Not so good	7 (1.7)	17 (7.6)		8 (1.4)	8 (3.4)	

**Chi-squared test.*
Missing data: <3.0%.

TABLE 4 | Variables associated with good wellbeing in a multiple logistic regression analysis ($n = 1{,}491$).

Variable	*B*	*SE*	χ^2	*p*	*OR*	95% CI
(Intercept)	−2.69	0.60	20.27	<0.001	–	–
Sex (male) reference	–	–	–	–	–	–
Sex (female)	0.57	0.48	1.40	0.236	1.76	[0.69, 4.49]
Economy (poor) reference	–	–	–	–	–	–
Economy (average economic situation)	0.69	0.38	3.32	0.069	2.00	[0.95, 4.21]
Economy (good economic situation)	1.19	0.37	10.45	0.001	3.27	[1.59, 6.72]
PA (once a week or less) reference	–	–	–	–	–	–
PA (twice a week)	0.23	0.19	1.53	0.217	1.26	[0.87, 1.83]
PA (three times a week or more)	0.41	0.14	8.32	0.004	1.51	[1.14, 1.99]
Body appearance (not satisfied) reference	–	–	–	–	–	–
Body appearance (satisfied)	1.22	0.13	85.11	<0.001	3.40	[2.62, 4.41]
Body function (not satisfied) reference	–	–	–	–	–	–
Body function (satisfied)	1.12	0.16	48.65	<0.001	3.07	[2.24, 4.21]

$\chi^2(8) = 262.44$, $p < 0.001$, Hosmer–Lemeshow, $p = 0.510$, Nagelkerke $R^2 = 0.236$. Variance Inflation Factors (VIFs) were calculated to detect the presence of multicollinearity between independent variables. All independent variables in the regression model have VIFs of 1.01–1.06.

The present study showed that a positive body image was significantly associated with good wellbeing, which corroborates the results of previous studies (Griffiths et al., 2017; Ra and Cho, 2017). However, approximately one-third of adolescents in our study were dissatisfied with their body appearance. Social media can be a contributing factor to body image, as adolescents are regularly exposed to various social media (Spurr et al., 2013) that portrays a slim body as ideal. Both adolescent males and adolescent females are affected by social media (Keles et al., 2020). Adolescent males largely strive for a more muscular body, while adolescent females predominantly desire a lean body (Spurr et al., 2013). Other factors that can negatively affect body image are stress, depression (El Ansari et al., 2014), and poorer financial conditions (Ren et al., 2018). The present study showed that adolescent females were more satisfied with their body's appearance and its function than were adolescent males, which differs from previous research. For example, a Dublin study found that 40% of adolescent males and 19% of adolescent females were satisfied with the appearance of their bodies (Lawler and Nixon, 2011). Other studies also showed similar gender differences in body satisfaction (El Ansari et al., 2014; Griffiths et al., 2017; Inchley et al., 2020).

The strengths of this study are its relatively large sample size and its acceptable response rate. However, data were only collected within a single municipality in southern Sweden, which may limit the generalizability of the results. The desire was to capture a good representation. However, a university is placed in the included municipality and the education level in the municipality is higher than average. Also, the four schools which participated had more university preparatory courses, compared with the school who declined participating, which had more vocational study programs. These factors lead to a sample with a higher socio-economic status than average in Sweden. Furthermore, the study's cross-sectional design is unable to establish causality. It may be that adolescents who report a positive wellbeing tend to be more physically active and to have a positive body image. However, the converse may also be true: adolescents who are physically active and have a positive body image tend to have a better wellbeing. PA was self-reported and not objectively measured, which is another limitation. A high proportion of the adolescents in our study rated their wellbeing as very good or quite good and perceived their family finances to be good. A possible explanation for these results is that the sample may contain a disproportionate number of affluent individuals. However, similar results can be seen in the Swedish contribution to the HBSC study, which found that most 15-year-olds in Sweden rated their wellbeing as high or very high (Public Health Agency of Sweden, 2019).

CONCLUSION

A positive body image, which include both body appearance and body function, and high PA levels were significantly associated with wellbeing in adolescents, which imply the importance of promotion of PA among young people. From a public health perspective, a better understanding of how PA can influence positive wellbeing may help inform politicians and school administrators and health care providers to incentivize children and adolescents to engage in PA both within and beyond the school's boundaries. Since physical self-concepts have been shown to be an even better predictor of behavior than characteristics such as height and weight, school PE together with school health care providers can promote positive body image and PA habits. What distinguishes our results from those of previous studies is that adolescent females in our sample reported positive wellbeing, positive body image, and PA levels equivalent and at times slightly higher than adolescent males, which can be demonstrated as a good example of non-specific gender behavior that can serve as a model for improved wellbeing among females. Approximately one-third of the participating adolescents did not rate their wellbeing as good. Further research is needed to determine the factors that can affect the wellbeing of adolescents to further improve health.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Regional Ethical Review Board (EPN 2015/113). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

PG and A-CS contributed to the design of the study. PG contributed to data collection. A-CS, IS, and JF drafted the manuscript. All authors contributed to the interpretation of the data, revised the manuscript, provided final approval, and agreed to be accountable for all aspects of work to ensure integrity and accuracy.

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Physical Activity in Late Prepuberty and Early Puberty Is Associated With High Bone Formation and Low Bone Resorption

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Background: Physical activity (PA) increases bone mass, especially in late prepuberty and early puberty, but it remains unclear if and how PA affects both bone formation and bone resorption.

Materials and Methods: We included 191 boys and 158 girls aged 7.7 ± 0.6 (mean ± SD) in a population-based PA intervention study. The intervention group (123 boys and 94 girls) received daily physical education (PE) in school (40 min/day; 200 min/week) from study start and during the nine compulsory school years in Sweden. The controls (68 boys and 64 girls) received the national standard of 1–2 classes PE/week (60 min/week). During the intervention, blood samples were collected at ages 9.9 ± 0.6 (n = 172; all in Tanner stages 1–2) and 14.8 ± 0.8 (n = 146; all in Tanner stages 3–5) and after termination of the intervention at age 18.8 ± 0.3 (n = 93; all in Tanner stage 5) and 23.5 ± 0.7 (n = 152). In serum, we analyzed bone formation markers [bone-specific alkaline phosphatase (bALP), osteocalcin (OC), and N-terminal propeptide of collagen type 1 (PINP)] and bone resorption markers [C-terminal telopeptide cross links (CTX) and tartrate-resistant acid phosphatase (TRAcP 5b)]. Linear regression was used to compare age and sex-adjusted mean differences between intervention children and controls in these markers.

Results: Two years after the intervention was initiated (at Tanner stages 1–2), we found higher serum levels of bALP and OC, and lower serum levels of TRAcP 5b in the intervention compared with the control group. The mean difference (95% CI) was for bALP: 13.7 (2.1, 25.3) μg/L, OC: 9.1 (0.1, 18.1) μg/L, and TRAcP 5b: −2.3 (−3.9, −0.7) U/L. At Tanner stages 3–5 and after the intervention was terminated, bone turnover markers were similar in the intervention and the control children.

Conclusion: Daily school PA in the late prepubertal and early pubertal periods is associated with higher bone formation and lower bone resorption than school PA 1–2

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times/week. In late pubertal and postpubertal periods, bone formation and resorption were similar. Termination of the intervention is not associated with adverse bone turnover, indicating that PA-induced bone mass benefits gained during growth may remain in adulthood.

Keywords: bone turnover, children, puberty, physical activity, school intervention

INTRODUCTION

Physical activity (PA) during growth induces bone mass benefits (Kannus et al., 1995; French et al., 2000; Valdimarsson et al., 2006; Alwis et al., 2008; Weaver et al., 2016). The pediatric osteoporosis prevention (POP) study, a prospective controlled study with daily school PA as an intervention, has shown that bone mass benefits may be reached on a population-based level by moderate PA (Valdimarsson et al., 2006; Alwis et al., 2008; Cronholm et al., 2020). Regular PA during growth increases peak bone mass (PBM) (Cronholm et al., 2020), defined as the highest level of bone mass in life, and high PBM is associated with high bone mass in adulthood (Tveit et al., 2015). PBM is important as it is estimated to predict 50% of the variance in bone mass at age 70 (Hui et al., 1990), and a 10% increase in PBM is expected to delay osteoporosis by 13 years (Rizzoli et al., 2010). Thus, it seems possible that high PA during growth may lead to life-long skeletal benefits.

All types of PA do not have the same osteogenic effect, and the same type of PA may have different effects during different maturational periods. Highly osteogenic PA includes dynamic activity with high loads in different skeletal directions with resting periods between exercise periods, while the number of repetitions seems of minor importance (Rubin and Lanyon, 1984; Turner and Robling, 2003; Rantalainen et al., 2010). Prospective controlled studies also suggest that PA has the greatest skeletal effect in the late prepubertal and early pubertal periods (Valdimarsson et al., 2006; Alwis et al., 2008; Cronholm et al., 2020). This notion is supported in tennis players where differences in bone mass are greater in the dominant vs. the non-dominant arm if the training was initiated before rather than after puberty (Kannus et al., 1995).

It is also important to identify whether PA-induced skeletal benefits acquired during growth remain in the long-term perspective (Karlsson et al., 2000; Tveit et al., 2015). If so, this could hypothetically reduce fracture risk later in life. Previous results from the POP study support this view, as daily school PA during the nine compulsory school years was followed by residual bone mass benefits in adulthood (Rosengren et al., 2021a,b). This view is also partly supported by others, showing that there are benefits but that these attenuate over time, raising the question of whether the benefits remain in a long-term perspective (Tveit et al., 2013a, 2015). A reduction in PA is also reported to be followed by an increase in bone resorption markers within days (Karlsson et al., 2003). However, studies on fractures support long-term skeletal benefits, indicating that PA during growth is associated with reduced fracture risk both during growth (Fritz et al., 2016; Cöster et al., 2017) and at older ages (Tveit et al., 2013b, 2015).

Bone turnover markers are due to the instant response to changes in PA (Karlsson et al., 2003), a possible way to increase the knowledge on the skeletal effects of PA. In adults, PA has been associated with elevated levels of bone formation markers and decreased levels of bone resorption markers (Karlsson et al., 2003). However, few studies have evaluated the effect of PA on bone turnover markers in growing children, mostly short-term and with contradicting results (Maimoun and Sultan, 2011). For example, Eliakim et al. (1997) found that in adolescent boys (Tanner stages 3–5) during a 5-week training program, bone formation markers increased and bone resorption markers decreased. In contrast, Daly et al. (1999) found no influence on bone formation in elite male gymnasts (Tanner stages 1–2) during an 18-month training period. Results from the few pediatric studies that have evaluated bone turnover markers during long periods of PA are conflicting (Banfi et al., 2010), and none have followed children with different levels of PA throughout puberty and into adult life. An overview of systematic reviews and meta-analyses regarding the effects of exercise on bone status suggested that "future studies should include bone biomarker measurements in the study design to complement radiological measurements to better understand the effects of exercise on bone" (Xu et al., 2016).

The purpose of this study was to evaluate whether children with daily school PA have higher bone formation and lower bone resorption (estimated through bone turnover markers in serum) than children with lower levels of PA, and if any residual group difference remains after the extra school PA was terminated. Our hypothesis was that children with daily PA would have high bone formation and low bone resorption, most obvious in the late prepubertal and early pubertal periods corroborating with the period where PA is known to have the greatest effect on bone mass (Karlsson et al., 2000; Tveit et al., 2015). Also, termination of daily school PA would be associated with low bone formation and high bone resorption. We specifically asked the following: do children in an intervention program with daily school PA (compared with children with regular school PA) have (i) higher bone formation and lower bone resorption, (ii) most obvious anabolic effect on bone metabolism in the late prepubertal and early pubertal periods, and (iii) lower bone formation and higher bone resorption with the termination of PA intervention?

MATERIALS AND METHODS

Study Design

The Pediatric Osteoporosis Prevention Study Design

The POP study is a population-based prospective controlled intervention study with the primary aim of evaluating the effects of daily school-based PA given during the nine compulsory school years (Linden et al., 2006; Valdimarsson et al., 2006; Detter et al., 2014). We invited all children in four government-funded neighboring elementary schools to participate in this study. The students were allocated to a specific school according to their residential address. The four schools were located in southwest Malmo, Sweden, in a township with homogenous socioeconomic and ethnic structures.

The Intervention Design

The first school that agreed to participate also agreed to increase physical education (PE) within the school curriculum and, therefore, was assigned as an intervention school. This school increased the amount of PE from the Swedish standard of 60 min PE/week to 40 min PE/day (200 min PE/week) from the beginning of school (grade one) until the last compulsory grade (grade nine). The three remaining schools (the control group) continued with the national school curriculum of 60 min PE/week provided in 1–2 lessons/week. Since PE is a compulsory school subject in Sweden, all children had to participate according to the school schedule. In all schools, the PE lessons were led by the regular teachers who supervised a variety of activities in the ordinary PE curriculum, including ball games and activities with running, jumping, and climbing. We have no information regarding the proportions of different types of activities, intensity, duration of each activity, or if a specific student put effort into the training. We also do not have information on voluntarily chosen spare time PA beyond organized spare time PA.

Endpoint Variables

At each evaluation, we measured height (cm) and weight (kg) using standardized equipment. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). During the first 3 years, a research nurse evaluated the Tanner stage (Marshall and Tanner, 1969, 1970), and thereafter, the children reported the Tanner stage by self-assessment. We used standardized non-validated questionnaires to evaluate lifestyle (Linden et al., 2006; Valdimarsson et al., 2006; Detter et al., 2014). The questionnaires, which registered tobacco use, alcohol use, current medical conditions, medication use, exclusion of dairy products, and organized PA (weekly activity by sports clubs or sports associations) during leisure time, were completed together with parents or guardians for younger ages. Each year, headmasters reported the duration of PE classes for their school. There was no objective registration with accelerometers or force plates to measure the duration and/or intensity of the PA. We also collected blood samples from age 9.9 ± 0.6 (mean ± SD). The samples were prepared by letting the blood clot for 30 min at 8°C, followed by centrifugation at 1,430 *g* for 10 min. The serum was then stored at −70°C until analysis.

Participants in the Pediatric Osteoporosis Prevention Study

All children who started first grade from 1998 to 2000 in the four schools were invited to be followed up annually during their compulsory school years. Of 564 children, 349 (217 intervention and 132 control children) agreed to participate. They were then 7.7 ± 0.6 years, all were in Tanner stage 1, and 98% were of Caucasian ethnicity. We followed the children annually during the nine compulsory school years and at ages 18.8 ± 0.3 and 23.5 ± 0.7.

Participants in This Report

In this report, we analyzed blood samples with the intervention ongoing in ages 9.9 ± 0.6 (n = 172, assessment 1) and 14.8 ± 0.8 (n = 149, assessment 2). To be included in the analyses, the children in assessment 1 had to be in Tanner stages 1–2 (defined as the late prepubertal and early pubertal periods) and in assessment 2 in Tanner stages 3–5 (defined as the late and postpubertal periods). Therefore, in assessment 2, we had to exclude one girl in the intervention group as she was still in Tanner stage 2, one girl in the intervention, and one boy in the control group with missing data on the Tanner stage (**Figure 1**). Thus, the analyses included 172 children in assessment 1 and 146 children in assessment 2. We also analyzed samples after the termination of the intervention, when the participants were 18.8 ± 0.3 (n = 93, assessment 3) and 23.5 ± 0.7 (n = 152, assessment 4) years, all in Tanner stage 5 (defined as the postpubertal period) (**Figure 1**).

Dropout Analysis

In a previous dropout analysis at baseline, we used the compulsory medical examination at school start and found no clinically relevant differences at study start in height, weight, or BMI between children who agreed and declined to participate (Linden et al., 2006). In another previous dropout analysis at age 9.9 ± 0.6, we found no clinically relevant difference in baseline height, weight, or BMI in children who agreed and declined to participate (Dencker et al., 2006). We also undertook a new dropout analysis and found similar height, weight, and BMI at each of the assessments 1–4 between those who gave blood samples and those who did not (**Supplementary Appendix 1**).

Laboratory Methods

All samples were analyzed in the same batch, with subjects' serum from the 4 schools randomized between plates. We analyzed serum bone-specific alkaline phosphatase (bALP), osteocalcin (OC), and N-terminal propeptide of collagen type 1 (PINP) representing markers of bone formation (Szulc et al., 2000) and C-terminal telopeptide cross links (CTX) and tartrate-resistant acid phosphatase (TRAcP 5b) representing markers of bone resorption (Szulc et al., 2000). The bALP, CTX, PINP, and TRAcP 5b were assessed using the Immuno Diagnostic System-Specialty Immunoassay System (IDS-iSYS) analyzer (Pharmatest Services, Turku, Finland). Serum OC was assessed using the N-MID ELISA Assay Kit (Department of Clinical Chemistry, Skane University Hospital, Lund, Sweden). Tests were run according to the manufacturer's instructions. The intra- and inter-CV% for bone markers assessed by Pharmatest Services, Turku, Finland were calculated by three quality control (QC) samples in each assay. The mean intra-assay CV% ranged: bALP: 0.6–1.8%; PINP: 1.4–2.7%; CTX: 0.5–7.0%; TRAcP 5b: 2.0–7.1%. The mean inter-assay CV% was bALP: 1.2%; PINP: 1.7%; CTX: 4.4%; and TRAcP 5b: 9.2%. The OC assay technical performance was assessed at the

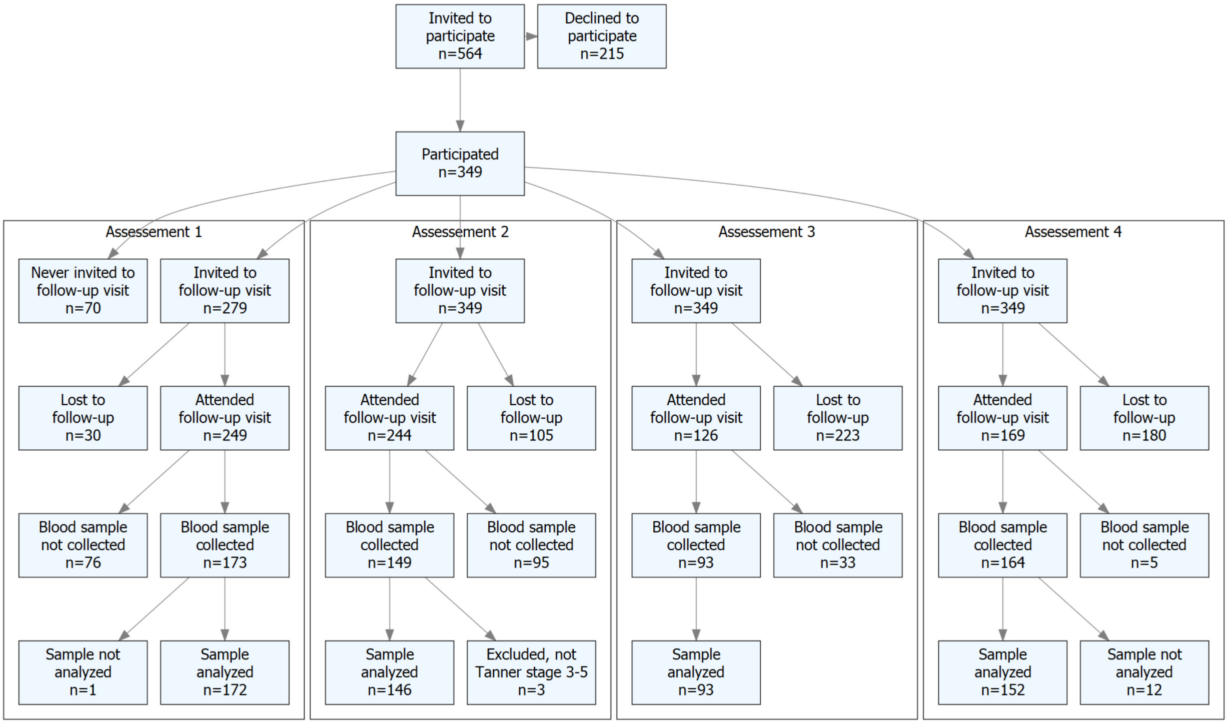

FIGURE 1 | Flowchart of study participants.

Department of Clinical Chemistry, Skane University Hospital, Lund, Sweden in a long-term follow-up of QC samples (over 1 year). The mean inter-assay CV% was 4.5%.

Statistics and Ethics

We used IBM SPSS Statistics® version 27 for all statistical analyses. Data are presented as numbers (*n*), proportions (%), or means ± SD. Age and sex-adjusted differences in bone markers between children in the intervention and control groups were estimated by linear regression and presented as mean differences with 95% CI. We regarded a $p < 0.05$ as a statistically significant difference. Outliers were defined as points that fall 1.5 to 3 times the interquartile range above the third quartile or below the first quartile and extreme outliers as points that fall more than 3 times the interquartile range above the third quartile or below the first quartile.

This study was approved by the Ethics Committee of Lund University, Sweden (LU 453-98; 1998-09-15), conducted according to the Declaration of Helsinki, and registered as a clinical trial (Clinical Trials.gov.NCT00633828). All children and parents/guardians provided written consent before the study started.

RESULTS

Data on anthropometry, pubertal stage, and lifestyle characteristics are presented separately for boys (**Table 1**) and girls (**Table 2**).

With ongoing intervention in the late prepubertal and early pubertal periods (assessment 1, 2 years after the intervention was initiated), we found higher serum levels of bALP and OC and lower serum levels of TRAcP 5b in the intervention compared with the control group. The mean difference (95% CI) was for bALP: 13.7 (2.1, 25.3) μg/L, OC: 9.1 (0.1, 18.1) μg/L, and TRAcP 5b: −2.3 (−3.9, −0.7) U/L (**Table 3**). We found no statistically significant group differences with ongoing intervention in the late and postpubertal periods (assessment 2) or after the intervention terminated (assessments 3 and 4) (**Table 3**). Outliers and extreme outliers are presented in a boxplot (**Figure 2**). Group differences in the late prepubertal and early pubertal periods remained after the exclusion of extreme outliers as well as all outliers (data not shown).

DISCUSSION

Children with daily school PA have in the late prepubertal and early pubertal periods higher mean levels of the bone formation markers bALP and OC and lower mean levels of the bone resorption marker TRAcP 5b than children with lower levels of PA, but not in the late and postpubertal periods. Three and seven years after termination of the intervention, there was no adverse bone metabolism (low bone formation/high bone resorption) in the individuals with former daily school PA. These results strengthen the view that daily school PA during compulsory school years is associated with residual bone mass benefits in adulthood (Rosengren et al., 2021a,b).

TABLE 1 | Anthropometry, pubertal development (Tanner stage), and lifestyle characteristics in the boys.

	Assessment 1		Assessment 2		Assessment 3		Assessment 4	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Participants (n)	51	42	53	29	31	18	51	25
Age (Years)	9.9 ± 0.6	10.0 ± 0.6	14.8 ± 0.7	15.0 ± 0.8	18.8 ± 0.2	18.8 ± 0.4	23.6 ± 0.7	23.4 ± 0.5
Height (cm)	140.5 ± 7.0	141.1 ± 7.2	172.6 ± 7.9	174.7 ± 8.8	182.0 ± 6.8	181.2 ± 5.9	180.4 ± 7.2	180.7 ± 6.5
Weight (kg)	35.0 ± 7.3	34.0 ± 7.5	61.2 ± 13.3	63.1 ± 13.4	77.3 ± 12.6	75.2 ± 12.3	78.9 ± 12.4	78.4 ± 10.7
Body Mass Index (kg/m^2)	17.6 ± 2.8	16.9 ± 2.5	20.4 ± 3.4	20.6 ± 3.6	23.4 ± 4.0	22.8 ± 3.1	24.1 ± 3.0	24.0 ± 2.9
Tanner (1–2/3–4/5) (n)	51/0/0	42/0/0	0/18/35	0/10/19	0/0/31	0/0/18	0/0/51	0/0/25
Exclusion of dairy products [n (%)]	N/A	1 (2%)	0 (0%)	0 (0%)	0 (0%)	1 (6%)	3 (6%)	1 (4%)
Chronic medical conditions [n (%)]	N/A	2 (5%)	4 (8%)	1 (3%)	6 (19%)	3 (17%)	17 (33%)	5 (20%)
Eating disorders (Bulimia, anorexia) [n (%)]	N/A	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)
Milk intolerance [n (%)]	N/A	0 (0%)	1 (2%)	0 (0%)	1 (3%)	2 (11%)	3 (6%)	3 (12%)
Gluten intolerance [n (%)]	N/A	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (6%)	0 (0%)	0 (0%)
Current medication [n (%)]	N/A	0 (0%)	2 (4%)	0 (0%)	0 (0%)	0 (0%)	2 (4%)	1 (4%)
Vitamin D supplements [n (%)]	N/A	N/A	N/A	N/A	1 (3%)	0 (0%)	1 (2%)	1 (4%)
Smoking [n (%)]	N/A	N/A	0 (0%)	0 (0%)	2 (6%)	5 (28%)	3 (6%)	0 (0%)
Drinking alcohol [n (%)]	N/A	N/A	6 (11%)	3 (10%)	31 (100%)	18 (100%)	49 (96%)	23 (92%)
Total organized PA (Hours/Week)	10.2 ± 4.6	5.4 ± 3.0	10.8 ± 5.1	6.4 ± 3.4	8.5 ± 7.0	4.5 ± 2.3	5.1 ± 4.4	5.2 ± 3.9

Data are presented as absolute numbers (n) with proportions (%) or as means ± SD.

TABLE 2 | Anthropometry, pubertal development (Tanner stage), and lifestyle characteristics in the girls.

	Assessment 1		Assessment 2		Assessment 3		Assessment 4	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Participants (n)	43	36	42	22	28	16	45	31
Age (Years)	9.6 ± 0.6	9.9 ± 0.6	14.7 ± 0.8	14.8 ± 0.9	18.8 ± 0.4	18.7 ± 0.3	23.6 ± 0.7	23.3 ± 0.6
Height (cm)	139.6 ± 6.1	140.4 ± 8.4	166.1 ± 5.9	165.7 ± 8.2	168.5 ± 5.3	168.3 ± 4.6	169.2 ± 5.6	167.8 ± 6.4
Weight (kg)	34.5 ± 6.6	34.4 ± 6.9	59.5 ± 10.3	55.3 ± 11.5	64.5 ± 8.9	63.1 ± 12.7	68.2 ± 11.9	63.4 ± 12.3
Body Mass Index (kg/m^2)	17.7 ± 3.1	17.3 ± 2.2	21.5 ± 3.6	20.0 ± 3.3	22.7 ± 3.0	22.2 ± 3.6	23.9 ± 4.2	22.4 ± 3.7
Tanner (1–2/3–4/5) (n)	43/0/0	36/0/0	0/26/16	0/11/11	0/0/28	0/0/16	0/0/45	0/0/31
Exclusion of dairy products [n (%)]	N/A	0 (0%)	0 (0%)	0 (0%)	3 (11%)	0 (0%)	4 (9%)	3 (10%)
Chronic medical conditions [n (%)]	N/A	0 (0%)	5 (12%)	0 (0%)	8 (29%)	0 (0%)	16 (36%)	10 (32%)
Eating disorders (Bulimia, anorexia) [n (%)]	N/A	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (9%)	2 (6%)
Milk intolerance [n (%)]	N/A	0 (0%)	0 (0%)	0 (0%)	2 (7%)	0 (0%)	1 (2%)	3 (10%)
Gluten intolerance [n (%)]	N/A	0 (0%	0 (0%)	2 (9%)	0 (0%)	0 (0%)	1 (2%)	1 (3%)
Current medication, including birth control pills [n (%)]	N/A	0 (0%)	1 (2%)	0 (0%)	13 (46%)	9 (56%)	20 (44%)	20 (65%)
Vitamin D supplements [n (%)]	N/A	N/A	N/A	N/A	0 (0%)	0 (0%)	2 (4%)	1 (3%)
Smoking [n (%)]	N/A	N/A	3 (7%)	3 (14%)	7 (25%)	3 (19%)	7 (16%)	5 (16%)
Drinking alcohol [n (%)]	N/A	N/A	2 (5%)	3 (14%)	24 (86%)	14 (88%)	43 (96%)	30 (97%)
Total organized PA (Hours/Week)	7.2 ± 3.0	4.2 ± 2.5	9.6 ± 4.0	5.8 ± 2.3	4.5 ± 2.7	4.5 ± 3.4	5.6 ± 5.5	4.8 ± 2.4

Data are presented as absolute numbers (n) with proportions (%) or as means ± SD.

The original aim of the POP study was not to once more show that specific bone-strengthening exercises in a voluntary program for children improves bone mass (Rubin and Lanyon, 1984; Kannus et al., 1995; French et al., 2000; Turner and Robling, 2003; Valdimarsson et al., 2006; Alwis et al., 2008; Rantalainen et al., 2010; Rizzoli et al., 2010; Tveit et al., 2015; Weaver et al., 2016; Cronholm et al., 2020). This is already known. Instead, we wanted to evaluate whether a PE program already used in school but extended to daily sessions in a population-based group of growing children (with some activities being more bone-strengthening and some less, and with some children being active in PE classes and some on lower levels) could be one approach to improve bone mass in society. When we in several publications have shown that this is possible (Linden et al., 2006; Valdimarsson et al., 2006; Alwis et al., 2008; Detter et al., 2014; Cronholm et al., 2020; Rosengren et al., 2021a,b), we wanted to explore in this study if and how increased gain in bone mass is associated with bone formation and bone resorption.

This study is the only published prospective study that has followed bone turnover markers in children from before puberty

TABLE 3 | Bone formation markers [bone-specific alkaline phosphatase (bALP), osteocalcin (OC), and N-terminal propeptide of collagen type 1 (PINP)] and bone resorption markers [C-terminal telopeptide cross links (CTX) and tartrate-resistant acid phosphatase (TRAcP 5b)] in the intervention and control group.

	Assessment 1			Assessment 2			Assessment 3			Assessment 4		
	Intervention	Control	Mean difference	Intervention	Control	Mean difference	Intervention	Control	Mean difference	Intervention	Control	Mean difference
Participants (n)	94	78	–	95	51	–	59	34	–	96	56	–
Age (years)	9.8 ± 0.6	9.9 ± 0.6	–	14.7 ± 0.7	14.9 ± 0.8	–	18.8 ± 0.3	18.8 ± 0.3	–	23.6 ± 0.7	23.3 ± 0.6	–
Bone formation markers:												
bALP (μg/L)	130.0 ± 37.8	116.1 ± 37.6	**13.7 (2.1, 25.3)**	89.4 ± 59.2	73.9 ± 43.4	11.6 (−2.5, 25.8)	23.9 ± 11.4	22.6 ± 8.9	1.2 (−2.5, 4.9)	17.2 ± 8.0	17.7 ± 8.1	−0.5 (−3.0, 2.0)
OC (μg/L)	125.6 ± 28.9	117.3 ± 30.1	**9.1 (0.1, 18.1)**	115.5 ± 61.9	104.1 ± 57.0	7.0 (−9.7, 23.8)	38.4 ± 10.9	40.5 ± 15.5	−2.0 (−6.7, 2.6)	27.4 ± 7.6	27.5 ± 7.8	0.2 (−2.2, 2.7)
PINP (μg/L)	389.7 ± 113.0	414.1 ± 196.4	−26.6 (−73.8, 20.7)	694.0 ± 480.4	644.4 ± 451.0	8.2 (−114.9, 131.3)	129.3 ± 56.1	142.1 ± 70.8	−13.2 (−34.7, 8.3)	85.1 ± 36.3	88.4 ± 41.6	−3.3 (−15.5, 9.0)
Bone resorption markers:												
CTX (μg/L)	1.7 ± 0.5	1.7 ± 0.5	−0.01 (−0.2, 0.1)	1.3 ± 0.9	1.3 ± 0.8	−0.02 (−0.3, 0.2)	0.5 ± 0.3	0.6 ± 0.4	−0.1 (−0.2, 0.1)	0.4 ± 0.3	0.3 ± 0.3	0.04 (−0.05, 0.1)
TRAcP 5b (U/L)	15.0 ± 5.5	17.1 ± 5.1	**−2.3 (−3.9,−0.7)**	13.1 ± 5.9	12.3 ± 5.1	0.3 (−1.2, 1.8)	4.2 ± 1.2	4.6 ± 1.2	−0.3 (−0.8, 0.2)	3.5 ± 1.1	3.5 ± 0.9	0.01 (−0.3, 0.3)

bALP data were missing in 1 intervention and 1 control child (assessment 1). OC data were missing in 3 interventions (1 in assessment 1, 1 in assessment 3, and 1 in assessment 4) and 7 control children (3 in assessment 1, 2 in assessment 2, and 2 in assessment 4). Data are presented as absolute numbers (n), means ± SD, or age and sex-adjusted mean difference with 95% CIs within parenthesis. Statistically significant differences are in bold text.

into adulthood in relation to different levels of PA. As previous pediatric studies have suggested that bone formation markers are positively correlated to the gain in bone mass (Lehtonen-Veromaa et al., 2000), our data, as well as previous POP studies (Valdimarsson et al., 2006; Alwis et al., 2008; Cronholm et al., 2020), support the thesis that daily PA is beneficial for the skeleton. This study adds knowledge by indicating increased bone formation (higher bone formation markers and lower bone resorption markers) in the group with daily school PA in the late prepubertal and early pubertal periods, the period with the greatest skeletal ability to respond to mechanical load (Blimkie et al., 1996; Valdimarsson et al., 2006; Alwis et al., 2008; Cronholm et al., 2020). In contrast, we found similar bone metabolism between intervention and control children in the late and postpubertal periods, corroborating with data showing that increased PA induces a lower skeletal response if initiated later in puberty (Kannus et al., 1995).

Another finding that may be of importance is the absolute higher values in most bone turnover markers, in both the intervention and control groups, in the late prepubertal and early pubertal periods (assessment 1) compared with the late and post-pubertal periods (assessments 2–4) (**Figure 2**). This indicates a high bone turnover in late prepubertal and early pubertal periods and may thus give a possible explanation as to why the skeleton is more responsive to mechanical load in late prepuberty and early puberty (Blimkie et al., 1996; Valdimarsson et al., 2006; Alwis et al., 2008; Cronholm et al., 2020). The findings of generally higher levels of bone turnover markers at younger ages and in early pubertal periods (assessment 1) compared with higher ages and late pubertal periods (assessments 2–4) indicate that comparisons in children should not be performed without considering age and pubertal stage.

In this study, we found no indications of adverse bone metabolic effects (low bone formation and/or high bone resorption) after withdrawal from the PA intervention. This provides a plausible explanation for the previously reported residual long-term bone mass benefits in individuals with daily school PA (Rosengren et al., 2021a,b). We were unable to draw causal conclusions regarding high PA in childhood and the absence of adverse effects on the bone turnover when the intervention is terminated. We cannot rule out a temporary adverse bone metabolism just after the program terminated, since we evaluated bone turnover markers 3 and 7 years after the program was terminated, in a period when a new steady-state may have been settled.

Participants in the former POP intervention group were also reported to have higher levels of PA after the program (Lahti et al., 2018), something that may have counteracted an adverse bone metabolism. We were also unable to exclude factors beyond the daily school PA that may be associated with bone turnover markers. Children in the intervention group may have developed greater knowledge of health-related issues, due to this consciously or unconsciously changing several health-related habits. For example, taking the stairs instead of the elevator, becoming more involved in spare time PA, and/or changing their nutritional intake. The fact that nutritional factors are of great importance during skeletal growth is supported by a systematic review

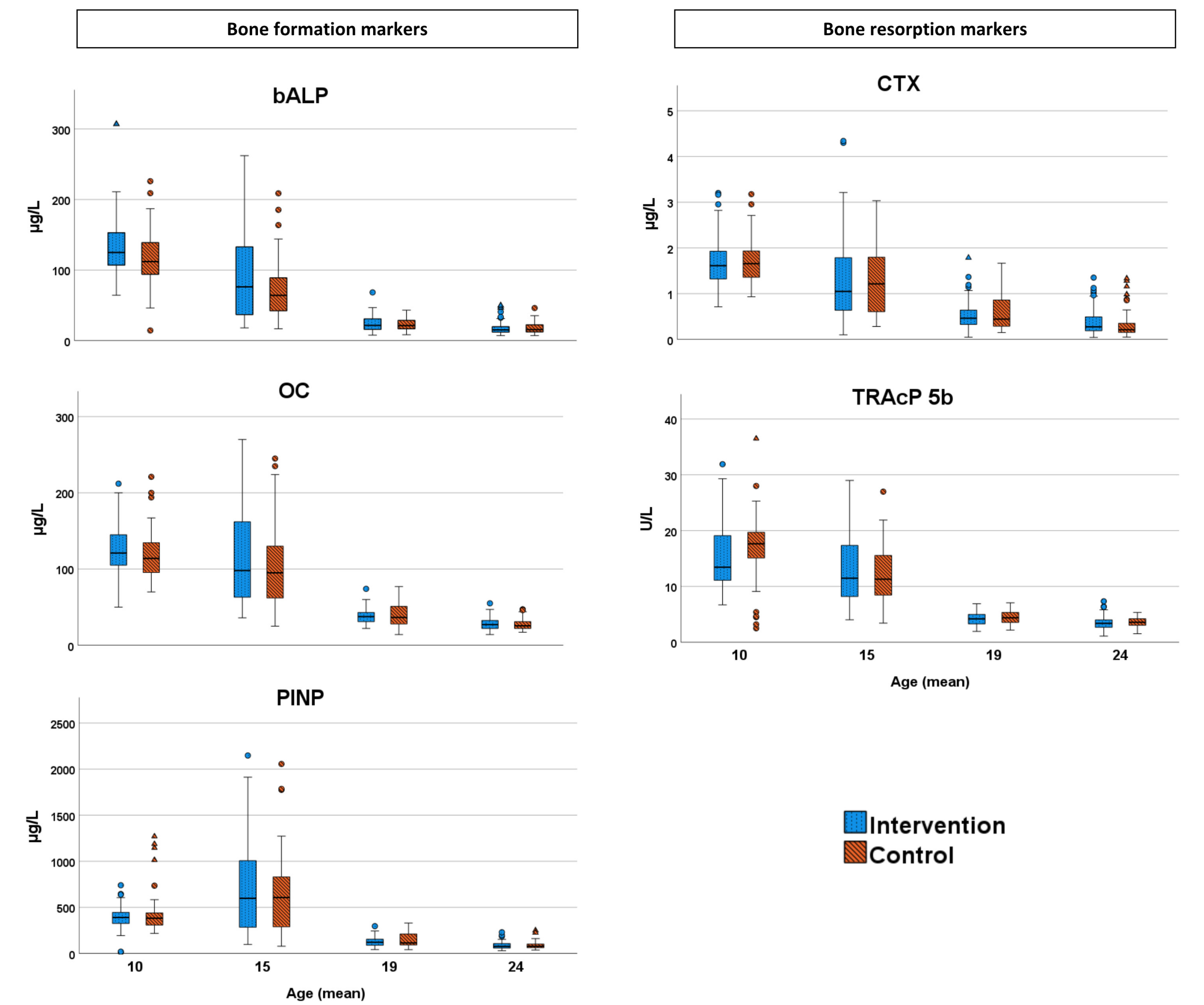

FIGURE 2 | Bone formation markers [bone-specific alkaline phosphatase (bALP), osteocalcin (OC), and N-terminal propeptide of collagen type 1 (PINP)] and bone resorption markers [C-terminal telopeptide cross links (CTX) and tartrate-resistant acid phosphatase (TRAcP 5b)] in the intervention and control group. Outliers are marked as circles and extreme outliers as triangles.

that infers PA and calcium intake as the two lifestyle factors that with the highest level of evidence were shown to improve PBM (Weaver et al., 2016). Other factors of importance include vitamin D and dairy intake (Weaver et al., 2016). However, the number of individuals in our study that excluded dairy products and/or used vitamin D supplements were so few and with no obvious group differences, and seems of lesser importance for our conclusions.

The few published studies on bone turnover markers in children report conflicting results (Eliakim et al., 1997; Daly et al., 1999; Lehtonen-Veromaa et al., 2000; Maimoun and Sultan, 2011), possibly as they include sports with different types of mechanical load and children in different pubertal stages, both of which could influence bone turnover markers (Lehtonen-Veromaa et al., 2000; Maimoun et al., 2013; Vlachopoulos et al., 2017). Another contributing factor could be that the children in the studies were on a competitive level (Lehtonen-Veromaa et al., 2000; Maimoun et al., 2013; Vlachopoulos et al., 2017), which may create a risk of delayed pubertal and skeletal maturation due to intense exercise (Georgopoulos et al., 1999). In contrast, this POP study evaluates a population-based intervention on a non-competitive level, including a variety of activities and evaluations performed during predefined maturational stages.

Study strengths include the prospective, controlled, population-based study design, with longitudinal data from before puberty all the way to adulthood. Study limitations include the lack of bone turnover data prior to the initiation of the intervention. The small sample size and the high dropout frequency are other drawbacks that introduce risks for selection bias and type II errors, as well as an inability to conduct sex and/or Tanner stage-specific subgroup analyses. However, the dropout analyses revealed no obvious selection bias, and we compared all children together and not by sex, to reduce the risk of a type II error. An assessment just after the program was terminated, as well as a longer post-intervention follow-up period would have been beneficial as we do not know whether there were any group differences in the first week/month after termination of the program and/or if the benefits remain in older ages. Since most children were of Caucasian ethnicity, living in a middle-class area, inferences cannot immediately be transferred to other ethnic groups and/or socioeconomic settings. The lack of individual randomization is another weakness, but the schools refused this at the study start due to practical problems with schedules. Further limitations include the lack of an objectively measured amount of PA. Thus, we are unable to draw conclusions regarding differences in the intensity of PA between the groups. It is possible that another intervention with higher intensity of extra training and/or with more bone-strengthening exercises, such as jumps and resistance training, could also have resulted in group differences after Tanner stages 1–2. Another concern is the use of self-assessment in the Tanner evaluation, known to be less accurate compared with assessment by a trained nurse or physician (Diemar et al., 2021). However, the use of self-assessment has been found acceptable in girls, while boys if anything overestimates their pubertal stage (Duke et al., 1980). However, we have no indications that the self-assessment would be different in the intervention and control groups.

In conclusion, daily school PA in the late prepubertal and early pubertal periods is associated with higher bone formation and lower bone resorption than school PA 1–2 times/week, while no difference is found in the late or postpubertal periods. We found no association between the termination of daily school PA and adverse bone turnover, indicating that PA-induced bone mass benefits gained during growth may remain in adulthood.

DATA AVAILABILITY STATEMENT

The registration of data and the study was performed confidentially and according to Swedish and EU data protection rules. This study is based on sensitive individual-level data protected by the Swedish personal data act. Access to full data is available upon request from the corresponding author, given that the person that is interested to use it receives ethical vetting. However, some aggregated tables can be provided by the corresponding author upon request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Lund University, Sweden (LU 453-98; 1998-09-15). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

JR and MK: conceptualization, data curation, funding acquisition, investigation, methodology, supervision, validation, and writing and review-editing. BR: conceptualization, data curation, formal analysis, investigation, methodology, and writing and review-editing. LJ: conceptualization, data curation, formal analysis, investigation, methodology, validation, and writing and review-editing. PS: data curation, formal analysis, investigation, methodology, and writing and review-editing. MD: investigation, methodology, and writing and review-editing. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphys.2022.828508/full#supplementary-material

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The Impact of Frame Running on Quality of Life in Young Athletes With Mobility Limitations

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Purpose: The para-athletic sport Frame Running is developed for persons with neurological impairments causing severe limitations of walking ability. Participating in sports can contribute to a better quality of life (QoL). It is unknown if participation in Frame Running contributes to QoL in children with mobility limitations. This study aims to explore the changes in QoL in children and youth who started Frame Running.

Materials and Methods: We conducted a cross-sectional study amongst young Frame Running athletes with mobility limitations due to various underlying causes, aged 6–19 years, who are members of one of the Frame Running groups in the Netherlands. For 62 athletes, parents completed the Psychosocial Impact of Assistive Devices Scale (PIADS) questionnaire (subscales: competence, adaptability, and self-esteem). For six athletes, parents were interviewed to obtain more in-depth insight in the perceived changes in the QoL of their children.

Results: Parents (of 58% boys, mean age 12 years 4 months; SD 3 years 3 months; 52% supported walkers) reported a significant positive change on all three subscales of the PIADS questionnaire since their children started Frame Running. Most change was experienced in the items performance, the ability to participate, happiness and self-confidence. Quotes of the parents who were interviewed elucidated these changes.

Conclusion: Frame Running increased QoL in young athletes with a mobility limitation. Frame Running may therefore be advised for these children and youth to improve QoL.

Keywords: quality of life, psychosocial impact, adapted sports, Frame Running, children with disabilities, self-esteem, competence, participation

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INTRODUCTION

Sports participation has numerous health benefits for typically developing children, for physical as well as psychosocial well-being (Tomporowski et al., 2011; Eime et al., 2013). Physical activity improves cardiopulmonary health, strength, flexibility and endurance, and has been related to reduce risks for cardiovascular diseases and specific cancers (Alves et al., 2016; Kubota et al., 2017). In addition, sports participation provides opportunities for social interaction, companionship and may therefore have major benefits for social and mental well-being (Street et al., 2007; Eime et al., 2010, 2013; Seippel, 2017). As such, sports participation enhances health-related quality of life

(QoL) in children and adolescents (Mitchell and Barlow, 2011; Sahlin and Lexell, 2015). Health-related quality of life is a broadly defined construct evaluating the health status from the person's perspective covering physical, emotional, mental, social, and functional domains (Bullinger et al., 2002).

Children with disabilities often experience problems in participating in sports (Shields and Synnot, 2016). For youth with mobility limitations [for example due to cerebral palsy (CP)] that limit daily living activities as well as athletic endeavors, physical activity is often a challenge (Fowler et al., 2007). Children and adolescents with disabilities less often engage in physical activities and sports compared to typically developing children and adolescents (Rimmer et al., 2004; Buffart et al., 2008; Zwier et al., 2010; van Brussel et al., 2011; Carlon et al., 2013; Lankhorst et al., 2015), while they may benefit as much or even more from the influence of sports participation and physical activities on psychosocial health (Te Velde et al., 2018), as these children and adolescents may experience low levels of self-worth and quality of life due to their physical limitations and body image concerns (Rimmer et al., 2004; Sawin and Bellin, 2010). Positive self-worth, self-perceptions, self-esteem, social support and self-efficacy are acknowledged indicators of psychosocial health and quality of life (Drakouli et al., 2015). Participation in active leisure time activities is associated with better physical well-being, improved sense of self, self-esteem, social competence, emotional well-being, increased quality of life, and social well-being in children with neurodevelopmental disabilities (Shikako-Thomas et al., 2008; Dahan-Oliel et al., 2012). Moreover, participation in sports and recreational activities promotes inclusion of children with disabilities in society.

Young people with disabilities indicated that the "lack of accessible and inclusive opportunities" was the most pertinent barrier (Wright et al., 2019). Especially for children with a severe disability it is sometimes difficult to find sports they can participate in, due to their specific motor problems. Some children who are unable to walk independently can take part in wheelchair sports, but for that they need relatively good manual abilities. For children with severe impairments in both upper and lower limbs the choice for sports is much more limited. The relatively new para-athletic sport Frame Running (formerly known as RaceRunning) has been developed for persons with disabilities and high support needs. Frame Running is a form of assisted running. The running frame (with three wheels, saddle, chest plate, and steer) supports the athletes and allows them to successfully ambulate (van der Linden et al., 2021). Frame Running is intended for individuals with a motor control impairment of a cerebral nature causing a permanent and verifiable activity limitation. Since 2015, Frame Running has been implemented in the Netherlands, and getting very popular with a fast growing numbers of athletes. Apart from the athletes with neurological conditions, also many athletes with other diagnoses who are not able to walk or run without support are engaged in Frame Running.

Although it is known that sports can contribute to increase of QoL in the general population, it is unclear whether and how Frame Running contributes to QoL in children with mobility limitations. The aim of this study is to explore changes in quality of life (e.g., competence, adaptability, and self-esteem) of young athletes since they started Frame Running. Moreover, we hypothesized that the change in QoL in children who are supported walkers would be larger because they probably have less opportunities to do sports than unsupported walkers.

METHODS

Participants

A convenience sample was recruited from national athletic sport clubs with a Frame Running group. Young Frame Running athletes were included if they met the following inclusion criteria: (a) age between 5 and 19 years; (b) a motor disability; (c) started Frame Running at least 3 months ago; (d) parents could understand the Dutch language well-enough to fill in the questionnaires. Exclusion criteria were: parents were unable to understand the questionnaire because of language problems.

Design

A cross-sectional research design was used. Questionnaires and interviews were conducted between April 2018 and February 2019. The study was approved by the Medical Ethical Committee (METC) of Amsterdam UMC, location Vrije Universiteit in Amsterdam. The research was conducted in line with the guidelines of Good Clinical Practice (Helsinki Declaration).

Procedure

Frame Running athletes were invited for this research project by an information leaflet via the Frame Running trainer. All parents and also adolescents older than 12 years signed for informed consent. One parent per Frame Running athlete filled in a questionnaire. A convenience sample of six parents, the first six who agreed to participate in this part of the study, were invited for a semi-structured interview.

Outcome Measures

Demographic information about sex, age, diagnosis, means of ambulation, number of months experience with Frame Running, and hours of Frame Running training per week was investigated by means of a general questionnaire. To be able to compare non-supported and supported walkers, the Gross Motor Function Classification System (GMFCS) (Palisano et al., 1997) descriptions for means of ambulation in daily life were used for all athletes (both with CP or other diagnoses) (Towns et al., 2018). GMFCS I and II were considered non-supported walkers; III–V were considered supported walkers.

To assess QoL quantitatively, the Psychosocial Impact of Assistive Devices Scale (PIADS) was used. The PIADS consists of a brief self-report questionnaire of 26 items, designed to assess the impact of an assistive device on psychological well-being and subjective QoL of the users (Day and Jutai, 1996; Day et al., 2002; Jutai and Day, 2002; Traversoni et al., 2018). The scale has three subscales: competence (12 items), adaptability (6 items), and self-esteem (8 items). The first subscale aims to assess the perceived impact of the device on functional independence, performance and productivity. The subscale adaptability evaluates the device-related ability to participate, along with the willingness to cope with new experiences and challenges and to adapt to different settings. The subscale self-esteem collects items referring to mood, self-confidence, self-esteem, and emotional well-being (Jutai and Day, 2002; Devitt et al., 2004). Each item on all subscales is measured on a seven-point Likert scale, ranging from −3 (maximum negative impact) to + 3 (maximum positive impact). The neutral score (zero score) represents no change or no perceived impact by using the device (Devitt et al., 2004; Traversoni et al., 2018). The results of the PIADS are reported as median scores for all three subscales and each item.

The PIADS is a reliable and valid measure and it has established content validity, discriminant validity and internal validity (Day et al., 2002; Jutai and Day, 2002). It has been shown to have good construct validity, good test–retest stability (t-test, p-values 0.77–0.85) and reliability (ICC: 0.77–0.90), internal consistency (Cronbach's alpha 0.95 for PIADS total score, 0.92 for competence subscale, 0.88 for adaptability subscale and 0.87 for self-esteem subscale) (Chae and Jo, 2014) and acceptable concurrent validity (ICC: 0.77–0.83) (Traversoni et al., 2018). It has been used in research with different assistive technologies, although not yet with the running frame. The Dutch translation was made for a European research project on the effects of an incontinence device (Macaulay et al., 2007). The PIADS was translated into Dutch by the local researcher and retranslated into English by an independent professional translator. This allowed for any difficulties with the translation to be addressed, such as changes in meaning and word identification.

A convenience sample of parents of six athletes was interviewed by means of a semi-structured interview to give qualitative in-depth information about the reasons for their scores on specific items of the PIADS.

Data Analysis

Descriptive statistics (e.g., frequency, means, standard deviation, range, and percentage) were used to describe the participants. PIADS item scores were converted to subscale scores by using the scoring sheet (Jutai and Day, 2002). To analyze if the median subscales scores were different from the neutral score (zero score, meaning no perceived impact by using the device), the one sample t-test was used. To analyze differences between the supported and non-supported walkers the Mann–Whitney test was used. For data analysis Statistical Package for the Social Sciences (SPSS) version 25 was used.

The six semi-structured interviews were recorded and transcribed verbatim. For this study especially the quotes about the PIADS items in which most change was experienced by the parents were reported.

RESULTS

From April 2018 to February 2019, all athletes of 21 Frame Running groups across the Netherlands were invited to participate by an information leaflet via their Frame Running trainer. An unknown amount of them would probably not fulfill the inclusion criteria, mostly because they were not participating in Frame Running more than 3 months and sometimes because of age. We have only included athletes who were still involved in Frame Running. In total 62 children and youth have signed up and were included and filled in the questionnaires. Most athletes were male (58%), had CP as their main diagnosis (58%) and 52% were supported walkers (GMFCS III–V). Their mean age was 12 years and mean experience with Frame Running was 13 months. There were no significant differences in sex, age, and Frame Running experience between the athletes whose parents were interviewed and the other athletes (see **Table 1** for more information).

PIADS Subscale and Items Scores

The median scores on the three subscales of the PIADS for the whole group were: competence 0.83 (Q1–Q3: 0.42–1.25), adaptability 0.91 (Q1–Q3: 0.50–1.50), and self-esteem 0.55 (Q1–Q3: 0.38–1.25) meaning an increase. The median scores for all three subscales were significantly different from zero (0) ($p < 0.001$; one-sample Wilcoxon Signed Rank Test).

There were no significant differences between the non-supported walkers vs. the supported walkers in baseline characteristics (sex $p = 0.473$, age $p = 0.293$, Frame Running experience $p = 0.841$) or in median scores of the three subscales ($p = 0.729$ for competence; $p = 0.365$ for adaptability; $p = 0.899$ for self-esteem) (see **Table 2**).

Most change was experienced in the items performance (subscale competence, median 2.00), the ability to participate (subscale adaptability, median 2.00), happiness (subscale self-esteem, median 2.00), and self-confidence (subscale self-esteem, -median 1.50) (see **Table 2**).

The parents who were interviewed elucidated these four items with the highest mean score by the following quotes. According to the Glossary of PIADS items (Day and Jutai, 1996), the item performance is described as "able to demonstrate your skills." Many parents elucidated the increase in performance on the running frame, but also in activities in daily life in their child by the comments: "*He can walk more easily, so he walks more than before*," "*Walking is really improving*," "*He can walk much longer because with Frame Running you work on fitness and now he can sustain activities in daily life longer*."

The item ability to participate is described as "ability to join in activities with other people." It is clear that Frame Running makes it possible for athletes to participate, in the Frame Running club itself, but also in competition or running events, together with children without a disability or sometimes with their siblings or family. Moreover, the running frame can be used in daily life which makes it possible for children to participate in play. Parents elucidated this: "*He can participate in competition with Frame Running*." One parent told: "*Especially on holidays, when we were on a camping site, she could participate and play with the other children with her running frame.*"

On the item happiness, described as "gladness, pleasure, and satisfaction with life," all parents mentioned that their child really liked to use the running frame, it makes them happy. These are quotes: "*You can see that he really likes Frame Running, it makes him happy.*" "*She really loves to do Frame Running; she has a lot of fun, together with team mates.*" "*Every evening the day before training is fun. Then he says: 'mama, tomorrow is Saturday.' And I ask him 'what is happening then?' he: 'I am going to do*

TABLE 1 | Characteristics of the participating Frame Running athletes.

	Total group (n = 62)	Interview (n = 6)
Sex, *n* (%)		
Girls	26 (42%)	1 (17%)
Boys	36 (58%)	5 (83%)
Age		
Years; mean (SD)	12 yr 4 mo (3 yr 3 mo)	10 yr 5 mo (2 yr 8 mo)
Range	5 yr 7 mo−19 yr 0 mo	6 yr 9 mo−13 yr 7 mo
Experience Frame Running		
Months; mean (SD)	13.0 (8.1)	11.3 (4.3)
Range (months)	3–48	6–18
Diagnosis, *n* (%)		
Cerebral Palsy	36 (58%)	3 (50%)
Other neurological disorders	15 (24%)	2 (33%)
Spina Bifida (3), genetic abnormality (3), TBI (2), epilepsy/ West syndrome (2), neurodegenerative disorder (2), Neurofibromatosis (1), Sturge Weber (1), HMSN (1)		*(Spina Bifida)*
Metabolic disease	4 (6%)	
Psychomotor delay	4 (6%)	
Down Syndrome (3); Sotos syndrome (1)		
Orthopedic disorders	2 (3%)	1 (17%)
AMC (1); Perthes (1)		*(Perthes)*
Unknown	1 (2%)	
Gross Motor Function Classification System; *n* (%)		
GMFCS I*	14 (23%)	2 (33%)
GMFCS II*	16 (26%)	1 (17%)
GMFCS III	15 (24%)	3 (50%)
GMFCS IV	10 (16%)	
GMFCS V	7 (11%)	

*N, number; %, percentage; SD, standard deviation; yr, year; mo, months. *Unsupported walkers.*
TBI, traumatic brain injury; HMSN, hereditary motor and sensory neuropathy; AMC, arthrogryposis multiplex congenital; GMFCS, Gross Motor Function Classification System.

Frame Running!"' Or this parent about the first time her daughter is trying Frame Running: '*If you see how much pleasure... the face of the children who were put on the running frame to try out… it is golden!*" "*He was shining the first time he was on the running frame!*"

Self-confidence, described as "self-reliance, trust in yourself, and your abilities," of the Frame Running athletes increased as illustrated by these parents: "*She has a lot of positive experiences, playing together with other children. She is able to go out on herself, I do not have to accompany her, she feels very confident in doing it on her own*" and "*Last Sunday we participated in a 1 mile run and then she became third, surprisingly. That was a very big party for her! It has a big impact, winning something or getting a medal. It is good for her self-confidence.*" And another parent told us: "*Having success and doing things on his own makes him grow*."

DISCUSSION

This study showed that parents of young Frame Running athletes reported a positive change in competence, adaptability, and self-esteem since their children started using a running frame by participating in a Frame Running athletic club. Not a single parent reported deterioration in these domains.

This is the first study, that we know of, that investigated changes in QoL since the start of Frame Running in a larger scale. The only other study which studied QoL after a period of Frame Running was the pilot study of Bryant et al. (2015). The authors introduced the Petra running frame to 15 non-ambulant children with CP in two special schools. A 12-week training period resulted in an improved ability to use the running frame. Qualitative interview data confirmed that children enjoyed using the running frame, although the authors did not find a change in data from a QoL questionnaire. This seems in line with our results of an increase in performance on the running frame, and an increase in happiness. The PIADS will be used in a recently started study on the effects of Frame Running by Ryan et al. (2020).

Our result that QoL and self-esteem increased after a period of Frame Running is in line with the findings of Te Velde et al. (2018), who showed that QoL and self-esteem was higher in children with a disability who participate in sports, in comparison with children with a disability who do not participate in sports. Maher et al. (2016) found a positive association between physical

TABLE 2 | Results on PIADS domains and item scores of Frame Running athletes.

	Unsupported walkers ($n = 30$) Median (Q1 to Q3)	Supported walkers ($n = 32$) Median (Q1 to Q3)	Total group ($n = 62$) Median (Q1 to Q3)
PIADS			
Competence	***0.92 (0.42 to 1.25)***	***0.75 (0.42 to 1.25)***	***0.83 (0.42 to 1.25)****
Competence	1.00 (0.00 to 2.00)	0.00 (0.00 to 2.00)	1.00 (0.00 to 2.00)
Independence	1.00 (0.00 to 2.00)	0.00 (0.00 to 2.00)	1.00 (0.00 to 2.00)
Adequacy	0.00 (0.00 to 1.00)	0.00 (0.00 to 1.00)	0.00 (0.00 to 1.00)
Confusion	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.00)
Efficiency	1.00 (0.00 to 1.00)	0.00 (0.00 to 1.00)	0.00 (0.00 to 1.00)
Productivity	1.00 (0.00 to 2.00)	1.00 (0.00 to 2.00)	1.00 (0.00 to 2.00)
Usefulness	0.00 (0.00 to 1.00)	1.00 (0.00 to 2.00)	0.00 (0.00 to 1.25)
Expertise	0.00 (0.00 to 1.00)	1.00 (0.00 to 2.00)	0.00 (0.00 to 1.00)
Skillfulness	0.00 (0.00 to 1.00)	1.00 (0.00 to 2.00)	1.00 (0.00 to 1.00)
Capability	1.00 (0.00 to 2.00)	1.00 (0.00 to 2.00)	1.00 (0.00 to 2.00)
Quality of life	2.00 (0.00 to 2.00)	1.00 (1.00 to 2.00)	1.00 (0.75 to 2.00)
Performance	2.00 (1.00 to 2.00)	2.00 (1.00 to 2.00)	2.00 (1.00 to 2.00)
Adaptability	***1.00 (0.67 to 1.50)***	***0.83 (0.33 to 1.33)***	***0.92 (0.50 to 1.50)****
Well-being	1.00 (1.00 to 2.00)	2.00 (0.00 to 2.00)	1.00 (0.75 to 2.00)
Willingness to take chances	1.00 (0.00 to 1.00)	1.00 (0.00 to 1.00)	1.00 (0.00 to 1.00)
Eagerness to try new things	1.00 (0.00 to 2.00)	1.00 (0.00 to 2.00)	1.00 (0.00 to 2.00)
Ability to participate	2.00 (1.00 to 3.00)	2.00 (1.00 to 2.00)	2.00 (1.00 to 3.00)
Ability to adapt to the activities of daily living	1.00 (0.00 to 1.00)	0.00 (0.00 to 1.00)	0.00 (0.00 to 1.00)
Ability to take advantage of opportunities	1.00 (0.00 to 1.00)	0.00 (0.00 to 1.00)	0.00 (0.00 to 1.00)
Self-esteem	***0.75 (0.50 to 1.25)***	***0.88 (0.38 to 1.13)***	***0.75 (0.38 to 1.25)****
Happiness	2.00 (1.00 to 2.00)	2.00 (1.00 to 2.00	2.00 (1.00 to 2.00)
Self-esteem	1.00 (1.00 to 2.00)	1.00 (0.00 to 2.00)	1.00 (0.00 to 2.00)
Security	1.00 (0.00 to 1.00)	0.00 (0.00 to 1.00)	1.00 (0.00 to 1.00)
Frustration	0.00 (−1.00 to 0.00)	0.00 (0.00 to 0.00)	0.00 (−0.25 to 0.00)
Self-confidence	2.00 (1.00 to 2.00)	1.00 (1.00 to 2.00)	1.50 (1.00 to 2.00)
Sense of power	1.00 (0.00 to 1.00)	0.00 (0.00 to 2.00)	0.00 (0.00 to 1.00)
Sense of control	1.00 (0.00 to 1.00)	1.00 (0.00 to 2.00)	1.00 (0.00 to 1.25)
Embarrassment	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.00)
Characteristics			
Age; mean (SD)	11 years 11 months (2 years 11 months)	12 years 10 months (3 years 8 months)	
Sex; boys (n; %)	16 (53%)	20 (63%)	
Frame Running experience; mean (SD)	12.8 months (8.67 months)	13.2 months (7.72 months)	

PIADS, psychosocial impact of assistive devices scale.
[*]Subscale scores differed significantly from 0 ($p < 0.001$).

activity, social and physical quality of life, and happiness in young people with CP. Other authors reported positive effects on QoL in children with disabilities after participating in adapted soccer and swimming (Feitosa et al., 2017) and in adapted hip-hop dance practice (Withers et al., 2019). Also interventions as an adapted cycling program had a positive effect on the emotional well-being of children with CP (Demuth et al., 2012; Pickering et al., 2013a,b). Moreover, several intervention studies on fitness training in children with CP reported positive short-term effects on QoL (Verschuren et al., 2007; Demuth et al., 2012) and on social participation (Verschuren et al., 2007).

Besides the positive change in all three subscales of the PIADS, we also looked more in detail at the items. Most change was experienced in the items performance, the ability to participate, happiness and self-confidence. Our result of a rather big change in the item "ability to participate" is in line with research by Pickering et al. (2013a,b). They showed that social participation of children with CP improved when they used an adapted bicycle. Also Jeffress and Brown (2017) showed that children who played power soccer (in a wheelchair) also felt more able to participate. Using a device can improve the ability to participate in a positive way. Parents reported that their children were more often able to participate, in the sport Frame Running itself at a regular athletics club, but also in play situations at school or at home, when the child was using the running frame. Sports in general has psychosocial benefits for the participants; it gives them more independency and the feeling they can fully participate in sports.

The increase in happiness and self-confidence we have found is in line with the study of Pickering et al. (2013a,b). They concluded that the children with CP who took part in an adapted cycling program enjoyed this experience and it improved their sense of well-being. When sports is fun and makes the children happy, it is more likely that they will continue to do sports.

In our study, both non-supported and supported walkers experienced the same increase in QoL which is a positive finding. Our hypothesis that Frame Running would be more beneficial for the supported walkers was not confirmed. Although Frame Running was developed for persons with severe motor disabilities based on neurological impairments, it also seems a good option for children with less severe motor disabilities or from another than neurological origin who cannot participate in regular sports.

Limitations

This study has some limitations. We have asked the parents to fill in the PIADS questionnaire instead of asking the athletes themselves. A recommendation for future research could be to ask the athletes to fill in the questionnaire, although for younger children and children with a cognitive disability it would probably be hard to understand the items of the PIADS. Moreover, we only interviewed parents and not the athletes themselves. In future research we recommend that young athletes themselves be included to learn about their personal experience.

There was a large range in experience with Frame Running. For the parents, recalling health status 2 years ago is very different than recalling 3 months ago. This could have affected the results by recall bias. Another limitation is a possible selection bias, because by the nature of this study, we only have data from athletes who were still using the running frame. We do not know what athletes who have stopped using the running frame would score. Also children who might have liked Frame Running, but their parents didn't (or did not have the means to support it) are not included. A recommendation for future research would be to recruit participants from the first time they tried the sport and then examine them after a fixed time frame, independent if they continued or not.

The cross-sectional design could be seen as a limitation because there is no comparison before and after introducing Frame Running or with those who are no longer active. The PIADS questionnaire measures a change in QoL, so is applicable for this design. A recommendation for future research could be to use a pre-post design with another QoL questionnaire and with a fixed time frame.

The heterogeneity of the study population could be seen as a limitation, although this is a real life representation of the Frame Running population.

CONCLUSION

We found improvement in the QoL of children and youth with a mobility limitation since they started using a running frame to participate in the sport Frame Running. Our results showed that the para-athletic sport Frame Running contributes to a positive change in competence, adaptability, and self-esteem of children with a mobility limitation.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medical Ethical Committee (METC) of Amsterdam UMC, location Vrije Universiteit in Amsterdam. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

PS, ME, LB, AE, and AB designed the study. PS and ME collected data, summarized results, and drafted the manuscript. All authors have reviewed and edited 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/fspor.2022.839285/full#supplementary-material

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The Effect of Voluntary Physical Activity in an Enriched Environment and Combined Exercise Training on the Satellite Cell Pool in Developing Rats

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Aim: Postnatal skeletal muscle growth is strongly associated with a satellite cell pool. Early adolescence might be a crucial period when different exercise training interventions have specific consequence on satellite cells. Pax7 and MyoD have been suggested as the leading indicators of satellite cell activation.

Methods: In this study, pre-adolescent male rats ($n = 18$) were either subjected to an enriched environment that facilitated physical activities or combined training or control for three weeks. The flexor hallucis longus muscle was removed for biochemical and histochemical analysis.

Results: Findings demonstrated that exercise trained rats displayed high levels of serum IGF-1 ($p < 0.05$). There was an increase in Pax7 ($p < 0.05$) and MyoD ($p < 0.001$) mRNA expression. A significant increase in the mean fiber area ($p < 0.01$), satellite cell ($p < 0.001$), and myonuclear numbers ($p < 0.01$) were also observed in both intervention groups. Importantly, enriched rats showed lower corticosterone levels ($p < 0.05$) compared to training ones. Regarding performance, trained and enriched rats had significant improvement in forelimb grip strength ($p < 0.01$) and load-carrying capacity ($p < 0.05$).

Conclusion: Type of physical exercise is an essential part in changing satellite cells pool. Different and frequent physical activities in an enriched environment can be effective for muscle development.

Keywords: voluntary physical activity, MRF, pax7, pre-puberty, combined training

1 INTRODUCTION

Pre-puberty is a critical time for skeletal muscle development. The postnatal myofiber growth seems to be strongly associated with the satellite cells (SCs) pool (Bachman et al., 2018). These types of myogenic cells are located between the basal lamina and sarcolemma of muscle fibers. The proper operation of SCs depends on paired box transcription factor 7 (Pax7) (von Maltzahn et al., 2013). In this case, skeletal muscle growth is controlled by muscle regulatory factors (MRFs), an essential family with important factors (MyoD, Myf5, Myogenin, and MRF4). MyoD expression is known to increase in the time of activation and proliferation of SCs. In particular, co-expression of Pax7 and

MyoD has been introduced as the primary indicator of SC activation (Martin and Lewis, 2012). Great SC activity has been observed until the onset of puberty and adolescence (Bachman et al., 2018). In rodents, this period begins at post-natal day (PND) 21 days and lasts approximately 30–49 days of life which is equivalent to 2–3 years old to 12–14 years old in humans (Holder and Blaustein, 2014).

Sensitive postnatal periods are characterized by rapid progress of neuromuscular and motor development (Beunen and Thomis, 2000). In this way, a dramatic increase in muscle fiber area and myonuclear capacity is evident (Bachman et al., 2018). There is abundant evidence that insulin-like growth factor-1 (IGF) is mainly responsible for skeletal muscle development and contributes to SC proliferation and differentiation (Mourkioti and Rosenthal, 2005). Thus, immature myofibers may be more susceptible to stimuli like exercise (Bachman et al., 2018).

The potential role of exercise in SC activation is well clarified (Dhawan and Rando, 2005). Training intervention-induced benefits on muscle structure have been indicated in animal and human studies (Martin and Lewis, 2012). One study specifically described that physical exercise training in 4-week-old rats enhanced SC number and myonuclear content in adulthood. Indeed, exercise exposure during the critical period of growth may have a synergistic role in the SC pool, which lasts into adulthood and leads to sustained effects (Smith and Merry, 2012). The impact of interventions depends on essential aspects of exercise, including the duration, intensity, and type (Martin and Lewis, 2012).

There are various types of physical activities in rodent models, including forced exercise training and voluntary physical activity (Gomes da Silva and Arida, 2015). In this case, endurance and resistance training enhances the SC pool (Martin and Lewis, 2012). However, few works have focused on combined endurance and resistance training during pre-pubertal and juvenile periods. Although the exact mechanisms of SC augmentation have not yet been accurately evaluated, the suitable combination of endurance and resistance training may lead to a more potent stimulus for muscle growth compared to each intervention alone (Murach and Bagley, 2016). Combined training can induce sufficient intensity and lead to changes in SCs by recruitment of fast-twitch fibers (Verney et al., 2008). In addition, it has been demonstrated that concurrent resistance and aerobic training improved muscular fitness (Alves et al., 2016). The relationships between improved muscular performance and IGF-1 have also been described (Cetinkaya et al., 2013), notably because the IGF contribution in SC proliferation and hypertrophy has been demonstrated (Lee et al., 2004). Moreover, muscle hypertrophy has been more evident in resistance than endurance training (Legerlotz et al., 2008). For example, the effects of a resistance training program has been evaluated in adult rats, where increased myogenin, MyoD, and IGF-I mRNA levels with enhanced muscle size was found (Aguiar et al., 2013). However, forced exercise training-induced negative stress could lead to muscle atrophy (Eldomiaty et al., 2020).

Voluntarily physical activities may not induce potential negative stress during forced exercise training (De Bono et al., 2006). In loaded and unloaded conditions, voluntary exercise paradigms have been used in existing animal studies (Smith and Merry, 2012). For example, pre-adolescents rats exposed to resistance running wheels and free-spinning running wheels displayed hypertrophy in different muscles and a significant number of SCs (Legerlotz et al., 2008). Physical enrichment is a novel approach where animals usually have access to running wheels and other motor elements, known as critical parts of enriched environments. In particular, climbing is a natural behavior in young animals. In this regard, resistance activities can be performed through ladders and steps in the cage (Spangenberg et al., 2005). Furthermore, toys and different objects are provided in ample space like a playroom (Sale et al., 2014). The nature of these environmental housing conditions can affect muscle biology by reducing stress levels. Numerous investigators have demonstrated the neural consequences of an enriched environment, but there is less information on muscular adaptations. Recently, one study demonstrated that different enriched environments could increase muscle development (Sudo and Ando, 2021). This finding is crucial because many benefits of enriched environment (EE) are gained in the early periods of life (Sampedro-Piquero and Begega, 2017). However, voluntary activities in an enriched environment are not the same as exercise training programs and may not elicit sufficient muscle load to cause adaptations in SCs and myonuclear domain (Kurosaka et al., 2012).

The satellite cell pool may be affected by the fibers type composition. Although limited information is currently available, there is evidence of differences in the number of satellite cells between different muscles and fibers. In this regard, more satellite cells have been reported in slow muscle and fibers (Yin et al., 2013). On the other hand, it has been found that MyoD expression levels are higher in fast muscles like FHL (Flexor Hallucis Longus) which needs further investigation (Hughes et al., 1997).

The effects of exercise on SCs have been studied, but essential changes during the pre-pubertal and juvenile periods are unclear. This stage of life represents a unique period in skeletal muscle development (Gabel et al., 2017). Exercise interventions may profoundly affect the SC pool and have long-term and enduring consequences. The type of physical training used during this period is an essential issue. The differences between training modalities may result in specific adaptations. Hence, the aim of this study was to assay the effects of voluntary physical activity in an enriched environment versus forced combined training on the SC pool in pre-adolescent rats' FHL muscles.

2 MATERIALS AND METHODS

2.1 Animals

We followed the "guidelines for planning animal research and testing" (Smith et al., 2017). The experimental protocols were approved by the Animal Care Committee of the Shahid Beheshti University (IR.SBU.REC.1398.007). Eighteen pre-adolescent male Wistar rat pups (from Laboratory Animals of the Razi

Vaccine and Serum Research Institute, Iran), 15 days old, were maintained in a controlled environment (21–23°C, 56% humidity, and 12-h light-dark reverse cycle) with their mothers. The animals were randomly divided into three groups: enriched environment (EE), combined exercise training (CET), and control group (C) (n = 6 per group), following weaning at PND 22 (Rostami et al., 2021a). The subjects were weighed weekly and had ad libitum access to food and water.

2.2 Forced Exercise Training and Enriched Environment

The rats in the CET group were subject to endurance) training even days) and resistance training (odd days) during 28–48 PND (Rostami et al., 2021a). First, the rats were adapted to treadmill running (Tajhiz Gostar Company Ltd., 2021) and ladder climbing (100 cm high, 2 cm grid steps, and 80° incline) for three days. Subsequently, the load-carrying capacity of animals was assessed at PND 25 and 26. The animals performed endurance training at 70% of maximum running speed (14–16 m/min). The first training session started with running for 20 min a day and then the duration of training was gradually enhanced to reach 45 min at the end of the third week. Resistance training with eight sets was performed. In this way, the rats climbed the ladder with 50, 75, 90, and 100% from the previous maximal load. When the task was completed, a load of 7 g was added until failure (Hornberger and Farrar, 2004; Huang et al., 2006).

In order to create voluntary physical activity, rats in the EE group were group-housed in large enriched cages (40 × 60 × 90 cm). This environment was composed of three floors, which animals could move among the floors by stairs and climb the cage walls. In addition, there were wheel running and ladders to promote physical activity. The animals had access to food pellets and water ad libitum on each floor and were not forced to do physical activities (Sale et al., 2014).

2.3 Physical Performance Assessments

To measure maximal load-carrying capacity, the rats climbed the ladder with a load equal to 75% of their body weight. Then, a weight of 7 g was added to the carrying bag. The maximum strength was calculated when animals could complete the climb (Hornberger and Farrar, 2004). Grip strength was assessed to evaluate the forelimb strength of rats. While the animal tightly grasped the horizontal bar with both paws, their tail was pulled back slowly and at a constant speed. Measurements were recorded when paws released from the bar (Meyer et al., 1979).

2.4 Samples Collection

After interventions, animals were anesthetized with carbon dioxide at PND 54. Blood samples centrifuged at 3000 rpm for 10 min at 4°C to extract serum (Eppendorf Centrifuge, 5415R). Next, muscle tissues were removed. Some of the collected FHL muscles (left side) were frozen in liquid nitrogen and keep at 80°C for biochemical measurements. For histological analysis, the rest of the tissues (right side) were fixed in 10% formalin in phosphate buffer. Subsequently, transverse sections with a thickness of 7 μm were prepared using a microtome (Leica, Wetzlar, Germany) at −20 °C.

TABLE 1 | The characteristics of the used primers.

Genes	Genbank accession No	Sequence (5′–3′)
Pax7	NM_001191984.1	F *CATTCTCAGCAACCCGAGTG* R *GAGATGGAGGAGGCAGAG*
MyoD	NM_176079.2	F *GACGGCTCTCTCTGCTCCTT* R *GTCTGAGTCGCCGCTGTAG*
GAPDH	NM_017008.4	F *AGGTCGGTGTGAACGGATTTG* R *TGTAGACCATGTAGTTGAGGTCA*

2.4.1 Enzyme-Linked Immunosorbent Assay (ELISA)

The enzyme-linked immunosorbent assay (ELISA) with 96-well kits (Korain Biotech Co.) was performed to assay basal serum IGF-I (E0709Ra) and corticosterone (E0496Ra) levels in sensitivity of 0.24 and 1.55 ng/ml, respectively (Rostami et al., 2021a). The manufacturer's instructions were used, and absorption was measured at a 450-nm wavelength.

2.4.2 Gene Expression Analysis (Real-Time Quantitative PCR)

One ml of QIAzol Lysis Reagent (QIAGEN, United States, Cat. No: 79306) was added to 100 mg of tissue and incubated at room temperature for five minutes to extract RNA from homogenized tissues (FHL muscles). Cold chloroform was then added, and the supernatant was transferred to a microtube containing RNAase-free water after centrifugation. Finally, the concentration and purity of obtained RNA were measured by a Nanodrop spectrophotometer (Thermo Scientific, United States). Optical density (OD) was evaluated at 260 and 280 nm, and OD260/280 ratio (around 2.0) indicated the RNA purity. cDNA was synthesized from 1 μg of total RNA. The process of cDNA synthesis was accordance with manufacturer's guidelines (Thermo Scientific, United States). For this purpose, 10 μL of Dnase-treated RNA was poured into the microtube, and 10 μL of cDNA synthesis kit was added. Finally, real-time PCR was performed by SYBR Premix Ex TaqTM II (Amplicon, Denmark) with an ABI StepOnePlus Real-Time PCR System (ABI Stepone, United States). mRNA level was normalized to the GAPDH mRNA level using the $2^{-\Delta\Delta CT}$ method. The characteristics of the primers used are presented in **Table 1**.

2.4.3 Immunohistochemical Analysis

For immunofluorescence staining, sections were washed in phosphate-buffered saline for 20 min (PBST, pH 7.4) and fixed with 4% paraformaldehyde for 15 min, followed by blocking step with 5% normal goat serum (NGS) in PBST for 30 min. After blocking, the muscle sections were incubated overnight with primary antibodies (anti-Pax7 at 1:500; Santa Cruz Biotechnology) in 1% NGS in PBST. After washing the sections, they were incubated for one hour at room temperature (anti-mouse IgG antibody at 1:500; Santa Cruz Biotechnology). Following additional washes, nuclei staining was developed with 4', 6-diamidino-2-phenylindole (DAPI; 1:

TABLE 2 | Bodyweight and performance measurements.

	Body weight (g)	Body weight changes (g)	Maximum weight carrying (g)	Grip strength (g)
C	146/9 ± 3.22	83.18 ± 20.28	111.3 ± 7.79	435.6 ± 16.34
EE	149.2 ± 2.87	81.24 ± 18.45	132.1 ± 11.78*	518.6 ± 15.95**
CET	147.0 ± 2.81	82.19 ± 18.56	153.6 ± 12.80*	512.9 ± 17.69**

Data are expressed as mean ± SEM. C, control; EE, enriched environment; CET, combined exercise training.

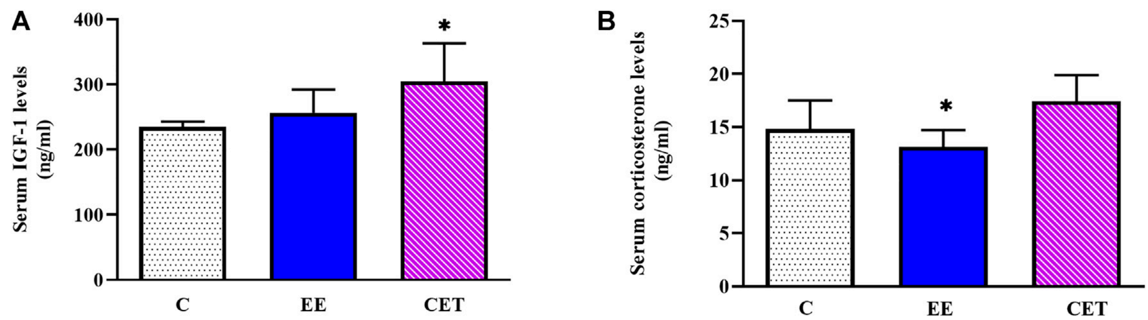

FIGURE 1 | Serum IGF-1 **(A)** and corticosterone **(B)** levels display a significant difference in preadolescent rats subjected to an enriched environment (EE) and combined exercise training (CET). $*p < 0.05$, vs. control group.

10,000; Sigma Aldrich) and then mounted (Vector Labs, Burlingame, CA, United States).

After the staining procedure, the images were analyzed using a fluorescence microscope (×20 objective) equipped with a digital camera (Olympus, Japan) to detect the satellite cells. The Pax7 (green) and DAPI staining (blue) were visible using the B2A and UV-2E/CT filters, respectively. As described previously, the numbers of SC and myonuclei per muscle fiber were calculated. In total, 15 areas in each muscle cross-section were randomly selected for SCs and myonuclei measurements. In this case, the number of SCs and myonuclei relative to the number of fibers evaluated in each section was determined. The percentage was calculated as the quotient of SCs and myonuclei. Total area was divided by the total number of fibers to determine the mean cross-sectional fiber area (IM 500, Leica) (Kojima et al., 2007).

2.5 Statistical Analysis

SPSS 20 Software was applied to analyze the data. Accordingly, normal distribution was first evaluated with the Kolmogorov-Smirnov test. Significant differences between groups were determined by Ordinary one-way analysis of variance (ANOVA) and Tukey post hoc test ($p < 0.05$).

3 RESULTS

3.1 Body Weight and Performance Measurements

We did not detect notable differences in body weight among groups over the 3 wk of intervention [$F (2, 6) = 0.002$, $p = 0.99$; **Table 2**] and at the end [$F (2, 15) = 0.28$, $p > 0.05$]. However, there were remarkable differences in load-carrying capacity [$F (2, 15) = 4.27$, $p = 0.03$] and compared to C group, 18 and 38% increase were found in the EE and CET groups, respectively. We also observed considerable differences in grip strength [$F (2, 15) = 8.20$, $p = 0.003$] between groups, such that 19% increase in the enriched rats and 17.7% increase in the trained rats were observed compared with controls. Load-carrying capacity and grip strength did not differ between CET and EE groups.

3.2 Serum IGF-1 and Corticosterone Levels

Serum IGF-1 levels were different considerably between groups [$F (2, 15) = 4.78$, $p = 0.03$; **Figure 1A**]. Greater IGF-1 was detected after CET compared with controls ($p < 0.05$), but no significant increase was found in the EE group. IGF-1 did not differ between CET and EE groups. This study also found remarkable differences in the circulating corticosterone levels [$F (2, 15) = 5.39$, $p = 0.01$; **Figure 1B**]. The EE rats exhibited significantly lower corticosterone levels compared with CET ($p < 0.05$). No differences were observed between the EE and C groups.

3.3 Pax7 and MyoD mRNA Expression

Regarding gene expression, there was a remarkable difference between groups in Pax7 levels [$F (2, 15) = 6.10$, $p = 0.01$; **Figure 2A**], with a significant increase observed in the EE group compared with C and CET ($p < 0.05$). In addition, greater Pax7 mRNA was found in CET rats than C group, while the changes were not significant ($p < 0.10$). MyoD levels were also different between groups [$F (2, 15) = 14.18$, $p = 0.0007$; **Figure 2B**]. The EE group showed significantly greater expression of MyoD mRNA compared

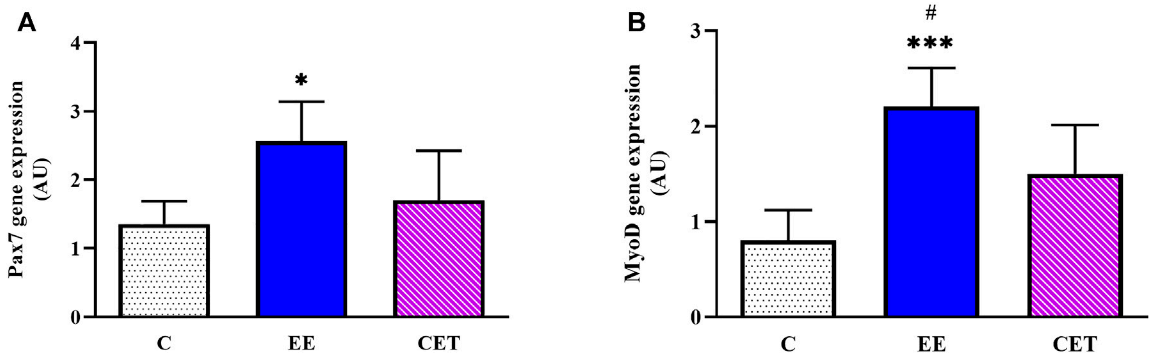

FIGURE 2 | Enriched environment (EE) and combined exercise (CET) significantly increased Pax7 **(A)** and MyoD mRNA levels **(B)** in preadolescent rats. *$p < 0.05$, ***$p < 0.001$ vs. control group. #$p < 0.05$ vs. CET group.

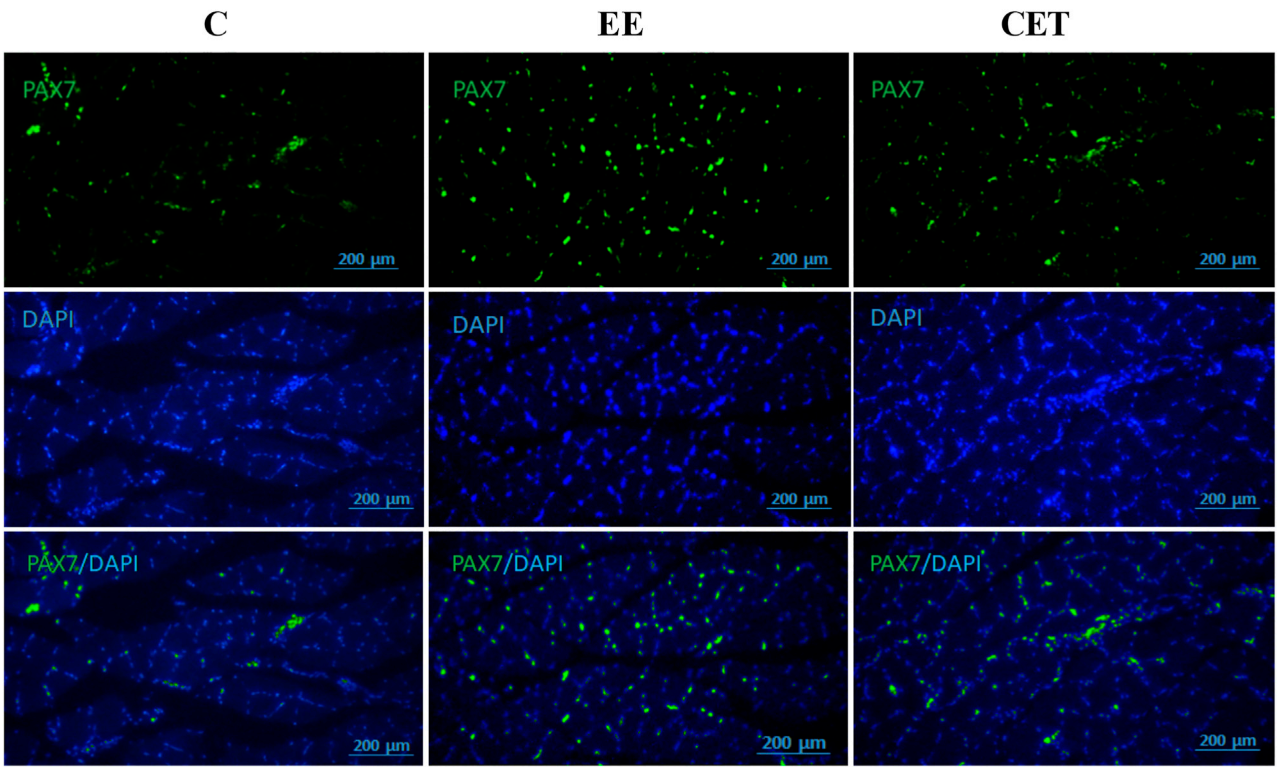

FIGURE 3 | Representative images of satellite cells and myonuclei. The immunostaining staining was used to detect Pax7 and myonuclei.

to C ($p < 0.001$) and CET ($p < 0.05$) groups. MyoD expression in the CET group was also higher than the C group.

3.4 Histological Properties of the FHL Muscle

Images of fiber area, satellite cell, and myonuclei by group are presented in **Figure 3**. Both interventions significantly affected mean muscle fiber area [F (2, 15) = 11.08, p = 0.0097; **Figure 4A**]. Compared to the C group, both EE and CET groups showed increased fiber area (both $p < 0.05$). Similarly, there was a significant difference between groups in the number of myonuclei per muscle fiber [F (2, 15) = 21.77, p = 0018; **Figure 4B**]. Post hoc analysis showed that the number of myonuclei per muscle fiber were greater in EE and CET rats compared with C (p <0.01 and $p < 0.05$, respectively). EE rats also had more myonuclei per muscle fiber compared with CET. There was a significant difference in the number of SC per muscle fiber [F (2, 15) = 39.19, p = 0.0004; **Figure 4C**], with more SC per muscle fiber observed in

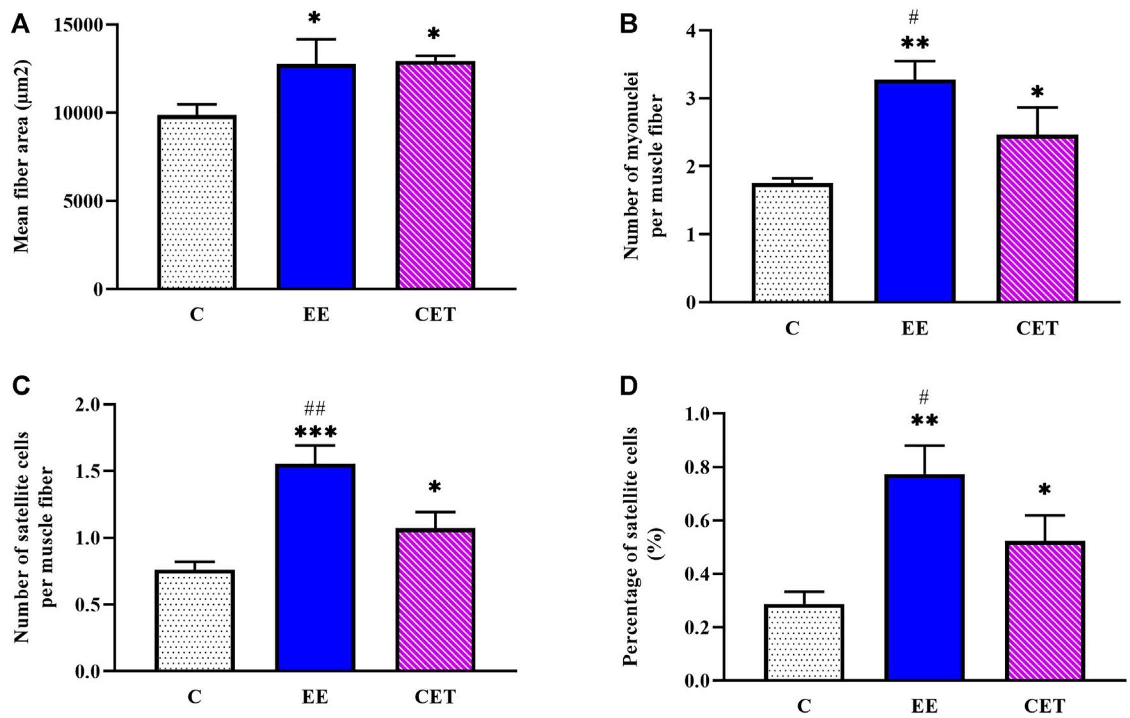

FIGURE 4 | Characteristics of satellite cells and myonuclei in preadolescent rats subjected to an enriched environment (EE) and combined exercise training (CET). A significant increase in mean fiber area **(A)**, the number of myonuclei per muscle fiber **(B)**, the number of SCs per muscle fiber **(C)**, and the percentage of SCs **(D)** was detected. *p < 0.05, **p < 0.01, ***p < 0.001 vs. control group. #p < 0.05, ##p < 0.01 vs. CET group.

the EE and CET groups (p <0.001 and p < 0.05, respectively). Moreover, the EE group had significantly more SC than the CET group (p <0.05). The percentage of SC also differed between groups [F (2, 15) = 23.59, p = 0.0014; **Figure 4D**). The percentage of SC in EE and CET groups was significantly higher than in the C group (p <0.01 and p <0.05, respectively).

4 DISCUSSION

The present study investigated the effect of two types of training interventions on satellite cells in the pre-pubertal period. This study demonstrated that voluntary physical activity in an enriched environment enhanced the gene expression of Pax7 and MyoD. However, there was a marginal increasing trend in combined exercise training group. Further, both conditions were characterized by significantly greater number of SCs, myonuclei, and mean fiber area of the FHL muscle compared with controls. Notably, the current study found significant differences in enriched rats compared to the training group and remarkably lower serum corticosterone level of the EE group. However, increased serum IGF-1 level was observed only in the combined exercise training. From a physical performance view, three weeks of either intervention improved muscle strength (forelimb grip strength and load-carrying capacity).

Different aspects of exercise can play a role in muscular adaptations (Martin and Lewis, 2012). Some studies have pointed out that running distance in endurance protocols correlated with a large SC pool (Kurosaka et al., 2009). In some studies, long-distance running is also associated with low body weight (Kurosaka et al., 2009). There was no significant difference in animal bodyweight that may be related to the short duration of the current intervention. Lack of remarkable changes in body weight can also be associated with increased lean muscle mass and decreased body fat following exercise protocols. SC activation has been observed in animal models following 6–13 week periods of endurance training (Kurosaka et al., 2009; Kurosaka et al., 2012; Mustofa et al., 2018). Besides, exercise intensity may also be a critical parameter when evaluating the training effects. For instance, SC pool enhancement in adult female rats was reported only following high-intensity running on the treadmill and remained unchanged in high-duration groups (Kurosaka et al., 2012). The trained rats ran on the treadmill at moderate intensity to endurance training. Additionally, progressive resistance training on a vertical ladder was performed three days a week. Regarding the type of training, the effect of endurance (voluntary free wheel exercise) and resistance (resistance wheel exercise) training in pre-adolescent rats was investigated in which enhanced SC numbers were found in both types of exercise (Smith and Merry, 2012). Therefore, it may be speculated that type of physical exercise training may have been a determining factor in the result observed. However, resistance training protocols have mainly reported exercise-induced muscle hypertrophy (Legerlotz et al., 2008). The current findings demonstrated that combined training enhanced Pax7 and MyoD levels. Although gene expression did not differ, trained rats displayed significant differences in the SC number, accompanied by greater myonuclear content and muscle fiber area compared with control rats. In line with these observations, increased SC and MRF expression number has been shown after resistance training in adult rats (Aguiar et al., 2013; Lim et al., 2018). The effects of forced, combined training have been rarely described in juveniles, whereas voluntary exercise models in loaded and unloaded conditions have been used in the pre-pubertal period.

In one study, four-week-old rats were housed with a free-spinning wheel from four to seven weeks of age, and no significant differences in muscle fiber nuclei and SC number were reported (Smith and Merry, 2012). On the contrary, this current study's intervention increased the number of SCs over three weeks. We provided an enriched environment with several accessories for voluntary physical activity. Since enriched rats had access to running wheels, part of the increase in the SC number could have been due to the high-speed intermittent activity on wheels, as observed by others (De Bono et al., 2006; Legerlotz et al., 2008). Voluntary physical activity and play in a large environment may have contributed to this process (Sale et al., 2014). Furthermore, ladders and stairs provided opportunities for juvenile rats to exhibit climbing behavior in their home cage. The cage walls also enabled rats to use the vertical space to climb (Baumans and Van Loo, 2013). Numerous climbing movements plus voluntary activity in running wheels probably influenced the myonuclear capacity resulting in increased muscle fiber area and MyoD expression (Smith et al., 2001). Following this idea, more myonuclear and large fiber sizes were reported in pre-adolescents rats exposed to resistance wheel training (Smith and Merry, 2012).

Interestingly, we found that enriched rats demonstrated more SCs and myonuclei numbers than the CET group. This group was subjected to cage motor stimuli continuously throughout the intervention. The volume of physical activities in a large environment might be effective in SCs activation and observed differences (Sudo and Ando, 2021). Moreover, there were lower corticosterone levels in the EE group compared to the CET. The duration and intensity of exercise training play role in physiological changes. In this study, according to the existing literature, a moderate-intensity training protocol was used, which may have led to physiological adaptation in the HPA (Hypothalamic Pituitary Adrenal) axis. As the training protocol is probably associated with the initial high activity of the corticosterone response, followed by a gradual adaptation to physical exercise (Leasure and Jones, 2008). On the other hand, social interactions, large spaces for voluntary physical activities, and enjoyment may have reduced HPA axis activity and corticosterone levels in enriched rats (Sale et al., 2014). Enriched animals probably did not experience potential negative stress during forced exercise training (De Bono et al., 2006; Baumans and Van Loo, 2013). Hence, these beneficial aspects of voluntary physical activity in an enriched environment could have led to significantly greater Pax7 and MyoD levels that together have been proposed as a critical indicator of SC activation (Martin and Lewis, 2012).

One possible explanation for a greater number of SC and mean fiber area in trained rats could be the pattern of muscle fibers recruitment given the nature of the physical exercise. Type II fibers are mainly recruited by resistance and high-intensity endurance training. The current study shows that FHL muscle fibers with glycolytic properties were stimulated by resistance activities in both intervention groups (Verney et al., 2008). Consequently, at least part of the increase in the MyoD gene expression may be due to muscle hypertrophy, as evidenced in adolescent rats (Ochi et al., 2011) and positive correlations between MRF expression and muscle hypertrophy (Aguiar et al., 2013). Moreover, increases in myofiber size have been associated with high myonuclear numbers in mouse skeletal muscle during 4–6 weeks of the postnatal period (Bachman et al., 2018). On the other hand, increases in myonuclear number may be related to changes in fiber type composition (Van Wessel et al., 2010). In particular, it has been evidenced that MyoD expression levels are higher in fast muscles (Hughes et al., 1997). In the present research, combining endurance and resistance training (physical activities in an enriched environment) probably plays a role in shifting myofibers toward the center of the muscle spectrum and increasing oxidative-glycogenic fibers. However, this research did not determine muscle fibers type and just studied FHL, often known as the fast-twitch muscle. Fiber type composition may change the satellite cells pool. Further studies are needed to investigate other muscle fiber types.

The number of SCs may also be affected by exercise-induced muscle damage in which damaged fibers release cytokines and growth factors (Carosio et al., 2011). In this case, IGF-1 is well known to increase following resistance training, contributing to muscle hypertrophy. Moreover, muscle-derived IGF-1 has been identified as the primary source of circulating this factor (Chargé and Rudnicki, 2004). The present study revealed that three weeks of combined exercise training increased the serum IGF-1 levels. Mechanical load seems to play a critical role in IGF-1 production (de Alcantara Borba et al., 2020). Regular exercise training, especially ladder climbing, could elicit muscle hypertrophy by stimulating IGF-1 secretion (Lee et al., 2004). On the other hand, IGF-1 level was significantly correlated with improved physical fitness (Cetinkaya et al., 2013). Accordingly, this study found a remarkable increase in load-carrying capacity and grip strength, which could clarify the role of IGF-1 in increasing the observed muscle adaptations. Previous studies have shown that pre-adolescent rats exposed to combined training showed decreased body performance after approximately one month of detraining, consistent with reduced serum IGF I levels (Rostami et al., 2021b). However, the IGF level did not display significant changes in the EE group. In this line, a study reported that long-term wheel running did not influence IGF-1 expression and reduced circulating levels of this factor (Matsakas et al., 2004). Enriched animals were not exposed to regular exercises compared to the training group. The intermittent activities in an enriched environment might not induce sufficient intensity to increase IGF-1 or have led to transient effects (Kurosaka et al., 2012; de Alcantara Borba et al., 2020). Physical activities with high frequency and low-pressure characteristics may activate SCs by affecting extracellular matrix (ECM) components. Therefore, damaged myofibers may release other factors such as hepatocyte growth factor (HGF) and have contributed to increased muscle fiber area and MyoD expression (Kurosaka et al., 2009). It is also imperative to note that increased strength in the pre-pubertal period usually depends on neural adaptations, including increased neuromuscular coordination and the recruitment of more muscle units. From this point of view, appropriate training interventions in this critical period can contribute to developing strength (Myers et al., 2017).

While performance measurements did not show significant differences between the CET and EE groups, higher maximum carrying capacity and lower grip strength were found in trained rats, compared to enriched ones. According to the movement mechanics, it can be realized that climbing a ladder in order to determine the maximum weight carrying is mainly done by involving large muscles and is a kind of gross movement. This function largely depends on the tone and strength of the muscles which are especially enhanced in progressive resistance training. However, grip strength as a fine motor skill requires the use of smaller muscle groups in the hands, wrists, and fingers. This isometric task is performed with strong contractions of the flexors. It seems that the permanent placement of animals in an enriched environment and as a result of numerous climbing movements has been effective in the observed differences (Butterfield et al., 2009; Gentier et al., 2013). Since the mechanisms by which physical exercise affects muscle development during the early adolescent period have been less studied and may be different from those of adulthood, much more work is needed to understand the underlying mechanisms.

In conclusion, combined exercise training or an enriched environment may be effective stimulants for increasing satellite cells and inducing hypertrophy. Type of physical exercise appears to be a critical factor in muscle adaptations. Different and frequent physical activities in an enriched environment with mild stress can be an effective muscle development approach. Moreover, exposure to suitable training interventions during the pre-pubertal period may elicit long-lasting developmental changes, which need to be investigated in future studies.

Practically, physical activity and musculoskeletal pressure are important for children's development. However, excessive physical stress may limit muscle growth and reduce children's participation in exercise programs. Since different activities are recommended in childhood, combining enjoyable resistance and endurance activities might be a suitable intervention that contributes to muscle development by stimulating different mechanisms.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/**Supplementary Material**.

ETHICS STATEMENT

The animal study was reviewed and approved by the All experiments were done in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH Publication No. 80–23, revised 1996) and were approved by the Animal Care Committee of Shahid Beheshti University (IR.SBU.REC.1398.007), Tehran, Iran.

AUTHOR CONTRIBUTIONS

RF was responsible for the study concept and design. SR, RS, and SS participated in the implementation of laboratory protocols and contributed to acquisition of cellular and molecular data. SR and RF assisted with data analysis and interpretation of findings. SR drafted the manuscript. RF provided critical revision of the manuscript for important intellectual content. All authors critically reviewed content and approved final version 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/fphys.2022.899234/full#supplementary-material

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SYSTEMATIC REVIEW
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The Physiological and Psychological Benefits of Dance and its Effects on Children and Adolescents: A Systematic Review

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Background: The aim of this review was to examine the physiological and psychological benefits of dance and its effects on children and adolescents. We consider the therapeutic benefits of dance and outline the potential of dance as an alternative therapy for certain pathologies and medical disorders. Secondly, we summarize the types of dances used in physical interventions, and comment on the methodologies used. Finally, we consider the use of dance as a different exercise modality that may have benefits for increased physical activity generally, and for increased physical education provision in schools.

Methods: A structured search strategy was conducted using the databases of PubMed, MEDLINE, Web of science, PsycARTICLES, and Social Science database. This review used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews. Studies that were published in the past 20 years were considered for inclusion. All written publications were searched for in English, and all articles included in this review were peer reviewed full papers.

Conclusion: The key findings from this review indicate that dance is a feasible alternative to traditional physical activity. The findings also indicate that dance provides physiological and psychological benefits to healthy and medically compromised populations. Implementation of dance programs in schools and society generally needs serious consideration by policy makers. We hope that the results of this review stimulate debate and provide the necessary evidence to profile dance as a viable alternative medium of physical activity. Comprehensive and integrated changes will be needed including economical and legislative support from politicians and associated governmental agencies. The findings reported here are important and have implications for health policy change, reconfiguration, and implementation.

Keywords: children, adolescent, dance intervention, dance therapy, physical activity, health policy and practice

1 INTRODUCTION

Physical Activity (PA) provides positive health benefits. The benefits include increases in cardiovascular fitness, physiological and psychological health, and musculoskeletal strength. In addition, PA has been successful in the prevention and treatment of diseases such as stroke, diabetic problems, high blood pressure, and certain cancers. PA has also been proven to be beneficial for maintaining a healthy body weight, enhancing quality of life, and contributing to individual well-being (WHO, 2020). PA also contributes positively in influencing social connectedness (Duberg et al., 2020). Equally, a decline in PA or lack of engagement, is one of the major risk factors associated with good health and mortality. Individuals not engaging in PA are prone to a 20%–30% risk of death increase compared to individuals participating in PA (WHO, 2020).

It has also been reported that engagement in regular PA is essential for healthy growth and development in children (WHO, 2020). The growth and developmental period in young people, is a time when negative social, and psychological experiences can affect cognitive, intellectual, and rational development (Lund et al., 2018). In support of this, most preventive strategies have increased success rates when the focus of the preventive strategy occurs in the early years and decades of life (Kieling et al., 2011). The World Health Organization (WHO) suggests that young people aged 5–17 years should participate in on average 60 min a day of moderate-to-vigorous exercise. The exercise type should mostly include aerobic activity executed over a 7-day period. The inclusion of high intensity performances, such as strength exercises, for at least 3 days a week is also desirable. The time spent participating in sedentary activities, particularly television and computer screen time, also needs to be minimized (WHO, 2020).

However, despite this, 80% of the world's adolescent population do not participate in physical activity (WHO, 2020). This figure is particularly alarming in female populations. One reason for lack of participation by females could be related to physical development. As females grow and develop, they become more aware of the significance of femininity, and involvement in exercise is often depicted as not corresponding to this image (Slater and Tiggemann, 2010). This problem has become even more acute during the COVID-19 pandemic. Quarantine stratagems have had a poor impact on PA. Research has revealed significant decreases in PA during this period (Tao et al., 2021). These undesirable health consequences of quarantine measures, that include psychological stress and greater physical inactivity, need consideration post quarantine to promote increased physical activity and associated health benefits (Füzéki et al., 2020).

Dance movement practice (DMP) is a type of art therapy that has been entrenched in modern culture for 70 years. Dance provides benefits for participants that are both personal and independent. Dance participation also provides physical and mental wellbeing (Tao et al., 2021). Further benefits include defining and consolidating body image; illuminating the ego; providing relief of physical tension, anxiety, and aggression, while decreasing cognitive and kinesthetic confusion. Dance also increases the capacity for interaction, increases pleasure, fun, and impulsiveness (Jeong et al., 2005). In addition, children subjected to emotional illness have certain emotional and physical limitations when engaging in traditional PA. Dance is a physical activity medium that can provide discrete and precise exercise prescriptions for these individuals.

Research related to dance interventions has demonstrated a rising trajectory in recent years. However, dance still needs to be recognized as viable physical activity alternative. In earlier reviews on children and adolescent populations, it was demonstrated that dance therapy could promote beneficial health aspects in children with autism spectrum disorders (Aithal et al., 2021). The research outlined that dance may be associated with positive physical, cognitive and sociological adaptations for children with emotional and physical problems, however, the selection of articles used in the study were of a poor quality and need to be viewed with caution (May et al., 2021). There are a further three articles focusing on the association between dance, well-being and health, however, there are some imperfections in the studies. These include not fully exploring the outcomes of the dance intervention including other types of PA (Mansfield et al., 2018); less coverage for age groups (Carson et al., 2017). In addition, some studies only verified the amount of time spent performing at moderate to vigorous intensities in children and adolescents during the dance class. Further studies need to expand on the potential benefits and exercise intensities and durations used in these groups (Dos Santos et al., 2021). To the best our knowledge, there are no existing studies that have explored fully the benefits of dance interventions for children and adolescents. Further research is required to systematically report on all aspects related to the benefits of dance as a viable physical activity for this population. Therefore, the purpose of this review was to select all the studies utilizing a dance intervention in children and adolescents over the past 20 years; examine the dance intervention method; verify the outcomes; summarize the strengths and limitations of the research; and to provide evidence that dance can be used for children and adolescents as a suitable and viable physical activity in the future.

The four main objectives of this systematic review were to examine: 1) The emotional and physical benefits of dance in children and adolescents; 2) To consider the benefits of dance as an alternative physical activity/therapy for children and adolescents with certain medical disorders; 3) To examine the types of dances selected for the interventions reviewed, and the specific training loads required. This information may be useful for future research and implementation; 4) To consider dance as an alternative PA for school physical education provision.

2 METHODOLOGY

2.1 Eligibility Criteria

Studies focusing on the use of dance as an intervention and studies that involved children and adolescents inclusive of up to 18 years of age were included. Studies that were written in English and published in the past 20 years were considered. Meta-

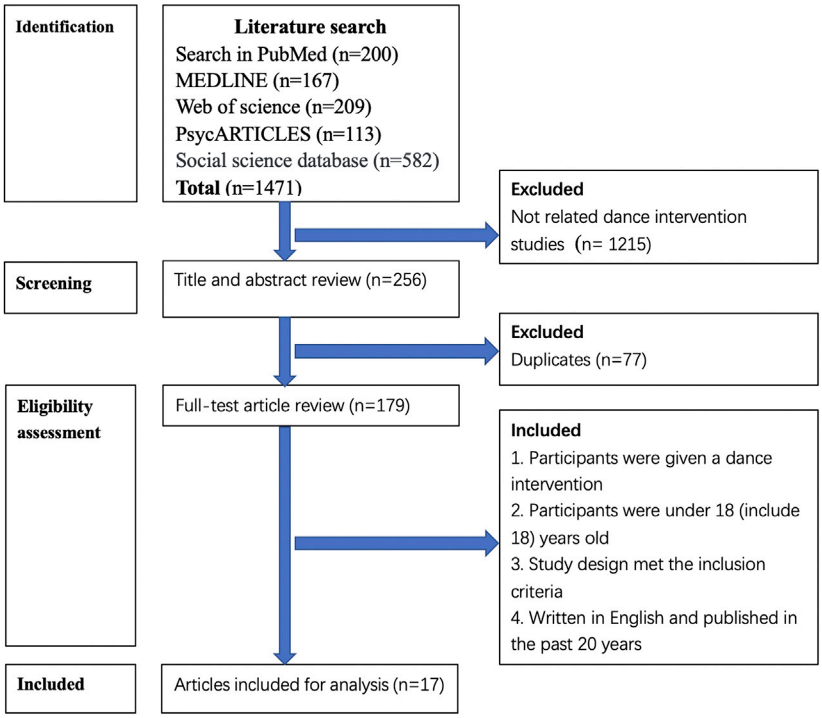

FIGURE 1 | Flowchart: Article selection process.

analyses or systematic review/review articles and pilot studies were excluded. Studies that used professional/semi-professional dancers as participants were also excluded. For inclusion in this review, each selected article must have been subjected to a peer review process prior to publication. In addition, the article had to present a clear, consistent methodology.

2.2 Information Sources and Search Strategy

A literature search was completed on 25 November 2021, articles were found by examining electronic databases to locate research studies that focused on the use of dance as an intervention for children and adolescents. The search methodology used in this study was based on the PICOS system (Jensen, 2017) and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). PROSPERO Registration Number is CRD42022326748. To locate articles for inclusion in this review the databases of PubMed, MEDLINE, Web of science, PsycARTICLES, and Social Science databases were comprehensively searched. Publications were identified for inclusion using the MeSH terms Children OR Teenager OR Adolescent OR Schoolchildren OR Student AND Dance OR Dancing OR Ballroom-dance OR Sport-dance OR Ballet OR Jazz OR Folk-dance OR Hip-Pop OR Square-dance OR Dance-movement-therapy OR Dance-effectiveness OR Dance-interventions. Additionally, other review or systematic review articles were used as guidelines to source articles that matched the inclusion criteria (Sheppard and Broughton, 2020).

2.3 Study Selection and Data Collection Process

Articles used in this review were selected by identification of the search terms contained in the full texts. Articles not meeting the inclusion criteria or meeting the exclusion criteria were discarded. **Figure 1** represents a flowchart of the process of identification and selection of relevant studies. The study selection process was confirmed by two authors (DT and JSB). If there was a disagreement between the two authors in the selection process, a third author (RS) contributed to resolving any article selection or exclusion issues.

Data extraction sheets were then developed. The first author (DT) extracted the data from included studies and the second author (JSB) checked the extracted articles. Any disagreements between authors was resolved by amicable discussion; if no consensus was accomplished, a third author (RS) decided the outcome. The following information for each study was extracted: 1) The citation information; 2) Participants demographics; 3) Dance intervention; 4) Study design/Measurements/Type of data; 5) Key findings.

2.4 Risk of Bias for Individual Studies

Risk of bias variables included random sequence generation, allocation concealment, blinding of patients and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other bias was examined following the Cochrane collaboration Risk of Bias Tool (Higgins and Altman, 2017; Higgins et al., 2011). 15 RCT

TABLE 1 | Summary of participant age groups, research design, methodological approach and outcome examined.

	Dance intervention type		Research design			Methodological approach			Outcome examined			
Gender group	**Choreographed**	**Other type**	**RCT**	**Non-RCT**	**Cross-sectional**	**Quantitative**	**Qualitative**	**Mix**	**Physiological**	**Psychological**	**Medical**	**Total studies for gender group**
Female	1	9	9		1	1	3	6	5	5		10
Both Gender	4	3	6	1		5		2	2	3	2	7
Total	5	12	15	1	1	6	3	8	7	8	2	17

Other type in the dance intervention part = Exergaming, African dance, Jazz dance, street, Contemporary dance, Traditional India dance, Folk dance, India classical dance, Hip-pop, Step dance, Educational dance, Dance-based PE, Dance and Yoga.

studies were divided into three categories, low risk, high risk, or unclear risk (when a study reported inadequate information to rate a specific domain). Risk of bias was also assessed separately using Review Manager 5.4.1 software. This assessment was completed by DT and RS independently; any disagreements on the risk of bias were adjudicated by JSB.

3 RESULTS

3.1 Study Selection and Characteristics

In total, 179 articles, after excluding duplicates, were identified by the literature search process. Following the inclusion and exclusion criteria, 162 were discarded resulting in 17 remaining articles (see **Figure 1**). Included articles were summarized into tables (see **Table 1** and **Table 2** for further details). Ten (59%) of the 17 studies recruited females as participants (Jeong et al., 2005; Robinson et al., 2010; O'Neill et al., 2011; Wagener et al., 2012; Duberg et al., 2013; Staiano et al., 2017b; Staiano et al., 2017a; Duberg et al., 2020; Sandberg et al., 2021; Högström et al., 2022), the remaining seven articles were studies inclusive of both genders (Morris et al., 2013; Anjos and Ferraro, 2018; Bollimbala et al., 2019; Oppici et al., 2020; Goswami et al., 2021; Raghupathy et al., 2021; Rudd et al., 2021). There were 15 (88%) studies that used randomized controlled trials (RCT) (Jeong et al., 2005; Robinson et al., 2010; Wagener et al., 2012; Duberg et al., 2013; Staiano et al., 2017b; Staiano et al., 2017a; Anjos and Ferraro, 2018; Bollimbala et al., 2019; Duberg et al., 2020; Oppici et al., 2020; Goswami et al., 2021; Raghupathy et al., 2021; Rudd et al., 2021; Sandberg et al., 2021; Högström et al., 2022), and 8 (47%) studies used both quantitative and qualitative mixed methods to collect data (Jeong et al., 2005; Robinson et al., 2010; O'Neill et al., 2011; Wagener et al., 2012; Duberg et al., 2013; Morris et al., 2013; Staiano et al., 2017a; Goswami et al., 2021). Included studies examined objective indicators and self-reported measurements with physiological (41%) (O'Neill et al., 2011; Morris et al., 2013; Staiano et al., 2017b; Staiano et al., 2017a; Anjos and Ferraro, 2018; Sandberg et al., 2021; Högström et al., 2022). psychological (47%) (Jeong et al., 2005; Robinson et al., 2010; Wagener et al., 2012; Duberg et al., 2013; Bollimbala et al., 2019; Duberg et al., 2020; Oppici et al., 2020; Rudd et al., 2021) and medical (12%) (Goswami et al., 2021; Raghupathy et al., 2021) included as the three main aspects of this study. The results and key concepts of the review are discussed below.

3.2 Risk of Bias Within Individual Studies

A summary of the risk of bias assessment is shown in **Figure 2**. Each study is outlined in **Figure 3**. According to the assessment criteria no studies were rated as being of low risk of bias. The primary reason for a high risk of bias was the lack of participant and personnel blinding (60%) across the majority of studies; other reasons were incomplete outcome data (20%) and other bias (20%) (the authors explained in the risk factors that may influence the results of the study) separately. Selective reporting (80%) and random sequence generation (67%) items in most studies were rated as low risk of bias, and most studies rated as being unclear risk of bias due to lack of clear reporting in allocation concealment (87%), other bias included (67%) and blinding of outcome assessment (53%) items.

3.3 Dance Selection

There is no consensus regarding the dance intervention type or intervention duration period in the existing literature. The ideal intervention would include different dance types for matching different participants (gender, religion, etc.). During the intervention, teaching supportively and non-judgmentally were important. A further important factor for consideration during dance implementation studies was cultural diversity. Certain traditional or special dances for certain areas and populations may demonstrate greater participation and better intervention performances and results. For further information see **Table 2**.

In relation to the articles selected for this review, they mainly included African dance (Robinson et al., 2010; Duberg et al., 2013; Duberg et al., 2020; Sandberg et al., 2021), Jazz (O'Neill et al., 2011; Duberg et al., 2013; Duberg et al., 2020; Oppici et al., 2020; Sandberg et al., 2021), Contemporary dance (Duberg et al., 2013; Sandberg et al., 2021), Exergaming video dance (Wagener et al., 2012; Staiano et al., 2017b; Staiano et al., 2017a), Ballet (O'Neill et al., 2011), Jazz dance, Tap dance (O'Neill et al., 2011), Street dance (Duberg et al., 2020; Sandberg et al., 2021), Hip-pop (Robinson et al., 2010), Step dance (Robinson et al., 2010), Fork dance (Bollimbala et al., 2019), Traditional Indian dance (Raghupathy et al., 2021), Education dance (Anjos and Ferraro,

TABLE 2 | Detailed summary of the study details.

Citations	Participant demographics	Dance interventions	Study design/Measurements/Type of data	Key findings
Wagener et al. (2012)	*n* = 40 Female Age 12–18 years old Obese adolescents United States	Exergaming (video game dance)	RCT 1. BMI 2. Perceived Competence Scale (PCS) 2. The Behavior Assessment System for Children-2 (BASC-2) 3. Parent Rating Scales-Adolescent version (PRS-A) 4. Adolescent Self-Report Scales (SRP-A) Quantitative and Qualitative	Positive impact of dance-based exergaming on obese adolescents' psychological functioning and perceived competence to continue exercise
Sandberg et al. (2021)	*n* = 112 Female Age 13–18 years old < Participants with stress-related mental health problems	African dance, different choreographies to popular music in the show/jazz dance, street and contemporary dance genre	RCT Pittsburgh Sleep Quality Index Qualitative	1. Dance intervention can be effective in decreasing daytime tiredness 2. Nonpharmacological interventions to decrease stress-related problems among adolescents
Rudd et al. (2021)	*n* = 55 Both gender Age 6–7 years old Primary school student Australia	Specially choreographed dance routine	RCT 1. Executive functions (working memory capacity, cognitive flexibility and inhibitory control) 2. Motor competence Quantitative	1. Dance intervention improved inhibitory control and potentially working memory capacity 2. Dance intervention did not improve motor competence beyond typical development
Raghupathy et al. (2021)	*n* = 36 Both gender Age 6–10 years old Children with DS India	Traditional India dance	RCT 1. Test of Gross Motor Development–2 (TGMD–2) 2. Four Square Step Test (FSST) 3. Pediatric balance scale Quantitative	1. The traditional Indian dance improved the locomotor skills of children with Down syndrome than that of neuromuscular exercises 2. Both the dance and neuromuscular training equally impacted the balance capacity
Morris et al. (2013)	*n* = 378 Both gender Age 9.75 ± 0.82 years old Primary school student United Kingdom	Specially choreographed dance routine	A non-RCT 1. Physical activity 2. Food intake 3. Anthropometric measure 4. Knowledge of healthy lifestyles 5. Psychological measures Quantitative and Qualitative	1. Significant increases in physical activity, endurance fitness and a reduction in the rate of increase in sum of skinfolds 2. There was no intervention effect on any of the dietary variables, knowledge, and the majority of psychological variables
Jeong et al. (2005)	*n* = 40 Female Age 16 years oldMiddle school student with depression Korea	Specially choreographed dance routine	RCT 1. Measurement of Psychological Distress (SCL-90-R) 2. Measurements of Neurohormones Quantitative and Qualitative	Dance movement therapy improved the negative psychological symptoms and modulated serotonin and dopamine concentrations in adolescent girls with mild depression
Bollimbala et al. (2019)	*n* = 34 Both gender Age 12 years old Primary school students India	Folk dance Specially choreographed dance routine	RCT 1. Convergent thinking 2. Divergent thinking Quantitative	1. Dance intervention improved convergent thinking 2. Participants with normal BMI improved in two divergent thinking components 3. Not permit us to establish a causal relationship between PA and the development of creative potential
Staiano et al. (2017b)	*n* = 41 Female Age 14–18 years old Overweight and obese girls	Exergaming (video game dance)	RCT 1. Physical examination and electrocardiogram 2. Anthropometry 3. Blood pressure 4. Body composition Quantitative	Exergaming reduced body fat and increased BMD

(Continued on following page)

TABLE 2 | (*Continued*) Detailed summary of the study details.

Citations	Participant demographics	Dance interventions	Study design/Measurements/Type of data	Key findings
Robinson et al. (2010)	*n* = 261 Female Age 8–10 years old African American or black girls	Hip-hop African dance Step dance	RCT 1. Body mass index (BMI) 2. Waist circumference, Triceps skinfold thickness, resting blood pressure and heart rate 3, Fasting serum insulin, glucose, lipid levels 4. Physical activity level 5. Television viewing, videotape viewing, video game and computer use 6. self-reported psychosocial measures Quantitative and Qualitative	1.Not significantly reduce BMI gain compared with health education 2. Potentially reductions in lipid levels, hyperinsulinemia, and depressive symptoms
Duberg et al. (2013)	*n* = 59 Female Age 13–18 years old Participants with stress and psychosomatic symptoms Swedish	African dance Jazz Contemporary dance	RCT 1. Self-rated health 2. Adherence to and experience of the intervention Quantitative and Qualitative	1. Improve self-rated health for adolescent girls with internalizing problems 2. The improvement remained a year after the intervention
Duberg et al. (2020)	*n* = 112 Female Age 13–18 years old Participants with stress-related somatic symptoms and emotional distress Swedish	African dance Jazz Street dance	RCT Questionnaires with somatic symptoms and emotional distress Qualitative	1. Dance interventions may reduce somatic symptoms and emotional distress in adolescent girls 2. May constitute a nonpharmacological complement to school health services
Isabelle de et al. (2018)	*n* = 85 Both gender Elementary school student Brazil	Educational dance	RCT Motor developments Quantitative	Educational dance helped the children's motor development
Staiano et al. (2017a)	*n* = 37 Female Age 14–18 years old Participants with overweight or obese United States	Exergaming (video game dance)	RCT 1. Anthropometric measurements 2. Physical activity level 3. Behavioral observation 4. Self-report survey Quantitative and Qualitative	Positive impacts on adolescent girls' self-reported PA, television viewing, self-efficacy, and intrinsic motivation
O'Neill et al. (2011)	*n* = 149 Female Age 11–18 years old Dance studios girls United States	Ballet Jazz Tap dance	Cross-sectional design 1. Anthropometric measurements 2. Physical activity level 3. Self- report surveyQuantitative and Qualitative	Dance classes can make an important contribution to girls' total physical activity
Oppici et al. (2020)	*n* = 80 Both gender Age 8.8 ± 0.7 years old Primary school children Australia	Jazz-dance choreography	RCT 1. Working memory capacity 2. Motor competence 3. Cognitive flexibility and inhibitory control Quantitative	1. Dance practice coupled with a high cognitive challenge could improve working memory capacity and motor competence in children 2. The difference between groups was not statistically significant
Högström et al. (2022)	*n* = 112 Female Aged 9–13 years old Diagnosed with FAP or IBS with persistent pain Sweden	Dance and Yoga	RCT Self-report 1. Maximum abdominal pain 2. bases and related information Qualitative	Significantly greater pain reduction
Jyotindea et al. (2021)	*n* = 59 Both gender Age 5–12 years old Participants with spastic diplegic CP	Specially choreographed dance routine	RCT 1.6-minute-walk-test 2.10-minute-fast-walk-test 3. Ashworth scale (MAS) 4. Tardieu scale (MTS) 5. Gross Motor Function Classification System (GMFCS) 6. Gross Motor Function Measure-88 (GMFM-88) 7. Cerebral Palsy Quality of Life (CP-QoL) Quantitative and Qualitative	Home-centered activity-based therapy is a feasible and practical modality of CP rehabilitation

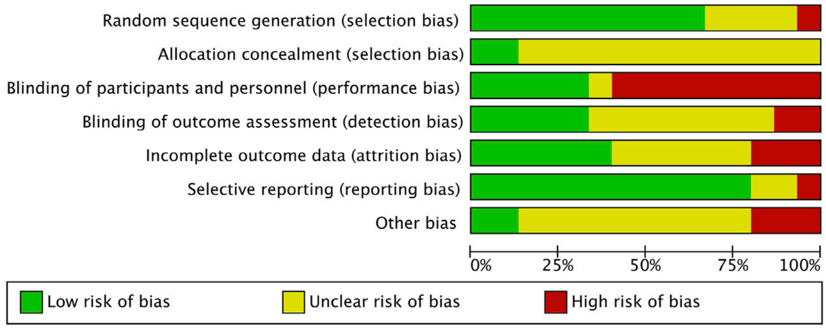

FIGURE 2 | The summary of risk of bias.

FIGURE 3 | Risk of bias for each study.

2018), Dance combined with Yoga (Högström et al., 2022), and specially choreographed dance routine (Jeong et al., 2005; Morris et al., 2013; Bollimbala et al., 2019; Goswami et al., 2021; Rudd et al., 2021).

For ethical reasons, control groups should be offered dance interventions following completion of the studies. Researchers should ensure professional choreography of dance interventions and make the routines both physically intense and enjoyable. Researchers should also consider the acceptability of dance for males in the process of wide-ranging dance promotion.

3.4 Intervention Monitoring

It is very important in dance study design to monitor intervention training loads. During dance interventions, setting a related exercise target Heart Rate (HR) to ensure that participants reach a predetermined level of exercise is essential. Depending on physical fitness levels, population groups, and ability, variations in intensity of exercise including high-intensity exercise or moderate to vigorous exercise may be used. The intervention duration should be longer than the time required for habit-forming at least to allow participants to continue dancing following the intervention. This important methodological issue has been neglected in previous studies. Only certain articles mentioned intervention monitoring, such as the use of Heart Rate (Wagener et al., 2012), and the Borg Rating of Perceived Exertion (RPE) (Borg 1998). However, scientific and professional monitoring of training intensities is lacking; experimental design and interventions are needed that are based on strong scientific evidence or follow the WHO guidelines (WHO, 2020).

3.5 Outcome Measure Summary

Outcome measures outlined in this review include objective measurement methods and self-rated measures of activity. We suggest that a combination of these two measurement methodologies will provide a more complete understanding of the participants' responses to the intervention results based on desired outcome measures (See **Table 2**).

Of the articles selected for this review, articles included objective measurements, such as anthropometric measurements (Robinson et al., 2010; O'Neill et al., 2011; Staiano et al., 2017a; Staiano et al., 2017b), physical activity levels (Robinson et al., 2010; O'Neill et al., 2011; Morris et al., 2013), heart rate (HR) (Robinson et al., 2010; Robinson et al., 2010; O'Neill et al., 2011; Staiano et al., 2017b), body mass index (BMI) (Robinson et al., 2010; Morris et al., 2013; Staiano et al., 2017b), blood pressure (BP) (Högström et al., 2022), blood samples for total cholesterol, triglycerides, glucose, insulin and high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LOD)-cholesterol, body composition (Robinson et al., 2010; Staiano et al., 2017b), Four-Square Step Test (FSST) (Raghupathy et al., 2021), Test of Gross Motor Development-2 (TGMD-2) (Raghupathy et al., 2021), plasma serotonin and dopamine concentrations (Jeong et al., 2005), 6-minute-walk-test, 10-minute-fast-walk-test (Goswami et al., 2021), executive functions (Oppici et al., 2020; Rudd et al., 2021), motor development (Anjos and Ferraro, 2018; Goswami et al., 2021; Raghupathy et al., 2021).

Questionnaire measurements, included the Perceived Competence Scale (PCS) (Wagener et al., 2012), Adolescent Self-Report Scales (SRP-A) (Wagener et al., 2012), Measure of Psychological Distress (SCL-90-R) (Jeong et al., 2005), Pittsburgh Sleep Quality Index (Sandberg et al., 2021), the scale for Self-efficacy for Physical Activity, the scale for Self-efficacy for Healthy Eating (Morris et al., 2013), Symptom Check List-90-Revison (SCL-90-R), Child Behavior Checklist (Oppici et al., 2020), McKnight Risk Factor Survey; Female African American Pre-adolescent Body Figure Silhouettes; 10-item short form of the Children's Depression Inventory; 10-item Rosenberg Self-Esteem scale (Robinson et al., 2010), Godin-Shephard Leisure Time PA, Intrinsic Motivation Inventory to assess their enjoyment and experience of playing exergames (Staiano et al., 2017a).

Outcome measures also included measures derived from the authors, such as participants-reported competency regarding maintaining regular exercise, internalizing and externalizing symptomatology, social stress, relationship with parents, interpersonal relationships, social skill and pro-social behaviors (Wagener et al., 2012), knowledge of healthy lifestyles test (Morris et al., 2013), questions regarding lifestyle, self-rated health, emotional distress, psychosomatic symptoms, feelings, depression, sleep, school, interests, friends, leisure time, and how the subjects enjoyed dance (Duberg et al., 2013), maximum abdominal pain (Högström et al., 2022), somatic symptoms and emotional distress (Duberg et al., 2020), executive functions, working memory capacity, cognitive flexibility, inhibitory control, and motor competence (Rudd et al., 2021).

4 DISCUSSION

4.1 Physiological Benefits of Dance

4.1.1 Dance Intervention Contributed to Access to Physical Activity

An acceptable exercise should be enjoyable, fun, safe and make the participants feel elated. The high participation rate and ease of acceptance and performance made dance interventions a sustainable and flexible alternative mediator to increase physical activity. Dance intervention programs can be performed in safe community spaces, free of charge. This provides a good opportunity for the parents to have more communication and social interaction with their children while facilitating intergenerational togetherness. These are good social outcomes for parental involvement with children in addition to providing a good family exercise environment (Morris et al., 2013). Previously, a dance study enrolled 149 girls (11–18 years-old) into dance intervention group. Activity was performed using structured dance classes in a dance studio. Dancing occupied 29 percent of the individual's moderate-to vigorous-physical activity (MVPA) (within 1 week). During intervention days the female participants were 70% more MVPA than non-program time (O'Neill et al., 2011).

4.1.2 Physical Fitness Improvement

Young people aged between 15 and 24 years encounter greater daytime fatigue than other age groups; this problem seems to be more severe among girls. Daytime tiredness increases in adolescents with health problems, these include sleep disturbances, and mental health issues. These associated psychological issues, somatic problems, and negative attitudes towards life decrease school achievement and satisfaction (Sandberg et al., 2021). An article investigating 8 months dance intervention, using a total of 48 classes over 24 weeks (except holidays), found that daytime fatigue significantly decreased in a dance intervention cohort at 8 months (p = 0.024). Follow up measures observed that there were still decreases at 12- and 20-months post intervention separately. The quality of sleep indicators also improved during the dance intervention. These included, falling asleep (p = 0.0037), less worried sleep (p = 0.041), and waking up during the night (p = 0.023). Daytime fatigue decreased without changes in sleep time, which suggests improvements in both sleep quality and well-being. The findings also indicate the facilitation of the creation of a healthy positive sleep cycle (Sandberg et al., 2021).

4.1.3 Dance in Combination With Traditional Physical Activity

A previous investigation examined combining a dance intervention with running activity using primary school students. The physical activity level, skinfolds reduction and endurance fitness showed the significant increases ($p < 0.05$) compared with a control group. For the secondary measurements, there were no change in dietary variables, knowledge, and majority of psychological indicators. However, the participants, teachers, and parents all responded positively. From the pupil's perspective, most pupils enjoyed practicing dance and had a positive experience from joining the dance competitions. The parents all expressed that their children had a pleasant feeling from participating from the program, and because of their involvement, had become more aware of their own physical activity lifestyles (Morris et al., 2013). Dance also seems to have a positive effect on certain neuromuscular and neurovascular conditions.

Globally, 13.5% of school-aged children are affected by functional abdominal pain disorders (FAPDs). FAPDs include irritable bowel syndrome (IBS), functional dyspepsia, abdominal migraine, and functional abdominal pain (FAP). Abdominal pain is accompanied by other symptoms, such as depression, anxiety, reduced life quality, and school absenteeism (Högström et al., 2022). Previously, a research article demonstrated that Yoga had beneficial effects in reducing pain intensity, absenteeism, and IBS-related symptoms. Dance is a relaxed rhythmical activity, and when combined with yoga, seems to provide physical and mental benefits that reduce pain. In addition, dance is an extremely popular activity for young females. This research examined the benefits of dance and yoga on FAP using a female population. The 121 participants in the study were 9–13 years old girls who were diagnosed with FAP or IBS with persistent pain. The dance and yoga interventions were performed on two occasions per week lasting 8 months conducted during after-school courses. The key findings indicated that dance in association with yoga works better for this population than standard conventional health care methods for reducing maximum pain aspects. We can further hypothesize that these activities in combination might have been the strength of this intervention, as dance contributes to cardiorespiratory and rhythmic aspects of movement while yoga helps with focus, relaxation, and introspection (Högström et al., 2022). The socialization potential of the intervention may also have had positive impacts. Opportunities to engage with new friends and to observe other girls suffering from similar symptoms may have also helped facilitate the positive responses observed.

4.1.4 Dance in Games

Over 60% of adolescents spend 73 min/day on video games (Staiano et al., 2017b). High levels of traditional and digital media use are linked to obesity, cardiovascular disease, and mental problems over the life course. These risks and associations have been observed to start in early childhood. Prolonged media use during preschool years is associated with increases in Body Mass Index (BMI). Body weight gain may be difficult to regress in combination with other risk factors, which increases the risk for greater weight gain and illness later in adult life (Robinson et al., 2010). This statement agrees with an international study that included almost three hundred thousand children and adolescents; the researchers found that watching TV 1–3 h per day led to a 10%–27% increase in obesity (Braithwaite et al., 2013).

As a result of the upsurge in computer use, some research studies have combined games and dance to cater for the characteristics of children and adolescents associated with media use and to minimize the effects of sedentary screen time. Dance-related computer games can increase the enjoyment and motivation of participation by allowing children and adolescents to take the initiative in selecting the variables of interest during the game. For example, participants can select the intensity levels, dance routines/mode, dance music, even dance game partners. In a research study investigating 36 h of dance exergaming lasting 12 weeks, researchers observed a decrease in adiposity and an increase in bone mineral density compared to a non-exercising control group (Staiano et al., 2017b). Furthermore, active video games (exergaming) facilitate exercise in a comfortable home environment, helps with exercise adherence and facilitates positive long-term changes in behavior. Recent studies have found exergaming to be far greater in enhancing energy expenditure when compared with non-active video games. The energy expenditure values obtained suggest that the intensities are comparable with moderate-intensity aerobic exercise (Wagener et al., 2012).

Active video game (exergaming) participation requires entire body movements. This results in light to moderate increases in energy expenditure and elevated heart rates. This could contribute to weight reduction and health benefits (Staiano et al., 2017a). In group settings, active video gaming may have benefits for increasing self-efficacy related to PA. There may also be beneficial effects for intrinsic motivation. Social cognitive theory suggests that behavioral change results from links among behaviors, the environment, and psychosocial variables (Staiano et al., 2017a). Group cohesion resulting from digital game play may be appealing to obese young people. These individuals are less likely to engage in traditional sports owing to excess weight, criticism, and bullying. Group active video play may provide a method of improving poor psychosocial health experienced by overweight and obese young people and facilitate increases in total PA levels (Staiano et al., 2017a). Future research is needed to investigate exergames and the design of dance games as enjoyable, sociable, motivating, and effective physical activity devices.

4.1.5 Motor Development

Motor development defines physical growth and the strengthening of a child's bones and muscles. It also defines an ability to move and touch his/her surroundings. For instance, if a child is good at gross motor skills such as crawling or walking, this affects cognitive development because he/she can easily move and explore their physical environment. In recent times, most children do not participate in PA outdoors; their favorite games no longer require large movements, and instead of using sports halls and open spaces, games are mostly played on cell phones, computers, or tablets (Anjos and Ferraro, 2018).

A randomized control study investigated a group who attended two classes of dance per week, over a 7-month period. The intervention was a specialized modified educational dance program. Using creative and ludic proposals, the intervention challenged the subjects to discover and experiment with new movement patterns and discover new ways of implementing the movements they already knew. The results of the study demonstrated significant improvements in motor development capabilities of the students exposed to educational dance lessons, compared with a control group. Both groups obtained positive results; however, the dance intervention group improved more. The improvements observed for motor skill development were maintained following cessation of the program. The author of the experiment stated that the practice of educational dance should be longitudinal as motor development is permanently evolving (Anjos and Ferraro, 2018).

4.2 Psychological Benefits of Dance

4.2.1 Alleviation of Depressive Symptoms

A recent experiment focused on African-American girls aged 8–10 years old and their parents or guardians who were involved in a dance intervention lasting 2 years. Fasting total cholesterol levels, low-density lipoprotein cholesterol, and depressive symptoms decreased significantly among girls in the dance treatment group. There were no significant differences between groups for BMI (Robinson et al., 2010). A further study examined 12 weeks of dance movement therapy in adolescents with mild depression. The results suggested that dance movement therapy demonstrated positive improvements in the symptoms such as somatization, obsessive-compulsive disorder, interpersonal sensitivity, depression, anxiety, hostility, paranoid ideation, and psychoticism. All these variables are related to negative metal health problems (Jeong et al., 2005). Fatigue, stress, insomnia, and psychological symptoms are directly or indirectly linked to circulating levels of serotonin and dopamine. The increased plasma serotonin concentrations and decreased dopamine concentrations indicate possible therapeutic benefits for the decreases in depression observed in the dance movement therapy group (Jeong et al., 2005).

4.2.2 Perceived Competence

Obese adolescents have sedentary existences and report feelings of embarrassment, fear of victimization and poor self-confidence about their ability to engage in exercise in group situations as powerful reasons for non-participation in physical activity (Wagener et al., 2012). In relation to this, a recent study considered a dance exergaming program in obese adolescents. The findings from the study indicated that the intervention group increased their perceived competence to participate in exercise from the start to the end of an exercise period compared with a control group (Wagener et al., 2012). Further benefits were that participants reported that there was an improvement in relationships with their parents. There was also a meaningful change in a high percentage of participants in the exergaming intervention that experienced improved internalizing and externalizing symptoms from baseline to the end of treatment compared to the control group. In addition, there was a very high adherence rate (98%) suggesting that group dance exergaming had a positive impact on improving obese adolescents' self-efficacy to continue exercising and to cope with any perceived barriers to exercise (Wagener et al., 2012).

4.2.3 Executive Function

Executive function plays a crucial role during childhood development. The developments include working memory capacity, inhibitory control, and cognitive flexibility (Rudd et al., 2021). Executive function is a particular area of interest during the developmental stages of early childhood and has been observed to be a superior indicator of academic achievement than IQ or socio-economic status (Oppici et al., 2020). Children with limited executive function are prone to a broad range of poor health and wellbeing outcomes in adulthood. Working memory is essential for understanding and making sense of new experiences as children develop over time. Low working memory capacity has been linked with poorer performance academically. As a result, designing suitable physical activity interventions that can improve working memory capacity in children are desirable and advantageous for children's development. The improvements in executive function will eventually lead to a more intellectual and capable society (Oppici et al., 2020).

Dance is often accompanied by music to create a constant sense of pleasure and motor stimulation, that is, synchronized with performance. This also provides participants with many opportunities for whole-body movement. To investigate this, an RCT that included an 8-weeks intervention was administered to 6–7-year-old children to assess the efficacy of four executive function measures. The measures were working memory capacity, cognitive flexibility, inhibitory control, and motor competence. The interventions included two dance syllabuses. The results showed that both dance syllabuses improved inhibitory control ability. The choreographed syllabus also developed working memory capacity; unfortunately, the improvement of motor competence did not exceed normal development (Rudd et al., 2021).

A further study explored the effects of working memory capacity and motor competence in primary school children using different teaching pedagogies and different cognitive challenges; the experimental results showed no statistically significant differences between groups. However, the dance teachers added a cognitive challenge by limited visual presentations and encouraged children to use memories and recall movement sequences in the high-cognitive group. The results of the study demonstrated the possibility and suitability of using dance practice in combination with high cognitive challenges to improve working memory and motor competence in children. It also contributed to social skills development and the integration and enhancement of emotional elements resulting from performing in groups (Oppici et al., 2020). In addition to the benefits of dance enhancing executive function, dance has been shown to be advantageous in the development of convergent thinking. Convergent thinking is associated with the process of solving problems and finding a solution to a problem (Bollimbala et al., 2019). Recent studies have shown that a 20-min dance protocol as part of a regular 30-min physical education session contributed to an improvement in convergent thinking (irrespective of their BMI status). An RCT study did not establish a correlation between dance class and the development of creative potential. However, in terms of divergent thinking components (fluency and flexibility), participants with normal BMI showed improvements following a dance class intervention. The dance class group also demonstrated an increase in convergent thinking compared to the control group (Bollimbala et al., 2019).

4.2.4 Internalizing Problems

Internalizing problems include depressed mood, low self-worth, and psychosomatic symptoms. Adolescent psychological health problems may have long-term negative effects on personal development; such as poor academic performance, social dysfunction, substance abuse, and suicide, especially in girls. Mental health problems have been cited to be some of the most alarming health issues and are estimated to affect 13% of children and adolescents globally. Female adolescents demonstrate a greater prevalence of health problems than their male counterparts. Females also experience greater levels of stress and somatic symptoms, and are more likely to experience pain and depression (Duberg et al., 2020). Results of an RCT demonstrated that a dance intervention significantly reduced somatic symptoms and emotional distress in adolescent girls after 8 months compared with traditional school health services (Duberg et al., 2020).

Another important study comprising adolescent girls aged 13–18 years old with internalizing problems who reported symptoms including pains in the head, stomach, neck, back, and/or shoulder, persistent feelings of tiredness, being worried, and being in low spirits, was completed using dance as the intervention. The intervention lasted 8 months, and self-rated health was measured using a single-item questionnaire which included general health, well-being, perceptions of symptoms, and vulnerability. The questionnaire has also been demonstrated to be both valid and reliable (Duberg et al., 2013). The dance intervention group improved their self-rated health far greater than the control group. The effects of the intervention remained for several months post intervention cessation. In addition, the results also demonstrated high adherence to the intervention and a positive experience for participants. This suggests that an intervention using dance is suitable for adolescent girls with internalizing problems (Duberg et al., 2013). The females participating in the study found the dance intervention to be enjoyable and undemanding, without any of the usual school pressures. The girls included had opportunities to provide input into the dance classes regarding the choice of music, and the girls participated in the creation of the choreography used. This may have created a sense of ownership for the participants, and the social developmental aspects are also important. The opportunity to make new friends and spend time participating in something they enjoy with others who have similar interests might be a powerful issue affecting recruitment, retention, and interest to participate (Duberg et al., 2013).

4.3 Medical Benefits of Dance

Down Syndrome (DS) is a congenital, genetic disorder caused by the presence of an extra partial or complete copy of chromosome 21. The neuromotor, musculoskeletal and cardiopulmonary systems are functionally problematic in children with DS and this impacts on their quality of life. Approximately fifty-eight percent of children with DS fail to meet the recommended 60 min of PA per day.

Traditional neuromuscular training lacks fun, creativity, and movement exploration. As an aesthetic movement art form, dance also has a positive psychotherapeutic impact, which may improve the intelligence and dual tasking of children with DS. In addition, children express their creativity and emotions such as joy, fun and happiness in the process of practicing and participating in dance, which provides children with body awareness, enthusiasm, and confidence. Ballet and Laban's dance have been demonstrated to improve balance, rhythm, and autonomous control in children who were DS patients. A previous study used traditional Indian dance as an intervention investigating outcomes in 36 children with DS. Traditional Indian dance appeared to be beneficial for improving locomotor skills and balance capacity in children with DS. The intervention was more effective when compared with traditional neuromuscular training. There were no adverse movement effects or discomfort recorded during and following the dance sessions. These findings outline the safety and feasibility of Indian dance regimes for this group (Raghupathy et al., 2021).

In addition to the studies mentioned above, a further RCT investigating dance performance outcomes included children between the ages of 5 and 12 years, clinically diagnosed with spastic diplegic cerebral palsy (CP). The participants had Gross Motor Function Classification System (GMFCS) Scores of II/III. In this study, dance exercise was one of eight activities that all children were expected to perform. The study evaluated the efficacy, feasibility, and safety of home-based activity rehabilitation programs for children with diplegic CP. The results of the study and methodology used suggested that dance exercise was a good choice to be added to this activity package for diplegic CP sufferers (Cygan et al., 2020; Goswami et al., 2021).

4.4 Strengths and Limitations

To the best of our knowledge, this is the first systematic review investigating children and adolescent development using dance as an intervention. For inclusion in this review, each selected article was subjected to a peer review process prior to publication. In addition, each article had to present a clear, consistent methodology which added to research integrity.

Limitations of this review include that some of the articles only used females as participants. Therefore, generalizations about the study findings to male populations are difficult. Future studies should focus on the adaptations of dance interventions using both genders as participants. This will provide compelling evidence about the benefits of dance while minimizing the effects of gender specificity. A further limitation was that some of the studies outlined in this review used self-reported measurement tools. This may have introduced an element of recall bias. There was also a limited number of articles that were deemed suitable for inclusion based on the selection criteria.

5 IMPLICATIONS OF DANCE EXERCISE

Schools in many countries have traditionally hosted some form of health education program to develop knowledge, skills, and behaviors related to health awareness. Schools are in a unique position to provide healthy and academic outcomes *via* the implementation of health and wellness policies. Most children spend more time in school than any other location except for the home. Schools are crucial and practical for managing and providing information about childhood health risks. Because of the relationships between health status and the ability to learn, schools are in an exclusive location to influence healthy lifestyles for students by health policy implementation. Schools need to seriously consider this advantageous position to produce a solid healthy foundation in the growth stage of children that will have an important and positive impact on individuals, families, and society.

Dance and in particular creative dance, enriches the performance, composition, and appreciation of human movement, with a particular focus on producing aesthetic value. Dance performed in groups provides a social type of physical activity. Dance is also beneficial for increasing self-trust, self-esteem, and self-expression in children and adolescents (Duberg et al., 2020).

Students who engage in dance at school show greater initial socialization skills and better academic achievement compared with individuals who do not participate in dance. Dance internalizes the systems involved in art forms, and both children and adolescents can use the experience gained as tools for thinking, behaving, and regulating the inner world of their minds. Certain schools in Mainland China, provide dance programs as part of after-curriculum activities that are available on a weekly basis.

The findings reported here can be of value to practitioners, policymakers, and educational staff. Because of teaching experience and having witnessed the positive effects of providing students with a broad selection of physical activities, many teachers and practitioners support dance-based physical education (PE). Despite this, dance-based schemes remain vulnerable to exclusion from the PE curriculum. This is more likely in schools where PE is viewed as a developmental tool for the preparation for participation in competitive sport. Certain schools also view PE lessons as a medium to enhance and refine elite athletic performers. Further research is needed to examine if participation in dance enhances athletic performance, increases competitiveness, and is complementary to athletic development. The findings of this review could be interpreted as providing further evidence for the value of retaining and developing dance-based PE in the school curriculum. The findings also support the importance of dance in physical education provision more generally.

A consensus survey of PE teachers should be conducted to understand the views and feasibility of PE teachers regarding including dance as a part of PE curriculum and the implementation of dance for the existing curriculum and syllabus. There are also essential factors such as teacher training and curriculum development that need consideration. In the long term, overall improvements in health and physical fitness parameters result in improvements in the quality of life for individuals. Health policy amendments are needed to provide further support for the place of dance within the physical education curriculum.

6 CONCLUSION

In conclusion, dance develops relationships, connects people, and increases feelings of joy and togetherness. Dance has virtually no venue restrictions. It can be practiced at home, in isolation, in groups, or anywhere with suitable spaces. Dance requires no special equipment, and this characteristic is suitable for low-income families and financially limited regions and countries. In summary, dance can be used as an appropriate and alternative physical activity mode for children and adolescents. The implementation of dance programs needs serious consideration by policy makers, schools, guardians and parents to produce greater long-term increases in physical activity in the foreseeable future. We hope that this systematic review will stimulate debate and provide more evidence for governments, schools, parents, and associated community officials to attach importance to dance as a medium of physical activity. Comprehensive and integrated changes are needed in relation to school/family/government/community partnerships. These changes include political and financial support from policy makers, and increased dance evaluation research that are important for a physical activity health policy reconfiguration and subsequent implementation.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

The manuscript underwent several revisions with substantial contributions provided by each co-author. DT and JSB designed the study and the data synthesis strategy. DT conducted the systematic review, extracted and summarized the data and created the figures and tables. DT and JSB wrote the present manuscript, while AC, RA-S, RS, YGU, TKT, QH, and YG contributed the writing and critically revised the paper. All authors provided critical feedback, and read and approved the final manuscript.

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Reliability and Validity of an Ultrasound-Based Protocol for Measurement of Quadriceps Muscle Thickness in Children

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Introduction and aims: Accurate determination of skeletal muscle size is of great importance in multiple settings including resistance exercise, aging, disease, and disuse. Ultrasound (US) measurement of muscle thickness (MT) is a method of relatively high availability and low cost. The present study aims to evaluate a multisite ultrasonographic protocol for measurement of MT with respect to reproducibility and correlation to gold-standard measurements of muscle volume (MV) with magnetic resonance imaging (MRI) in children.

Material and methods: 15 children completed the study (11 ± 1 year, 41 ± 8 kg, 137 ± 35 cm). Following 20 min supine rest, two investigators performed US MT measurements of all four heads of the *m. quadriceps femoris*, at pre-determined sites. Subsequently, MRI scanning was performed and MV was estimated by manual contouring of individual muscle heads.

Results: Ultrasound measurement of MT had an intra-rater reliability of ICC = 0.985–0.998 (CI 95% = 0.972–0.998) and inter-rater reliability of ICC = 0.868–0.964 (CI 95% = 0.637–0.983). The US examinations took less than 15 min, per investigator. Muscle thickness of all individual quadriceps muscles correlated significantly with their corresponding MV as measured by MRI (overall $r = 0.789$, $p < 0.001$).

Conclusion: The results of this study indicate that US measurement of MT using a multisite protocol is a competitive alternative to MRI scanning, especially with respect to availability and time consumption. Therefore, US MT could allow for wider clinical and scientific implementation.

Keywords: ultrasonography, skeletal muscle, children, magnetic resonance imaging, hypertrophy, atrophy

1 INTRODUCTION

An accurate determination of skeletal muscle mass is of great importance when investigating muscle adaptation during hypertrophy (Aagaard et al., 2001; Morse et al., 2005; D'Antona et al., 2006; Franchi et al., 2018) and atrophy (Abe et al., 1997; LeBlanc et al., 2000; Alkner and Tesch, 2004; Maurits et al., 2004; Rittweger et al., 2005; Petterson et al., 2008; Dirks et al., 2016; Johnson et al., 2018). Several methods for assessing or estimating skeletal muscle size have been described including bioimpedance (Salinari et al., 2002), computerized tomography (Van Roie et al., 2013), magnetic resonance imaging (MRI) (Walton et al., 1997; Alkner and Tesch, 2004; Nordez et al., 2009) and ultrasound (US) (Miyatani et al., 2002; Miyatani et al., 2004; Reeves et al., 2004; Sanada et al., 2006; Moreau et al., 2010; Baldwin et al., 2011; Scott et al., 2012; Strasser et al., 2013; Tillquist et al., 2014; Fukumoto et al., 2015; Giles et al., 2015; Nakatani et al., 2016; Hadda et al., 2017; Matta et al., 2017; Stock et al., 2017; Franchi et al., 2018; Pardo et al., 2018; Filippo et al., 2019; Mechelli et al., 2019; Cheon et al., 2020; Betz et al., 2021; Lee et al., 2021; Mpampoulis et al., 2021; Takahashi et al., 2021). Muscle volume (MV) estimated from multiple cross-sectional areas (CSA) using MRI is considered the current gold standard, however, this process is time consuming and labor-intensive (Nordez et al., 2009), therefore the feasibility of MRI is limited, especially for repeated measurements in large cohorts. Alternatives like computerized tomography could also be utilized, however, the exposure to ionizing radiation makes it unsuitable, especially for children (Nakayama et al., 2019). On the contrary, ultrasonography (US) is a method that allows quick and mobile scanning at a low cost without ionizing radiation.

For a protocol of US scanning to be useful, it needs to be reliable throughout repeated scans (i.e., intra and inter-rater reliability) (Hadda et al., 2017; Pardo et al., 2018; Filippo et al., 2019; Takahashi et al., 2021) and be valid to reference modalities (i.e., MRI-estimated MV) (Miyatani et al., 2002; Miyatani et al., 2004; Franchi et al., 2018; Liegnell et al., 2021). However, the literature is mainly focused on measuring the Muscle thickness (MT) of *m. rectus femoris* (RF) and to some extent, the thickness of *m. vastus intermedius* (VI) underneath (Moreau et al., 2010; Galindo Martín et al., 2017; Hadda et al., 2017; Pardo et al., 2018; Takahashi et al., 2021). Some have investigated the other muscles of the *m. quadriceps femoris* (QF) (Moreau et al., 2010; Franchi et al., 2018; Cheon et al., 2020; Betz et al., 2021; Mpampoulis et al., 2021), and others have utilized a multisite approach, measuring all the individual muscles of the QF (Cadore et al., 2012; Strasser et al., 2013; Matta et al., 2017; Santos and Armada-da-Silva, 2017; Lee et al., 2021). These studies utilized varying methodologies, and none have provided conclusive evidence of both validity, compared to MRI, and intra and inter-rater reliability. Consequently, data on both reliability and validity of an easy-to-use US scanning protocol encompassing all heads of the QF is lacking, especially in children. Children, especially pre-pubertal, could have differing muscle distribution and properties compared to adults, however, data regarding this is to our knowledge lacking.

We aimed to establish a time-effective ultrasound method for determining MT of all four heads of the QF, that is, applicable to children and correlates to MRI-measured MV. We hypothesized that such a protocol could be reliably performed by two independent investigators and that the results would have a strong correlation to MRI-measured muscle volume.

2 MATERIAL AND METHODS

2.1 Participants

Fifteen healthy children (7 females and 8 males) with mean age, body mass, and height ±SD of 11 ± 1 year, 41 ± 8 kg and 137 ± 35 cm, were included. Recruitment was carried out at a local primary school with children aged 10–12 years in Eksjö, Sweden. The children volunteered to participate in a pilot study focusing on resistance exercise in children, including bilateral US and MRI examinations of the thigh. Informed assent was obtained from the children, after receiving age-appropriate information. The legal guardians provided both written and verbal informed consent. The study was approved by the Swedish Ethical Review Authority (EPM DNR: 2020-07112) and was conducted in accordance with the Declaration of Helsinki.

2.2 General Design

The participants underwent US followed by MRI on the same occasion. All participants were instructed to refrain from heavy sports, exercise, and physical education 24 h prior to MRI and US scanning. Prior to the US and MRI all participants remained in supine rest for a minimum of 20 min to avoid differences in muscle size due to skeletal muscle fluid shifts caused by gravitational forces (Berg et al., 1993). The participants were transported in the supine position from US to the MRI facility.

2.3 Ultrasound

A b-mode ultrasound machine (FlexFocus 500, BK Medical, Herlev, Denmark) was used with fixed settings (Db = 75, mHz = 15, Hz = 3/26) for all ultrasound examinations, only the depth was altered. A linear probe (Linear Array 8670, BK Medical) was used with the ultrasound machine. Images were stored directly on the machine. During scanning, participants remained relaxed in a supine position, feet fixed in a u-shaped pillow (Lassekudde, Solann, Stockholm, Sweden). Great care was taken to eliminate tissue compression by the probe, ensured using ample amounts of water-soluble transmission gel and the preservation of an intact curvature of the skin. The ultrasonographic investigation was performed by two investigators with limited previous sonographic experience. However, they underwent training for approximately 3 h prior to this study by an experienced sonographer.

The probe was placed in an axial orientation, perpendicular to the quadriceps femoris muscle. The points of measurement were performed at set intervals along the axis derived from measuring the distance from spina iliaca anterior superior (SIAS) to the proximal edge of patella.

During initial pre-study trials, the inter-rater reliability of SIAS to patella measurement was deemed to have sufficient

TABLE 1 | Sites of measurement and muscles measured at each site.

Muscle	Site of measurement
RF	½ between anterior superior iliac spine and the proximal aspect of the patella, at the point of greatest thickness
VL	½ between anterior superior iliac spine and the proximal aspect of the patella, at the point of greatest thickness
VI	Measured at the same site as both RF and VL, directly underneath the measured muscle thickness of RF and VL. Mean MT of both measurements reported as VI.
VM	¾ between anterior superior iliac spine and the proximal aspect of the patella. The medial portion of the patella linear to the lateral aspect of the probe

Depicting the exact points of ultrasound measurement, RF = m. rectus femoris*, VL = m.* vastus lateralis*, VI = m.* vastus intermedius *and VM = m.* vastus medialis*.*

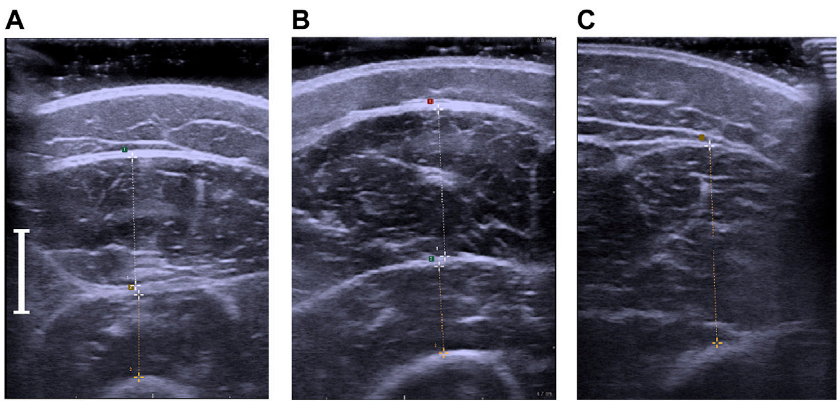

FIGURE 1 | (A). Ultrasonographic measurement of the m. rectus femoris and m. vastus intermedius. **(B)** Ultrasonographic measurement of the m. vastus lateralis and m. vastus intermedius. **(C)** Ultrasonographic measurement of the m. vastus medialis. The white indicator shows the length of 1 cm.

reproducibility. Furthermore, in our planned future implementation we intend to utilize a guiding ink-marking in-between measurements. Therefore, the same measurement of SIAS to patella was used. However, each of the investigators performed independent measurement of the distance. Both legs were scanned during the same session. Muscles measured were *m. rectus femoris* (*RF*), *m. vastus lateralis* (*VL*), *m. vastus intermedius* (*VI*), and *m. vastus medialis* (*VM*), exact measurement sites are shown in **Table 1**. The point of measurement for RF (Giles et al., 2015; Stock et al., 2017; Pardo et al., 2018; Cheon et al., 2020; Takahashi et al., 2021), VI (Giles et al., 2015; Cheon et al., 2020), VL (Giles et al., 2015) and VM (Giles et al., 2015) were derived from previous literature and experience from pretesting. At each of the measuring sites three pictures were taken and evaluated. If the variance of MT exceeded 10 percent, measured from the lowest value to the highest one, additional measurements were taken. Measurements varying more than 10 percent of the mean were excluded. This process was repeated until three values not exceeding the 10 percent threshold were acquired. Measurements of MT were performed directly during the scanning in machine native software, **Figure 1**.

2.4 Magnetic Resonance Imaging

All the participating children tolerated the MRI scan without any discomfort. During scanning, participants were placed in a similar position to that used during ultrasound scans. An initial scout image was taken to identify the area of interest, from SIAS to tibiofemoral articulating surfaces of the knee joint. The scans were performed using a 1.5 T MRI scanner (Siemens Symphony Tim, Munich, Germany) to acquire 52 slices of axial

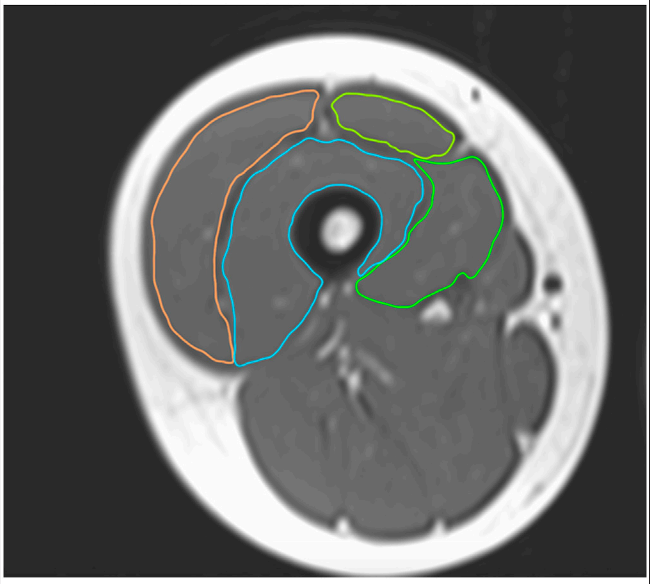

FIGURE 2 | The contouring process of the m. quadriceps femoris for MV estimation of the individual muscle heads.

images. One T1-weighted scan was performed using the following settings: Field of view 400 mm, repetition time = 637 ms, echo time = 12 ms, voxel size = 1.7 × 1.3 × 7.0 mm, slice thickness = 7.0 mm and interslice thickness = 1.4 mm.

2.4.1 Postprocessing

Image processing was performed in Osirix lite (Pixmeo, Geneva, Switzerland) for manual identification of the quadriceps muscle and contouring. Contouring was performed using a drawing tablet and pen (Wacom Intuos M, Wacom, Saitama, Japan). Contours of RF, VM, VI, and VL were drawn individually, **Figure 2**. We aimed to contour only muscle tissue and care was taken to exclude the fascia. No consideration for intramuscular non-contractile tissue (e.g., fat) was taken. Every second MRI slice was contoured. Determination of MV was performed using Cavalieri's approximation (Walton et al., 1997; Nordez et al., 2009), **Eq. (1)**.

$$\textbf{Muscle volume} = \sum_{n} e_i \times CSA_i \quad (1)$$

Equation 1: Where n is the available slices, CSA_i is the cross-sectional area at slice i and e_i is the distance between i and i+1.

A total of 623 unilateral MRI slices were contoured at a pace of approximately 40 slices per hour. Most slices included all four heads of the QF. However, for the most proximal portion of the thigh, mainly RF was detected and in the distal aspect of the thigh, only VM was delineated.

2.5 Intra- and Inter-Rater Reproducibility of Ultrasound Scanning and Magnetic Resonance Imaging Postprocessing

Two investigators performed ultrasound scans on all the participants in a standardized fashion as previously described. Intra-rater reproducibility was calculated from the three separate scans performed in the same session. Inter-rater reproducibility was calculated from the mean of both investigators' measurement of each muscle.

The postprocessing, i.e., contouring of MRI images, was performed by one investigator. Intra-rater reliability was calculated from repeated contouring of 10 percent of total slices ($n = 63$), randomly selected. Both measurements were performed by the same contourer but separated in time by over a month.

2.6 Statistics

The statistical analyses were performed using SPSS statistics 27 (IBM, Armonk, NY, 2020). Initially, descriptive statistics were used to characterize the dataset. Thereafter, intraclass correlation coefficient (ICC) was calculated to identify reproducibility between repeated measurements, between sonographers. A two-way mixed model, single measures and absolute agreement were used for the evaluation of inter-rater reproducibility. A two-way mixed model, average measures and absolute agreement was used to evaluate intra-rater reproducibility. Intraclass correlation coefficient values were interpreted by the ranges defined by Koo et al. (Koo and Li, 2016). Standard error of measurement (SEM) and minimal detectable change (MDC) was calculated from standard

TABLE 2 | Intra- and inter-rater reliability of US scanning.

	Mean (mm)	Mean range (mm)	ICC (CI 95%) (data without exclusion)	SEM (mm)	MDC (mm)	Mean (mm)	Mean range (mm)	ICC (CI 95%) (data without exclusion)	SEM (mm)	MDC (mm)	ICC (CI 95%) (data without exclusion)	SEM (mm)	MDC (mm)
RF	18.76	0.58	0.995 (0.991–0.997) [0.992 (0.986–0.996)]	0.20	0.55	18.71	0.63	0.993 (0.988–0.997) [0.992 (0.985–0.996)]	0.24	0.66	0.968 (0.933–0.984) [0.971 (0.940–0.986)]	0.5	1.39
VL	20.13	0.54	0.995 (0.990–0.997) [0.988 (0.979–0.994)]	0.18	0.49	20.15	0.69	0.990 (0.982–0.995) [0.989 (0.979–0.994)]	0.25	0.69	0.906 (0.813–0.954) [0.903 (0.807–0.953)]	0.75	2.08
VI	13.87	0.49	0.994 (0.988–0.997) [0.987 (0.975–0.993)]	0.13	0.36	13.99	0.71	0.983 (0.968–0.991) [0.987 (0.975–0.993)]	0.24	0.66	0.944 (0.888–0.973) [0.941 (0.881–0.971)]	0.42	1.16
VM	24.83	0.56	0.995 (0.992–0.998) [0.992 (0.986–0.996)]	0.20	0.55	25.37	0.70	0.991 (0.982–0.996) [0.991 (0.982–0.996)]	0.24	0.66	0.926 (0.802–0.969) [0.925 (0.813–0.967)]	0.73	2.02
Total	91.48	1.37	0.997 (0.994–0.998) [0.995 (0.990–0.997)]	0.42	1.16	92.22	1.57	0.996 (0.993–0.998) [0.996 (0.993–0.998)]	0.46	1.27	0.963 (0.923–0.982) [0.963 (0.918–0.983)]	1.44	3.99
MT													

Depicting the mean and mean range of muscle thickness, separated by muscle and investigator. Mean range referrers to the mean interval form lowest to highest measurement. Intraclass correlation coefficient of each triplet of measurement, between investigators one and two, separated into each of the measured muscles and a total. Furthermore, inter-rater reliability is depicted divided by muscle. Within the brackets ICC from the first three measurement including the values otherwise excluded and remeasured is shown.

RF = m. rectus femoris, VL = m. vastus lateralis, VI = m. vastus intermedius and VM = m. vastus medialis.

ICC, intra class correlation; SEM, standard error of the measurement; MDC, minimal detectable change.

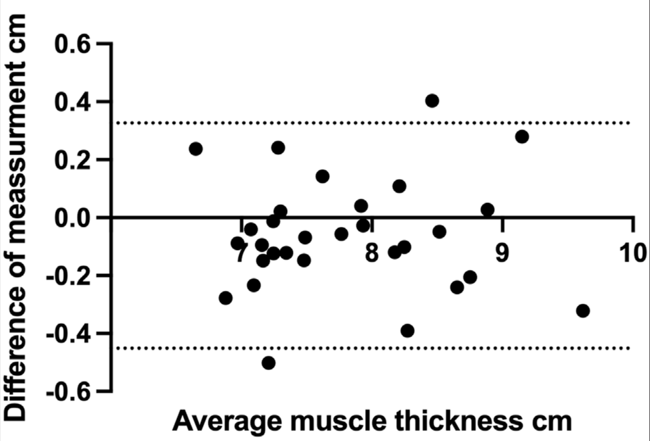

FIGURE 3 | Bland-Altman graph depicting the difference between the two investigators in respect to total muscle thickness measured by ultrasound.

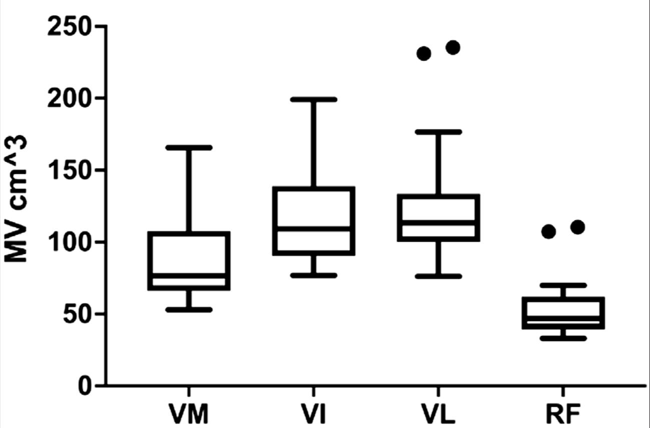

FIGURE 4 | The muscle volume of VM, VI, VL and RF. The horizontal line shows the median, while the box encompasses the 50th percentile and the whiskers encompass the minimum and maximum values, outliers are displayed as points. Outliers are defined according to Tukey, as values exceeding more than the 75 percentile plus 1.5 IQR. RF = m. rectus femoris, VL = m. vastus lateralis, VI = m. vastus intermedius and VM = m. vastus medialis.

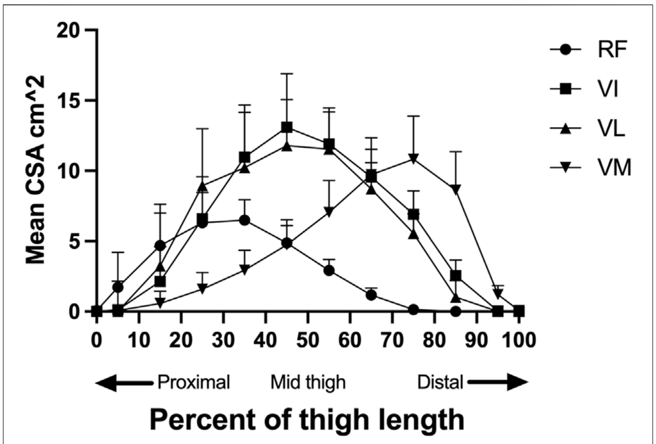

FIGURE 5 | The distribution of mean muscle area of each group (RF, VI, VL, VM) along the length of the thigh, standardized for length. The standard deviation is depicted by the error bars. The first percentile is the most proximal slice where RF was still identifiable, and the one hundred percentile is the most distal slice where m. Vastus Medialis is still identifiable. RF = m. rectus femoris, VL = m. vastus lateralis, VI = m. vastus intermedius, VM = m. vastus medialis and CSA= Cross-sectional area.

TABLE 3 | Correlation between MV and MT.

	All measurement	First measurement
RF	0.702**	0.655**
VL	0.638**	0.660**
VI	0.734**	0.630**
VM	0.693**	0.724**
Total MT	0.789**	0.755**

* = p ≤ *0.05* ** = p< *0.001.*
Spearman correlation coefficients between MRI measured MV and the mean US measured MT. Furthermore, correlation analysis was preformed between MRI measured MV and first value of US measured MT. All of the initial measurements of MT were used, including those who later were excluded du to variance, in all of the other analysis. RF = m. rectus femoris, *VL = m*. vastus lateralis, *VI = m.* vastus intermedius *and VM = m.* vastus medialis, *MT* = muscle thickness, *MV* = muscle volume.

deviation and ICC as described by Filippo et al. (Filippo et al., 2019). Initial descriptive statistics showed that multiple variables had a non-normally distributed pattern. Therefore, Spearman correlation was used to allow for comparisons between non-normally distributed and normally distributed variables. Values of $p < 0.05$ were considered significant.

3 RESULTS

3.1 Ultrasonography

Ultrasonographic scanning and measurements of both thighs took less than 15 min per investigator and participant. Out of a total of 450 measurements (three measurement sites, five measurements in total, three repetitions, two limbs and 15 participants), 20 measurements exceeded >10% variance in range and were hence excluded, this accounted for 4.4% of the total measurements. Intraclass correlations between the two investigators measurements of the SIAS-patella distance was ICC = 0.936 (CI 95% 0.860–0.966). Mean values of measured MT per muscle and investigator are shown in **Table 2**, complemented by the mean range of the repeated measurements and the intra- and inter-rater reliability measured by ICC. The agreement of the two investigators regarding total MT is depicted in **Figure 3**.

3.2 Magnetic Resonance Imaging

The mean MV calculated by Cavalieri's approximation is depicted in **Figure 4**. The VI and VL had the largest total volume closely followed by the VM, while RF had a smaller volume. The muscles also had differing dominant portions along

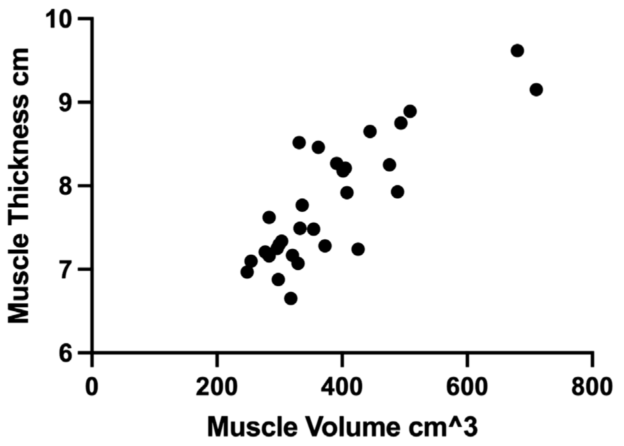

FIGURE 6 | The correlation between total muscle thickness of each limb measured by ultrasound and the corresponding muscle volume measured by MRI.

the length of the thigh, shown in **Figure 5**. Repeated contouring of CSA had an ICC of 0.983 compared to initial contouring, indicative of a high degree of agreement.

3.3 Inter-Modality Correlation

Ultrasonographic measurements of MT had a correlation ranging from r = 0.514 to 0.789 with respect to their corresponding MV measured by MRI, **Table 3**. The total MRI MV to total US MT had the strongest correlation, shown in **Figure 6**. The same analysis was also performed using only the first US measurement of MT, including outliers, to evaluate the value of repeated scanning during the session, **Table 3**.

4 DISCUSSION

The present study shows that this multisite protocol of ultrasonographic assessment of quadriceps MT can be reproduced in a reliable manner in children, supporting results from previous studies in adults (Miyatani et al., 2004; Sanada et al., 2006; Franchi et al., 2018). Our approach proved feasible to perform within a limited time frame and was easy to conduct for investigators with limited prior ultrasonographic experience. This multisite ultrasonographic protocol had a high intra- and inter-rater reliability and a strong correlation to MV measured with MRI.

Intra-rater reliability for the US measure of MT was within the "good" and "excellent" range (Koo and Li, 2016). The ICC values varied for the different muscles; however, the confidence intervals were overlapping. The current study presents a good to excellent inter-rater reliability, in line to those of previous studies (Tillquist et al., 2014; Zaidman et al., 2014; Hadda et al., 2017; Filippo et al., 2019; Mechelli et al., 2019; Betz et al., 2021; Takahashi et al., 2021). However, variations in methodology including site(s), time in-between measurements and number of measurements make direct comparisons difficult.

The ultrasonographically measured MT correlated strongly to the corresponding MRI-measured MV, similar to those of previous studies (Miyatani et al., 2002; Miyatani et al., 2004; Nakatani et al., 2016; Franchi et al., 2018). However, none of these studies employed a multisite measuring approach, thus not providing a sufficient framework of whole QF measurements to directly compare and evaluate this protocol with. Consequently, this study provides new unique results regarding the correlation of a multisite MT protocol of the *m. quadriceps femoris* to its MV.

The difference using only the first US measurement of MT instead of the mean of three after exclusion of outliers proved to be less substantial, the number of measurements could potentially be reduced and still maintain a sufficient correlation to MRI MV. A similar trend can be seen using only the first three measurements without exclusion of outliers for the reliability tests, **Table 2**, indicating that exclusion of outliers also had a less substantial effect.

Interestingly, *m. rectus femoris* had the smallest range of MV, **Figure 3**, indicating that it might constitute fundamentally different properties than the other vasti muscles. Previous studies have also shown that the RF has unique properties, as a two-joint muscle, regarding hypertrophy and activation compared to the other vasti muscles (Ema et al., 2013; Earp et al., 2015; Mangine et al., 2018). The present literature has primarily focused on RF MT and thus further studies investigating the other quadriceps are warranted.

A large aspect of the applicability of this protocol is to follow changes to specific stimuli over time, such as resistance exercise-induced hypertrophy. In this specific scenario, the value of estimating MRI measured MV is of less interest than capturing the change over time. Therefore, studies investigating repeated multisite US-measured MT over time, during the course of muscle adaptation and comparing it to MRI-measured CSA and MV, would be of great value.

5 LIMITATIONS

Intra-rater testing was performed in the same session, while care was taken to remove the probe from the thigh in-between measurements, a potential risk of bias remains. The use of the same measuring point between SIAS and patella, resulted in a potential bias since the investigators were not fully independent from each other's measurements. The population investigated in this study was limited to healthy children aged 10–12 years, however, we believe this protocol would be applicable in an adult as well populations suffering from myopathology, although, this should be further confirmed.

6 CONCLUSION

This study presents a multisite ultrasound protocol for determination of quadriceps muscle thickness that has high inter-rater reliability and a strong correlation to MRI-measured MV. This method represents a possible alternative to MRI in settings where MRI scanning is not feasible due to time and/or financial constraints. In the case of limited resources and demand for longitudinal follow-up, multisite ultrasonographic MT measurements may represent a solid alternative.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Swedish Ethical Review Authority (EPM DNR: 2020-07112). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

EH conducted study design, preparation and data gathering, data analysis and drafted the manuscript, KT conducted study design, preparation and data gathering, FvW conducted study design and preparation, LF conducted study design and preparation, PM conducted study design and preparation, BA conducted study design, preparation and data gathering. All authors read, edited, and approved of the final manuscript.

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Stable physical activity tracking during children's guided active play

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Objective: Physical activity (PA) decreases during childhood with PA tracking statistics showing moderate coefficients in early childhood moving to poor coefficients in late childhood. The age-related instability of PA tracking is attributed to variations in age-related PA behaviors when quantifying PA in different settings (in/out of school, sports camps, and habitual PA). This study has examined the stability of age-related PA for children (from 7 to 11 years) during self-paced guided active play (GAP) sessions separated by 12 months.

Methods: Children (n = 65) recruited from community camps in two consecutive years were assessed for growth and PA participation during GAP sessions (1 h·d^{-1} on 2 d·wk^{-1}) using cooperative games. Accelerometer outputs were used to quantify PA and estimate energy expenditure (EE) and moderate-to-vigorous PA (MVPA). Tracking statistics were assessed by Spearman coefficients (r) and agreement scores for percentile rankings (Kappa (k)) after a 1-year interval.

Results: Grouped data for PA tracking (EE) over the 1-year interval showed strong coefficients (r = 0.88, p = 0.001) and moderate agreement scores (k = 0.54). Boys and girls showed similar results. During the 1-year interval, the MVPA tracking coefficient was r = 0.54 (p = 0.01) with a moderate k score of 0.47. Age-related PA (EE) tracking coefficients at 7 (r = 0.90), 8 (r = 0.88), 10 (r = 0.82), and 11 (r = 0.83) years showed strong coefficients except at 9 years (r = 0.51).

Conclusion: Children's age-related PA tracking (EE and MVPA) is stable during self-paced GAP assessed over a 1-year interval. Since PA tracking is stable in self-paced GAP, GAP should be included in children's PA intervention strategies to improve health and fitness.

KEYWORDS

play, accelerometer, health, school-aged years, tracking

Introduction

Physical activity (PA) participation and physical fitness (PF) positively impact children and adolescent health- and performance-related outcomes (Poitras et al., 2016; Verswijveren et al., 2018). Despite the importance of PA, surveillance reports for PA behaviors show lower participation rates among school-aged children leading to an increased prevalence of childhood obesity and cardiovascular risk factors (Guthold et al., 2018). As a result, public health strategies emphasize increasing PA behaviors throughout childhood to maintain and improve health outcomes (Bangsbo et al., 2016). To help inform health-related intervention strategies during childhood development, the use of tracking, which refers to the stability or maintenance of a variable's rank over time, has been proposed. Reports show that variables with a high degree of tracking are important for the planning and implementation of intervention strategies to improve health-related outcomes (Malina, 1996, 2001).

Evidence from cross-sectional studies suggests that PA participation decreases with increasing age over the school age and adolescent years (Barnes et al., 2013). Tracking statistics for PA show moderate correlation coefficients in early childhood moving to poor correlation coefficients in the adolescent years (Malina, 1996, 2001; Caldwell et al., 2016). Specifically, moderate tracking correlation coefficients for total PA and moderate-to-vigorous PA (MVPA) were reported for 1-year intervals during the preschool years (<5 years) (Caldwell et al., 2016). The stability of tracking statistics for PA from grades 5 to 8 was reported to be lower for a time at MVPA and energy expenditure (EE) with boys showing stronger tracking than girls (Roth et al., 2018). During late childhood (10–12 years) and adolescence (13–14 years), inter-age correlations for total PA were lowest, ranging from $r = 0.03$ to $r = 0.18$, respectively, (Fortier et al., 2001). Explanations used to describe these varied age-related trends for PA tracking statistics include (a) measurement assessment errors when using survey, recall, physiological, and/or movement sensors, (b) study design challenges (i.e., 1 day a week or multiple days per weekday and/or weekend), and (c) the variety in PA responses based on the type or nature of PA opportunities, such as organized vs. unorganized activity and sports vs. play (Jago et al., 2017; Khawaja et al., 2020). In addition to challenges associated with measurement, study design, and type of PA, it has been proposed that tracking studies of PA engagement should not only consider physiological demands of PA but also psychosocial and environmental factors that will contribute to promote PA participation (Malina, 1996, 2001; Pettee-Gabriel et al., 2012; Jago et al., 2017). Free and active play has been reported to provide the physiological, psychological, and environmental contexts that support PA levels from early childhood to adolescents (Truelove et al., 2017). As a result, PA programs that focused on active play might be attractive for use in tracking studies comparing early-middle-late childhood. To date, tracking statistics for PA determined using active play for children and adolescents are not available in the literature.

Guided active play (GAP) is characterized by self-paced, freely chosen, and fun activities incorporating positive role models to encourage children to engage in PA (Truelove et al., 2017). The PA in GAP programs is provided through the use of cooperative (social) games that are classified and clustered into games that exhibit low and high EEs (Howe et al., 2010; Belcastro et al., 2012). In addition, the range of EE and MVPA for cooperative games has been reported to be repeatable from week to week for school-aged children (Belcastro et al., 2012). The physiological requirements for active EE and intensity of PA are provided by the use of cooperative games that increase the total active time and higher levels of MVPA in community-based settings, such as afterschool and community recreation centers (Moghaddaszadeh et al., 2016; Hollis et al., 2017; Khawaja et al., 2020). The psychosocial and environmental correlates of PA are supported by the guided play/fun components of GAP programs that are reported to enhance positive PA behaviors (enjoyment, social interaction, and encouragement) and reduce the negative influences and/or barriers (bullying and low self-efficacy) (Moghaddaszadeh et al., 2016; Truelove et al., 2017; Khawaja et al., 2020). Together these attributes support the use of guided or facilitated active play, using cooperative games as a good candidate for PA tracking during childhood and adolescence. Whether children's participation in the guided active playing of cooperative games shows stable and high tracking statistics that are maintained from childhood to adolescence is not available in the literature.

The purpose of this study was to determine the PA tracking statistics during self-paced GAP sessions separated by 12 months, delivered in a summer day camp setting. PA was assessed for the group and on a gender-specific basis for school-aged children (7–11 years). A cross-sectional analysis of different age groups was conducted to explore the effectiveness of GAP in tracking across childhood since the school ages (7–11 years) cover many of the important age-related stages of development (Malina, 1996, 2001). Tracking statistics for variables were determined with Spearman correlation coefficients and agreement scores (Cohen's *kappa*) for children based on tertial rankings. The identification of stable or non-stable PA tracking statistics from GAP programs, assessed over a 1-year tracking interval, will be relevant for planning children's community-based PA studies/interventions for school-aged children and adolescents.

Materials and methods

Children participating in this study ($n = 65$ with 28 girls and 37 boys; 7–11 years) were a convenient sample living in a large urban city and registered in a subsidized community summer 5-day camp program. The summer program operated from Monday to Friday (9:00 a.m. to 3:30 p.m.) with a typical day comprised of arts/crafts (25%/day), aquatic activities (10%/day), free time (15%/day), physical activities (25%/day), and social activities (25%/day). The GAP program that consisted of fun, self-paced-based cooperative games were delivered during a 1-h afternoon PA session. With support from the Community Recreation Center, the children's parents/guardians participated in an information/orientation session where they received informed consent material describing procedures, benefits, and the risk of the GAP PA program. Parents/guardians completed a Physical Activity Readiness Questionnaire (PARQ) and provided signed consent for children's participation.

During the initial baseline year and the 1-year follow-up, children were assessed two times for body composition on 2 different days (9:00–10:00 a.m. on Monday and Tuesday) and participated in two GAP sessions on 2 different days (1:30–2:30 p.m. on Tuesday and Thursday). All testing protocols at the baseline and the 1-year follow-up were conducted using the same research team. The procedures used in this study were approved by the University's Human Participants Review Committee.

To complete the GAP sessions, 65 children were randomly divided into two groups of 30–35 and participated in self-paced PA for 1h·d^{-1} duration using age-appropriate cooperative games (Belcastro et al., 2015; Truelove et al., 2017; Moghaddaszadeh and Belcastro, 2021). Each group played 5–6 games reported to elicit a range of moderate-to-vigorous intensities (Howe et al., 2010; Belcastro et al., 2012), with one water break introduced halfway through the session. The games included: Giants Wizards Elves, Shipwreck, Octopus, Clothes Pin Tag, Four Corners, Archers Tag, Dr. Dodgeball, Crash, Monkey in the Middle, Handball, Croc-Croc, Line Tag, Toilet Tag, What Time is it Mr. Wolf, Bacon Tag, 4-corner Soccer, 4-corner Basketball, Zombie Tag, Fishes and Whales, Blob Tag, Soccer Baseball, Pizza Oven, The Floor is Lava, and Flip the Fish. The GAP sessions included non-instructional role models (guides) at a ratio of 5:1 for children-to-guide (West and Shores, 2008; Truelove et al., 2017; Moghaddaszadeh and Belcastro, 2021). Experienced undergraduate senior kinesiology majors, with 15 h in a combination of workshops (encouragement strategies; bullying) and simulated children's program delivery (rules of the games and practicing skills), served as positive role models and provided visual encouragement to children to expand their experiences. No instructions and feedback were provided during the sessions, and no child was forced to play games. The cooperative games were conducted in a temperature-controlled (20°C) gymnasium.

Physical activity was quantified during each session using ActiGraph GT3X+ Accelerometers (ACCs). ACCs were placed at the hip with elastic bands and outputs expressed as a vector in counts per 10 s (cnts·10 s^{-1}). Oxygen consumption (VO_2) was estimated using a laboratory-generated linear regression equation with a standard error of estimate (SEE) of 0.75 ml·kg^{-1}min^{-1} for children during treadmill exercise and 3.23 ml·kg^{-1}min^{-1} when playing active games (Moghaddaszadeh et al., 2018). To classify the volume and intensity of PA, the VO_2 estimates derived from ACC outputs were used to calculate total EE in a 55-min session (kcal·55 min^{-1}). Intensity levels, assessed with metabolic equivalents (METs), were predicted by linear regression based on ACC vector outputs, and the percent of time spent at different METs was determined and described as sedentary (0–1.5 MET), very light (1.6–2.9 MET), light (3–3.9 MET), moderate (4–5.9 MET), and vigorous (>6 MET). Finally, the percentage of time spent at each intensity level (expressed as % PA) was determined for each child during all GAP sessions (Belcastro et al., 2015; Moghaddaszadeh et al., 2016; Moghaddaszadeh and Belcastro, 2021). Because of the intermittent (stop-start) nature of PA when children play self-paced cooperative games, classifying time at sedentary activity from movement patterns determined by cutoff points underestimated the metabolic cost of recovery periods occurring between short bursts (Moghaddaszadeh et al., 2018). This increased metabolic response (i.e., metabolic recovery) that occurred at a time when minimal to no movement (i.e., <150 cnts 10 s^{-1}) occurred was not captured by the accelerometer. The metabolic cost during recovery has been reported to be important in children's physiological adaptations to exercise (Falk and Dotan, 2006).

Anthropometric variables that included body mass, standing height, and waist circumference were measured two times and averaged as described (Moghaddaszadeh and Belcastro, 2021). Height was measured to the nearest 1.0 cm with a portable stadiometer. Body mass was measured to the nearest 0.2 kg with a standard beam scale. Waist circumference was measured to the nearest 0.5 cm with a standard measuring tape placed above the hip bones. Body mass index (BMI) was calculated as body weight in kilograms divided by height in meters squared (kg· m^2).

Descriptive and statistical analyses (using SPSSv24) of variables for body composition and levels of PA at baseline and 1-year follow-up were assessed by paired *t*-tests with *p* levels $p < 0.05$, $p < 0.01$, and $p < 0.001$. Tracking was assessed using Spearman rank order correlation coefficients to quantify individual rank stability for each variable between baseline and 1-year follow-up with *p* levels $p < 0.05$, $p < 0.01$, and $p < 0.001$. Correlation coefficients of <0.30 were interpreted as low, those of 0.30–0.60 were interpreted as moderate, and those of >0.6 were interpreted as strong (Caldwell et al., 2016). Children were divided into tertials for each variable (Fortier et al., 2001) and the Cohen's Kappa (*k*) statistic was used to determine the stability within tertials from baseline to 1-year follow-up. The strength of the agreement scores was interpreted using the following schemes: poor (κ = 0.00–0.20), fair (κ = 0.21–0.40), moderate (κ = 0.41–0.60), good (κ = 0.61–0.80), and strong (κ = 0.81–1.0) (Munoz and Bangdiwala, 1997).

Results

Children increased body mass, height, BMI, and waist circumference from baseline (BL) to 1-year follow-up (FUI) (Table 1). Girls were younger at baseline (8.4 ± 1.6 years) when compared to boys (9.3 ± 1.7 years; $p < 0.05$). Girls also had statistically less body mass and a lower BMI at baseline (Table 1).

TABLE 1 Participant characteristics described by means and standard deviations (M ± SD), minimum, maximum, and normality with Shapiro-Wilk skewness statistic for selected body composition measures obtained during summer camps at baseline (BL) and 1-year later (FU1).

Anthropometric measurement		Year	M ± SD	Min	Max	Skew
Total (n = 65)	Age	BL	8.9 ± 1.7	6.0	11.0	−0.325*
		FU1	9.9 ± 1.7	7.0	12.0	−0.302*
	BM	BL	37.5 ± 12.8	15.5	71.5	0.735*
		FU1	42.6 ± 14.5*	15.8	78.8	0.620*
	HT	BL	140.0 ± 15.6	108	188.2	0.470
		FU1	145.2 ± 15.1*	108	174.0	−0.144
	BMI	BL	18.7 ± 4.0	11.1	30.8	0.895*
		FU1	19.7 ± 4.4*	12.6	33.2	1.27*
	WC	BL	56.4 ± 19.2	46.5	89.5	0.631*
		FU1	67.8 ± 12.4	20.2	97.3	−0.195*
Girls (n = 28)	Age	BL	8.4 ± 1.6[a]	6.0	11.0	−0.007
		FU1	9.3 ± 1.7	7.0	12.0	0.006
	BM	BL	32.7 ± 9.2[a]	18.8	54.3	0.587
		FU1	37.6 ± 11.2*	21.2	61.7	0.455
	HT	BL	135.8 ± 15.9	112.2	188.2	1.39*
		FU1	140.3 ± 14.2*	118.0	168.2	0.315
	BMI	BL	17.5 ± 3.2[a]	11.1	24.2	0.174
		FU1	18.7 ± 2.9*	12.5	24.5	0.241
	WC	BL	63.2 ± 7.7	48.5	81.8	0.293
		FU1	66.4 ± 9.2	52.0	83.8	0.347
Boys (n = 37)	Age	BL	9.3 ± 1.7	6.0	11.0	−0.676*
		FU1	10.3 ± 1.7	7.0	12.0	−0.624*
	BM	BL	41.2 ± 14.1	15.5	71.5	0.435
		FU1	46.3 ± 15.7*	15.8	78.8	0.403
	HT	BL	143.1 ± 14.8	108	174.2	−0.163
		FU1	149.0 ± 14.9*	108	177.0	−0.543
	BMI	BL	19.7 ± 4.4	13.3	30.8	0.893*
		FU1	20.4 ± 5.1*	13.6	33.2	1.10*
	WC	BL	67.3 ± 11.6	46.5	89.5	0.461
		FU1	70.2 ± 12.0*	53.0	97.3	0.832*

Body composition measurements included body mass (kg) (BM), height (HT) (cm), body mass index (BMI) (kg·ht^2), and waist circumference (WC) (cm). Comparisons for BL and FU1 and for girls vs boys at BL were *$p < 0.05$.

Descriptive statistics that included means and standard deviations (SDs), minimum and maximal results, normality statistics, correlation coefficients, and measures of agreement for all PA measures are given in Table 2. Within the grouped data, increases were observed for EE (20%), vigorous PA (VPA) (46%), and MVPA (14%) occurred over the 1-year interval ($p < 0.05$). Gender differences for estimated (EE) during GAP from baseline to 1-year follow-up were increased for girls and boys by 25 and 18%, respectively, with boys having higher EE as compared to girls during the GAP ($p < 0.05$). VPA and MVPA were statistically higher for boys. Tracking coefficients during guide active play sessions were strong for estimated EE (r = 0.88) and moderate for percentages of time at VPA (r = 0.52) and VPA (r = 0.54) for the grouped data. Agreement measures showed moderate Kappa scores for estimated EE and percentage of time at MPA and MVPA from 0.47 to 0.57 (Table 2). Estimated EE tracking coefficients and percentage of time at MVPA were similar for girls and boys during the 1-year interval. Boys had greater tracking coefficients for the percentage of time at VPA (r = 0.55) vs. girls (r = 0.36). Agreement measures showed comparable moderate Kappa scores for estimated EE and percentage of time at MVPA from 0.41 to 0.49 for girls and 0.48 to 0.52 for boys.

Means and SDs, correlation coefficients, kappa scores, and classifications for EEs and PA intensity analyzed over 1-year intervals starting at 7, 8, 9, 10, and 11 years ($n = 65$) are shown in Table 3. The age-related changes in EE showed that the older children (10 and 11 years) had statistically greater

TABLE 2 Means and standard deviations (M ± SD), minimum, maximum, Shapiro-Wilk skewness, correlation coefficients, kappa statistics, and classifications for the physical activity measures obtained during a summer day camp program that included guided active play sessions (55 min) at baseline (BL) and 1-year later (FU1).

Physical activity measurement		Year	M ± SD	Min	Max	Skew	Spearman correlation BL vs. FU1	Kappa BL vs. FU1 (Class)
Total (n = 65)	EE	BL	207.8 ± 71.3	95.1	373.4	0.536*		
		FU1	250.1 ± 84.6*	93.1	463.4	0.659*	0.88***	0.54 (mod)
	SED	BL	32.7 ± 12.1	9.0	67.0	0.873*		
		FU1	30.1 ± 13.3	6.7	56.5	0.214	0.54**	0.38 (fair)
	MPA	BL	24.6 ± 5.9	9.5	42.1	0.108		
		FU1	25.3 ± 5.8	13.8	40.5	0.056	0.38	0.57 (mod)
	VPA	BL	11.8 ± 5.8	2.6	31.0	0.989**		
		FU1	17.3 ± 7.6*	5.1	40.4	0.889**	0.52**	0.14 (poor)
	MVPA	BL	36.5 ± 8.4	9.7	58.0	−0.110		
		FU1	41.5 ± 11.0*	21.1	69.5	0.402	0.54**	0.47 (mod)
Girls (n = 28)	EE	BL	171.6 ± 50.0[a]	105.7	294.9	0.607		
		FU1	214.8 ± 60.4*	106.2	344.5	0.419	0.82***	0.49 (mod)
	SED	BL	40.2 ± 12.7[a]	18.0	67.0	0.677		
		FU1	36.1 ± 13.5	8.0	56.5	−0.546	0.11	0.22 (fair)
	MPA	BL	23.3 ± 6.7	9.5	38.1	0.033		
		FU1	23.2 ± 5.0	15.7	34.2	0.110	0.10	0.06 (poor)
	VPA	BL	9.8 ± 5.1[a]	2.6	24.1	0.735		
		FU1	13.2 ± 5.5*	5.1	30.8	1.14*	0.36	0.03 (poor)
	MVPA	BL	33.1 ± 8.0[a]	9.7	44.2	−1.06		
		FU1	36.4 ± 9.1	21.1	64.9	0.732	0.49**	0.41 (mod)
Boys (n = 37)	EE	BL	234.2 ± 73.0	95.1	373.4	0.162		
		FU1	276.9 ± 91.1*	93.1	463.4	0.371	0.89***	0.53 (mod)
	SED	BL	27.1 ± 8.1	9.0	43.5	0.012		
		FU1	25.7 ± 11.5	6.7	53.2	0.757	0.60***	0.13 (poor)
	MPA	BL	26.6 ± 5.1	16.2	42.0	0.673		
		FU1	26.9 ± 5.9	13.8	40.5	−0.186	0.16	0.11 (poor)
	VPA	BL	13.4 ± 6.1	4.0	31.0	1.11*		
		FU1	20.5 ± 7.6*	9.2	40.4	0.765	0.55***	0.26 (fair)
	MVPA	BL	39.0 ± 7.8	21.6	58.0	0.662*		
		FU1	47.4 ± 10.0*	27.2	69.5	0.389	0.48***	0.48 (mod)

Measurements included estimated energy expenditures (EE) in kilocalories per 55 min. The intensity of the guided active play sessions was described with the percentage of time spent in sedentary (Sed) behaviors [<1.5 metabolic equivalents (MET), the percentage of time spent in moderate physical activity (MPA; 4–6 MET), the percentage of time spent in vigorous physical activity (VPA; >6 MET), and accumulated percent time in moderate and vigorous physical activity (MVPA; >4 MET)]. $^{*}p < 0.05$: $^{**}p < 0.01$; $^{***}p < 0.001$. Girls vs. boys at BL were $^{a} = p < 0.05$.

EE than the younger children (7–9 years; Table 3). None of the intensity-related components was different across the age ranges. When considering tracking statistics, strong correlation coefficients for EE were observed at each age with younger children showing higher coefficients except for the 9-year-old children, the Kappa statistics for EE showed moderate agreement scores for the older children, while the younger children had fair agreements scores except for the 8-year-old children. The tracking of sedentary behavior during the GAP program demonstrated the lowest correlation coefficients at 7 and 8 years (average of r = 0.25) and the strongest correlation coefficients at 10–11year (average of r = 0.70). Kappa scores were classified as fair across the age range with the exception of children at 9 years that demonstrated a poor agreement score. Regarding the percentage of time at VPA of PA, children demonstrated stronger tracking coefficients at 7 years (r = 0.78), which was lowered to r = 0.42 at 11 years. Kappa scores for children at 7 years were classified as good, with poor classifications noted for children at 8–10 years. Regarding the time at MVPA, statistically significant coefficients were

TABLE 3 Age-related means and standard deviations (M ± SD), correlation coefficients, kappa statistics, and kappa classifications for the physical activity measures obtained during summer camps guided active play sessions (55 min) at baseline (BL) and 1-year later (FU1).

Physical activity measurement	EE		SED		MPA		VPA		MVPA	
Year	**BL**	**FU1**	**BL**	**FU1**	**BL**	**FU1**	**BL**	**FU1**	**BL**	**FU1**
					7 years (G4:B5)					
M ± SD	171.5 ± 42.0	200.0 ± 49.3*	29.2 ± 9.7	29.1 ± 12.4	25.3 ± 8.6	26.4 ± 4.7	13.6 ± 3.5	18.2 ± 6.6*	38.9 ± 6.0	44.6 ± 7.4*
Spearman's Correlation	0.90***		0.27		0.35		0.78**		0.55*	
Kappa (Class)	0.33 (fair)		0.33 (fair)		0.17 (poor)		0.67 (good)		0.17 (poor)	
					8 years (G10:B6)					
M ± SD	175.2 ± 43.9	221.4 ± 70.4	35.8 ± 15.7	37.1± 12.9	24.5 ± 10.2	22.7 ± 5.2	13.1 ±10.1	15.3 ± 8.0	37.6 ± 14.5	38.0 ± 12.0
Spearman's Correlation	0.91***		0.12		0.25		0.51*		0.72**	
Kappa (Class)	0.43 (mod)		0.21 (fair)		0.07 (poor)		0.19 (poor)		0.30 (fair)	
					9 years (G6:B7)					
M ± SD	195.6 ± 58.5	226.1 ± 44.2	37.6 ± 14.9	28.2 ± 13.0	22.2 ± 4.6	26.8 ± 5.9*	11.3 ± 5.3	15.5 ± 7.2*	33.5 ± 8.3	42.4 ±12.1**
Spearman's Correlation	0.51		0.56*		0.74**		0.48		0.82***	
Kappa (Class)	0.31 (fair)		0.17 (poor)		0.07 (poor)		0.07 (poor)		0.18 (poor)	
					10 years (G3:B8)					
M ± SD	224.8 ± 44.0	278.4 ± 70.1[a]	32.9 ± 10.1	32.8 ± 15.1	24.3 ± 3.6	24.1 ± 4.4	10.7 ± 4.1	17.3 ± 5.5**	36.5 ± 6.6	46.5 ± 14.3***
Spearman's Correlation	0.82***		0.60*		0.29		0.41		0.76*	
Kappa (Class)	0.45 (mod)		0.31 (fair)		0.09 (poor)		0.10 (poor)		0.21 (fair)	
					11 years (G5:B11)					
M ± SD	273.9 ± 71.0	323.3± 73.4*[b]	30.5 ± 10.2	26.0 ± 12.8*	25.3 ± 3.8	25.9 ± 7.0	11.2 ± 4.9	20.6 ± 10.2***	36.5 ± 6.6	46.5 ± 14.3***
Spearman's Correlation	0.83***		0.79**		0.05		0.42		0.50	
Kappa (Class)	0.41 (mod)		0.21 (fair)		0.10 (poor)		0.21 (fair)		0.42 (mod)	

Measurements included estimated energy expenditures (EE) in kilocalories per 55 min. The intensity of the guided active play sessions included the percentage of time spent in sedentary (SED) behaviors [<1.5 metabolic equivalents (MET), the percentage of time spent in moderate physical activity (MPA; 4–6 MET), the percentage of time spent in vigorous physical activity (VPA; >6 MET), and accumulated time in moderate and vigorous physical activity (MVPA; >4 MET)]. $^*p < 0.05$: $^{**}p < 0.01$; $^{***}p < 0.001$. Age comparisons $^a = p < 0.05$ for 10 vs. 7–11 $^b = p < 0.05$ for 11 vs. 7–10 $^b = p < 0.05$.

observed for children at 7–10 years, but not for those at 11 years (Table 3).

Discussion

The aim of the study was to determine PA levels during GAP and investigate PA tracking statistics over a 1-year interval from early to late childhood. PA levels for GAP were assessed during 55-min of self-paced playing of cooperative games two times at baseline and two times at 1-year follow-up. Previous findings have reported that PA and intensity of PA show low-to-moderate tracking coefficients during childhood with inter-age correlations higher in early childhood and dropping in late childhood with boys tracking higher than girls (Malina, 1996, 2001; Caldwell et al., 2016). The lower PA tracking statistics throughout childhood are more evident for longer (6, 9, and/or 12 years) as compared to shorter (1, 2, or 3 year) age intervals (Malina, 2001). To our knowledge, no reports have investigated tracking of PA during GAP using total estimated EE and percent time at different PA intensities (MVP, VPA, and MVPA) in children in early, middle, and late childhood. Our results show strong levels of tracking for EE, VPA, and MVPA over a 1-year interval for school-aged boys and girls participating in self-paced games in a GAP format. Therefore, our play-based results open up the need to consider the benefits of tracking children's PA in settings that will encourage and engage children in positive PA behaviors rather than restrict observations to habitual activity (Moghaddaszadeh et al., 2016; Truelove et al., 2017; Khawaja et al., 2020).

Changes in PA levels quantified by self-reporting tend to show declines in early childhood (5.7–7.9 years) (Crane et al., 2018), middle-late childhood, and adolescents (8.8–12.1 years) (Fortier et al., 2001; McMurray et al., 2003). Other studies had similar results when using previous day recall (Pate et al., 1999) and 3-day sweat rates (10.5–11.5 years) (Janz et al., 2000). In the present study, accelerometer-quantified PA levels during GAP showed increases in estimated EE (kcal·55 min^{-1}), %VPA and %MVPA for children (6–11 years) during a 1-year interval. Gender differences tended to show similar increases for boys and girls in estimated EE and %VPA, but a lower %MVPA for girls. In addition to the grouped data, aged-related PA levels showed an increase in estimated EE for children at 7–11 years over the 12 months. The age-related changes and gender differences noted in this study suggest that older children engage in more PA than younger children and boys engage in more PA than girls during active play. Our findings are consistent with previous work during GAP, which suggests increases in total PA of 22% for all children over a 2-year interval, with boys increasing by 27% and girls by 17% when participating in a children's lifestyle and energetics program (Kelly et al., 2007).

There are limited reports available for PA tracking of children from early-middle-late childhood with GAP. One study reported a lower PA tracking coefficient ($r = 0.37$) over a 2-year interval during early childhood participation in a lifestyle and energetic program (Kelly et al., 2007). The majority of studies have assessed tracking statistics over several days/hours during habitual PA and/or organized sports participation with a few studies using a play-based approach. Furthermore, the variations in tracking statistics reported in previous PA studies have used a variety of age groups, tracking intervals, methods, and measurement tools (Jago et al., 2017; Khawaja et al., 2020). It has been suggested that attention must be given to PA settings/approaches when comparing tracking statistics to assess children's PA behaviors (Malina, 1996, 2001). Our results for PA tracking of estimated EE during GAP revealed strong coefficients ($r \geq 0.8$) and moderate agreement ($\approx$0.50) scores for grouped school-aged children. For PA intensities, the %VPA and %MVPA showed moderate tracking coefficients of $r = 0.52$ and $r = 0.54$, respectively. Gender differences showed that boys had higher levels of EE, %VPA, and %MVPA with less sedentary time during the GAP as compared to girls. Boys and girls showed strong tracking and moderate agreement scores for EE and %MVPA, with only the boys showing statistically greater %VPA tracking. Age-related EE increased from 7 to 11 years with stable tracking coefficients observed at each age, except for 9 years. The tracking coefficients for %MVPA and sedentary time showed increased stability with increasing age, while coefficients for %VPA showed less stability from 7 to 11 years. These findings that are analyzed over a 1-year tracking interval and a cross-section of children in early, middle, and late childhood provide "proof-of-concept" for tracking PA using self-paced playing of cooperative games in a GAP format to promote PA participation. These findings demonstrate the importance and practicability of children's self-paced GAP in providing consistent stable PA tracking throughout middle and late childhood. Finally, evidence suggests that children are more likely to participate in PA with a freely chosen guided play environment, which aligns with the self-paced, cooperative, and non-competitive nature of this program (Pettee-Gabriel et al., 2012; Jago et al., 2017). The pattern of the traditional exercise programs tends to be prolonged and continuous, whereas children's normal activity pattern is in short bursts, approximately 3 s in duration. The facilitated play has been reported to promote higher levels of PA as compared to the traditional exercise programs (Moghaddaszadeh et al., 2016; Truelove et al., 2017). The reported increase in total PA with cooperative, non-competitive games is also likely attributed to the program's encouragement of play and aspects of child wellbeing. The program allows children to experience the joys of movement through the playing of various games and the language used to promote PA participation during play encourages movement (Pyle and Danniels, 2017; Truelove et al., 2017; Moghaddaszadeh and Belcastro, 2021).

There are some limitations to the interpretation of these results. First, although tracking studies can occur over longer time intervals, a 1-year interval reflects an important proportion of a child's life. Many important growth and developmental processes occur, which may elicit changes in PA behaviors during the 12 months. Investigating longer time intervals would increase the potential impact of these results. Second, a longitudinal study over many years and with many more children would enhance the generalizability of the results. Although the study only included 65 children over a 1-year interval, it tracked children across the school ages (7–11 years) that cover many of the important age-related stages of development. Although our sample size was not sufficiently large to stratify the results by age, preliminary analyses showed age-appropriate differences for growth variables across the groups. Hence, we believe that our findings are based on a representative sample of children covering early, middle, and late childhood. Third, our analyses did not contain a control group. In defense, study designs used in "real-world" settings, such as community center summer day camps, are challenging and often associated without the benefits of a control group with the naturally emerging situations requiring use of quasi-experimental study designs. Although this approach may comprise the generalizability of our results, we view these results as exploratory and serve as a "proof-of-concept" for children's play-based studies. Fourth, PA outputs for GAP may be affected by the summer camp environment and the nature of the games played. Our study used the same research team for each session over the 1-year interval. The success of the GAP sessions was influenced by a respectful partnership developed between the research team and the community center administration. All GAP sessions were delivered with a common series of games, reported to be reliable and repeatable over time (Belcastro et al., 2012, 2015). Finally, we used estimated MET levels derived from accelerometer outputs and not vector cut-points to classify children's PA intensity during GAP (Moghaddaszadeh and Belcastro, 2021). Currently, there are no sets of PA cutoff thresholds for a short burst, frequent start-and-stop PA behaviors that occur with children playing cooperative games. This is not a trivial matter, and we reported the increased metabolic demands that persist when children show very low ACC vector outputs (Moghaddaszadeh et al., 2018). Notwithstanding these limitations, the need to confirm the stability of PA tracking for children's play should consider the use of a larger sample size in follow-up years to accurately assess the influences of developmental and maturity stages and include several follow-up years with increased intervals between ages.

In summary, the evidence suggests that children are more likely to participate in PA within an unstructured play environment consisting of a self-paced, cooperative (social), and non-competitive nature of GAP. This approach to track children's PA participation may promote stronger relationships between cardiometabolic risk factors during development. With the growing obesity epidemic, it is important to rephrase the way in which PA is promoted, in a way that children and parents find meaningful.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Office of Research Ethics (ORE), Human Participants Review Committee, York University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

AB and AM for conception and design of research. AM, UT, EL, and CL delivered the physical activity program and collected the data. UT, EL, and CL analyzed the data and prepared tables/figures. AB and AM interpreted results of experiments and prepared the initial manuscript. All authors approved the final version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Neuromuscular electrical stimulation to augment lower limb exercise and mobility in individuals with spastic cerebral palsy: A scoping review

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Background: Neuromuscular Electrical Stimulation (NMES) is an emerging assistive technology applied through surface or implanted electrodes to augment skeletal muscle contraction. NMES has the potential to improve function while reducing the neuromuscular impairments of spastic cerebral palsy (CP). This scoping review examines the application of NMES to augment lower extremity exercises for individuals with spastic CP and reports the effects of NMES on neuromuscular impairments and function in spastic CP, to provide a foundation of knowledge to guide research and development of more effective treatment.

Methods: A literature review of Scopus, Medline, Embase, and CINAHL databases were searched from 2001 to 2 November 2021 with identified inclusion and exclusion criteria.

Results: Out of 168 publications identified, 33 articles were included. Articles on three NMES applications were identified, including NMES-assisted strengthening, NMES-assisted gait, and NMES for spasticity reduction. NMES-assisted strengthening included the use of therapeutic exercises and cycling. NMES-assisted gait included the use of NMES to improve gait patterns. NMES-spasticity reduction included the use of transcutaneous electrical stimulation or NMES to decrease tone. Thirteen studies investigated NMES-assisted strengthening, eleven investigated therapeutic exercise and demonstrated significant improvements in muscle structure, strength, gross motor skills, walking speed, and functional mobility; three studies investigated NMES-assisted cycling and demonstrated improved gross motor skills and walking distance or speed. Eleven studies investigated NMES-assisted gait and demonstrated improved muscle structure, strength, selective motor control, gross motor skills, and gait mechanics. Seven studies investigated NMES for spasticity reduction, and five of the seven studies demonstrated reduced spasticity.

Conclusion: A growing body of evidence supports the use of NMES-assisted strengthening, NMES-assisted gait, and NMES for spasticity reduction to improve functional mobility for individuals with spastic CP. Evidence for NMES to augment exercise in individuals with spastic CP remains limited. NMES protocols and parameters require further clarity to translate knowledge to clinicians. Future research should be completed to provide richer evidence to transition to more robust clinical practice.

KEYWORDS

cerebral palsy, exercise, transcutanenous electric nerve stimulation, gait, neuromuscular electrical simulation

1 Introduction

Cerebral palsy (CP) is the most common motor disability in childhood, affecting 1.5 to 4 per 1,000 live births and presenting as spastic, dyskinetic, and ataxic types of CP, depending on the location of early brain injury (Bax et al., 2005). Spastic CP is the most common type of CP characterized by four interrelated neuromuscular impairments associated with corticospinal tract injury: muscle weakness, short muscle-tendon length relative to bone, spasticity, and impaired selective motor control (SMC) (Bax et al., 2005; Wright M. et al., 2012; Zhou et al., 2017). Dyskinetic CP is characterized by involuntary muscle contractions imposed on purposeful movement, limiting functional mobility, and is thought to be associated with basal ganglia injury (Sanger, 2015). Ataxic CP impairs balance and coordination associated with an injury in the cerebellum of the brain (Imamura et al., 1992; Rankin et al., 2010). Depending on the location of brain injury, an individual may present with symptoms of more than one type of CP (Schiariti et al., 2018). This review focuses on neuromuscular electrical stimulation (NMES) application to augment lower limb exercise for individuals with spastic CP, affecting around 80% of children with CP (Novak, 2014; CDC, 2020). Spastic CP can involve unilateral or bilateral limbs. In milder cases of CP, the lower limb is more affected distally, than proximally. Functional mobility in spastic CP is described by the Gross Motor Function Classification System (GMFCS). GMFCS levels range from I to V, with GMFCS I being mild and GMFCS V being the most severe (Palisano et al., 2007), and are reported in this review.

NMES is an emerging assistive technology applied as surface stimulation through electrodes placed over the skin or directly to the muscle via implanted electrodes to initiate or augment skeletal muscle contraction through intact peripheral nerves (Mooney and Rose, 2019; Wright et al., 2012). NMES applied through surface electrodes is the most common application as it is a non-invasive technique and generally well tolerated (Mooney and Rose, 2019). Electrodes are commonly placed over the motor point where the motor nerve innervates the muscle (Botter et al., 2011). The application of NMES to achieve functional movements is often referred to as Functional Electrical Stimulation (FES) (Masani and Popovic, 2011). The application of low-intensity electrical stimulation primarily targeting nerves, referred to as Transcutaneous Electrical Nerve Stimulation (TENS), is routinely used for pain management and has the potential to improve motor function in patients with neurodegenerative disorders (Levin and Hui-Chan, 1992; Vance et al., 2012; Kroeling et al., 2013). NMES applications include the use of NMES-assisted strengthening, NMES-assisted gait, and NMES spasticity reduction.

NMES parameters that control stimulation vary based on clinical application, targeted muscles, and individual tolerance (Maffiuletti, 2010). Parameters reported in this review include stimulation frequency, intensity, pulse width, timing (on/off ratio), and ramp. The frequency of electrical stimulation refers to the number of times a pulse of current is applied within one second, measured in Hertz (Hz). Higher frequencies generally produce more muscle activation as long as the individual pulses reach muscle fibers after their refractory period, do not result in neurotransmitter depletion, or do not block nerves otherwise (e.g., nerve blocking with monophasic high-frequency stimulation or with charge-balanced kilohertz frequency alternating current), therefore, it generates more force and can lead to increased fatigue and lower tolerance (Chaudhuri and Behan, 2004; Gorgey et al., 2009; Wegrzyk et al., 2015). Intensity or pulse amplitude refers to the amount of current delivered, or the voltage applied to the electrodes (respectively resulting in change of the current delivered) during each pulse. It is measured in milliamperes (mA) for current-controlled and Volts for voltage-controlled stimulation, where the current is proportional to the voltage. Pulse width refers to the duration between the start and end of each electrical pulse and is typically reported in microseconds (μs). Longer pulse widths are associated with increased muscle force; however, shorter pulse widths may provide patients with more comfort and increased tolerance (Mogyoros et al., 1996; Knash et al., 2003; Mang et al., 2011, 2011). Timing (on/off) refers to the duration the stimulation with a given frequency is turned on versus turned off, typically reported in seconds, whereas ramp refers to the gradual increase followed by a gradual decrease in stimulation intensity to facilitate adaptation, reduce the likelihood of discomfort, and promote smooth gradations of tetany between different muscle groups (Baker et al., 2000; Bijak et al., 2005).

A growing body of evidence supports the use of NMES in the treatment and care of individuals with CP (Mooney and Rose, 2019; Novak et al., 2020). In this review, treatments were categorized into NMES-assisted strengthening exercises (therapeutic exercise and cycling), NMES-assisted gait (overground and treadmill walking for neuroprosthetic and neurotherapeutic effects), and NMES for spasticity reduction (during strengthening exercise and gait which typically targets spastic muscles with lower frequency stimulation using TENS parameters). The ultimate goal of NMES for individuals with CP is to improve functional mobility and quality of life.

Muscle weakness is a common impairment in individuals with CP and significantly impacts their ability to function and participate in activities. Weakness is primarily caused by neurological impairment, including reduced motor-unit firing and by muscle structural changes including in the muscle fascicles such as fatty replacement, in sarcomeres, and in muscle fiber size variability (Huijing, 1998; Elder et al., 2003; Lieber et al., 2004; Foran et al., 2005; Rose and McGill, 2005; Malaiya et al., 2007; Stackhouse et al., 2007; Barber et al., 2012; Noble et al., 2014; Zhou et al., 2017). Evidence indicates that use of NMES for augmenting exercise increases microvascular perfusion in the stimulated skeletal muscle (Clemente et al., 1991; Moloney et al., 2006; Bahadori et al., 2017). This decreases the diffusion distance in the stimulated muscle tissue and enhances the exchange of nutrients and metabolites between the blood and tissue, improving physiological muscle function. Given the vital role of muscle tissue (e.g., in maintaining stable glucose metabolism), NMES might further benefit the overall quality of life in individuals across all GMFCS levels.

Accurate interpretation of research requires relevant, validated outcome measures. Therefore, this review includes studies that report outcome measures recommended as Common Data Elements (CDE) by The National Institute of Neurological Disorders and Stroke (NINDS) (Grinnon et al., 2012). The CDE database is structured by diagnosis and includes CDEs recommended for CP.

Using the NINDS CDE database, there are several ways to measure and assess changes in strength in individuals with CP (Table 1). These include both direct strength measures, such as Manual Muscle Testing and Maximum Voluntary Isometric Contraction Testing, as well as measures of functional mobility, such as temporal-spatial parameters of gait (Lee et al., 2008), 3D gait analysis of kinematics and kinetics including the Gait Deviation Index (GDI) (Schwartz and Rozumalski, 2008), 6 Minute Walk Test (6MWT) (Maher et al., 2008) which reflects gait distance, Timed Up and Go (TUG) (Kaya Kara et al., 2019), and Gross Motor Function Measure (GMFM) (Russell et al., 2000). Although not CDE outcomes, dynamometry and timed sit to stand are often used to reflect changes in muscle strength and function in individuals with CP. Changes in muscle physiology can be assessed indirectly through muscle structure using musculoskeletal ultrasound (US) and Magnetic Resonance Imaging (MRI). Our review also identified in certain studies the CDE measures of Selective Control Assessment of the Lower Extremity (SCALE) (Fowler et al., 2009) for assessment of SMC.

This scoping review examines the application of NMES to augment lower extremity exercises for individuals with spastic CP, and reports the effects of NMES on neuromuscular impairments and function in spastic CP, to provide a foundation of knowledge that can guide research to advance the field and provide more effective treatment.

2 Methods

Given the extent of the literature, we determined that the most appropriate type of review for this field is a scoping review (Pollock et al., 2022). The primary goal of our review was to give a comprehensive assessment of the current use of NMES for augmenting exercise for individuals with spastic CP. We also sought to identify knowledge gaps to guide future research directions. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist was utilized to guide this review (Tricco et al., 2018).

A literature search was completed using Scopus, Medline, Embase, and CINAHL databases with additional publications referenced through the primary search. The search was completed on 2 November 2021, using the following keywords and Boolean operators: “spastic cerebral palsy” AND “neuromuscular electrical stimulation” OR “functional electrical stimulation”. The inclusion criteria for the articles were as follows: 1) the study involved individuals with CP, 2) the study reported outcome measures recommended by CDE for CP and were related to muscle strength and function, gait temporal-spatial parameters, and kinematics as identified in Table 1; 3) the study incorporated a known NMES dosage (session, duration, and frequency) with a known exercise component, such as strengthening, cycling, gait training; 4) the study was available in English; and 5) the study was published as a full-text manuscript. The exclusion criteria for the articles were as follows: 1) NMES was not a component of the study, 2) exercise was not a component of the study, 3) duration of treatment period was less than 4 weeks or not reported; 4) investigated muscles were not involving lower extremities; 5) articles were from dissertations, conference posters, or abstracts, 6) studies were published before 2001.

Using recommendations by the National Institute of Neurological Disorders and Stroke (NINDS), the authors used publications reporting at least one common data element (CDE)

TABLE 1 NINDS Common Data Elements (Grinnon et al., 2012) outcome measures identified in the articles reviewed, assessing motor function, spasticity, movement, functional mobility, and Quality of Life.

US	Ultrasound
MRI	Magnetic Resonance Imaging
6MWT (Maher et al., 2008)	6 Minute Walk Test
TUG (Kaya Kara et al., 2019)	Timed Up and Go
WS	Walking Speed
IGA	Instrumented Gait Analysis
GDI (Schwartz and Rozumalski, 2008)	Gait Deviation Index
SAGV	Stride Analysis and Gait Variability
OGS (Mackey et al., 2003)	Observational Gait Scale
GMFM (Russell et al., 2000)	Gross Motor Function Measure
PEDI (Haley, 1992)	Pediatric Evaluation of Disability Inventory
LAQ (Mackie et al., 1998)	Lifestyle Assessment Questionnaire
PEM-CY (Coster et al., 2010)	Participation and Environment Measure for Children and Youth
WeeFIM (Ottenbacher et al., 2000)	Functional Independent Measure for Children
COPM (Law et al., 1990)	Canadian Occupational Performance Measure
SCALE (Fowler et al., 2009)	Selective Control Assessment of the Lower Extremity
MAS (Mutlu et al., 2008)	Modified Ashworth Scale
TS (Gracies et al., 2010)	Tardieu Scale

Common data elements (CDE) by the national institute of neurological disorders and stroke (NINDS).

outcome measures specific to the diagnosis of CP. Each publication was given a level of evidence based on the Oxford Centre for Evidence-Based Medicine 2011 Level of Evidence guidelines (Howick, 2011). Data were extracted by the authors (KG, CJ, KS, BB) for each publication but unblinded to the results of other authors.

3 Results

The initial 5-database search resulted in 168 publications, and an additional 41 articles were identified from references. Fifty-one articles were duplicates. The authors used titles and abstracts to screen the publications for the relevance of exercise programs involving the lower extremity. Fifty-seven articles were discarded due to diagnoses other than spastic CP or study aims outside the scope of exercise. One hundred and one articles, including seven review articles, met criteria and were fully reviewed by the authors; however, 68 were excluded upon further review for different populations (n = 5), absence of CDE for CP outcome measures (n = 6), lack of NMES intervention (n = 10), inadequate or unreported treatment duration (n = 10), lack of exercise component (n = 11), language other than English (n = 2), muscle groups other than lower extremities (n = 6), non-qualifying publication type (n = 15), and published before 2001 (n = 3). Based on these inclusion criteria, this scoping review includes a total of 33 articles, 26 intervention studies, and seven reviews. See Figure 1 for the publication search flow chart.

The literature was categorized by the application of NMES, including NMES-assisted strengthening, NMES-assisted gait, and NMES for spasticity reduction. Extracted variables included the study's aim study design, age of participants, sample size, limb involvement (bilateral and/or unilateral), GMFCS level, device type, targeted muscle, NMES dose (number of weeks, sessions per week, and time per session), NMES parameters (frequency, intensity, pulse width, timing, ramp, waveform, and mode), and CDE outcomes recommended by NINDS, detailed in Tables 2–4.

3.1 Neuromuscular electrical stimulation-assisted strengthening

A total of fourteen articles were included for NMES-assisted strengthening, as shown in Table 2. NMES-assisted strengthening interventions included NMES augmenting therapeutic exercise, pre-operative surgical preparation, post-operative recovery, and NMES-assisted cycling. Several articles overlapped in the type of intervention, such as strengthening and spasticity reduction.

3.1.1 Neuromuscular electrical stimulation-assisted therapeutic exercise

Eleven studies reported NMES-assisted therapeutic exercise intervention: one case report (Daichman et al., 2003), one case series (Greve and Colvin, 2021), one pilot study (Stackhouse et al., 2007), two prospective trials (Nunes et al., 2008; Rajalaxmi

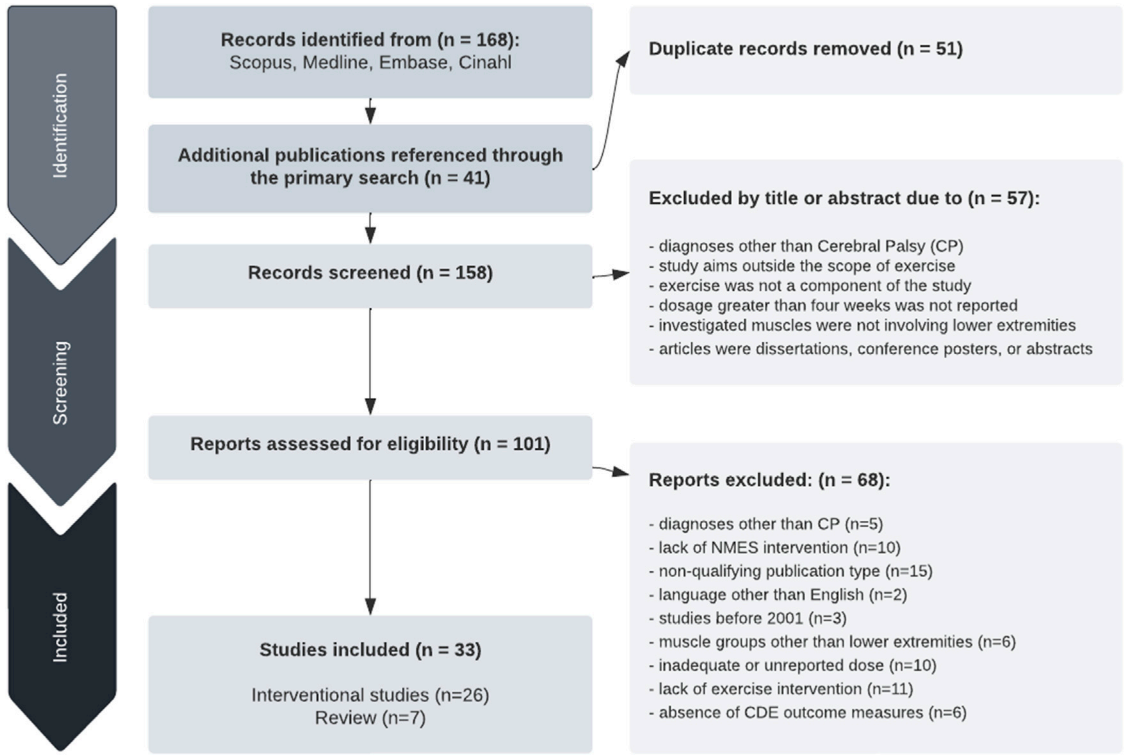

FIGURE 1
PRISMA flowchart of the study selection process.

et al., 2017), two prospective controlled studies (Karabay et al., 2015; Mukhopadhyay et al., 2017), and four randomized controlled trials (RCT) (Kerr et al., 2006; Khalili and Hajihassanie, 2008; Arya et al., 2012; Qi et al., 2018). Strengthening involved both home and clinic interventions using portable NMES devices with surface or implanted electrodes focused on the quadriceps, gastrocnemius, and tibialis anterior muscles. NMES was applied during positioning, stretching, facilitated exercises, strengthening, activities of daily living, balance, posture, and gait exercises (Daichman et al., 2003; Kerr et al., 2006; Stackhouse et al., 2007; Khalili and Hajihassanie, 2008; Nunes et al., 2008; Arya et al., 2012; Karabay et al., 2015; Mukhopadhyay et al., 2017; Rajalaxmi et al., 2017; Qi et al., 2018; Greve and Colvin, 2021). Dosage consisted of 15–60 min, one to seven times per week for 4–16 weeks. See Table 3 for specific NMES parameters and dosage for each study.

Ten studies using NMES-assisted therapeutic exercise reported improvements in muscle structure, strength, gross motor skills, WS, and functional mobility (Daichman et al., 2003; Stackhouse et al., 2007; Khalili and Hajihassanie, 2008; Nunes et al., 2008; Arya et al., 2012; Karabay et al., 2015; Mukhopadhyay et al., 2017; Rajalaxmi et al., 2017; Qi et al., 2018; Greve and Colvin, 2021). Two studies examined muscle cross-sectional area (CSA) using ultrasound or MRI and found an increase in CSA values of the quadriceps (Stackhouse et al., 2007), tibialis anterior (Karabay et al., 2015), and gastrocnemius (Karabay et al., 2015). Two studies reported an increase in quadriceps strength assessed with dynamometry (Daichman et al., 2003; Stackhouse et al., 2007). Six studies conducted the GMFM (Kerr et al., 2006; Nunes et al., 2008; Arya et al., 2012; Mukhopadhyay et al., 2017; Qi et al., 2018; Greve and Colvin, 2021), and four of the six studies reported positive changes in gross motor skills (Nunes et al., 2008; Mukhopadhyay et al., 2017; Qi et al., 2018; Greve and Colvin, 2021). Two studies reported improvement in functional mobility using the PEDI (Daichman et al., 2003) and FMS (Greve and Colvin, 2021). Studies also reported improvement in gait (Daichman et al., 2003; Arya et al., 2012; Mukhopadhyay et al., 2017; Rajalaxmi et al., 2017), WS (Stackhouse et al., 2007; Arya et al., 2012; Mukhopadhyay et al., 2017; Qi et al., 2018), and endurance (Greve and Colvin, 2021) following NMES. Five studies (Daichman et al., 2003; Kerr et al., 2006; Stackhouse et al., 2007; Khalili and Hajihassanie, 2008; Greve and Colvin, 2021) commented on adherence with 90–100% tolerance for using NMES by individuals participating in these studies. See Table 4 for CDE outcomes and results of each study.

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TABLE 2 Articles reviewed reporting level of evidence, participant characteristics, NMES intervention, and outcomes measures.

Intervention/ Authors (year)	NMES Intervention	Evidence Level	Study Design	Age (years)	Sample Size	GMFCS Level	Limbs	Muscle	NMES Duration (weeks)	Frequency of use (days/ week)	Session duration (min)
Strengthening											
Arya et al. (2012)	Strengthening	2	RCT	7–14	10	-	Bilateral, Unilateral	Quads, TA	4	4–5	20–30
Daichman et al. (2003)	Strengthening, Spasticity Reduction	4	CR	13	1	-	Bilateral	Quads	6	3–4	5–15
Greve and Colvin, 2021)	Strengthening	4	CS	9–15	3	II	Bilateral	Quads	6	7	15–30
Karabay et al. (2015)	Strengthening, Spasticity Reduction	3	PCS	3–14	28	I-V	Bilateral	GS, TA	4	5	30
Kerr et al. (2006)	Strengthening	2	RCT	5–16	60	-	Bilateral	Quads	16	5	60
Khalili and Hajihassanie, 2008	Strengthening, Spasticity Reduction	2	RCT	11–14	11	-	Bilateral	Quads	4	3	30
Mukhopadhyay et al. (2017)	Strengthening	3	PCS	7–14	26	I-III	Bilateral, Unilateral	TA	12	5	30
Nunes et al. (2008) (Nunes et al., 2008)	Strengthening	3	PT	7–15	10	-	Unilateral	TA	7	1–2	30
Qi et al. (2018)	Strengthening	2	RCT	4–9	100	-	-	TA	6	5	20
Rajalaxmi et al. (2017)	Strengthening, Spasticity Reduction	3	PT	5–10	30	-	Bilateral	TA	8	5	15–20
Stackhouse et al. (2007)	Strengthening	3	PS	8–12	11	II-III	Bilateral	Quads, GS	12	3	15/muscle
Armstrong et al. (2020)	Cycling	2	RCT	6–18	21	II-IV	Bilateral, Unilateral	Gluteals, Quads, HS, GS, TA	8	3	30
Johnston and Wainwright, 2011	Cycling	4	CR	49	1	II	Bilateral	Gluteals, Quads, HS, GS	12	3	30
Özen et al. (2021)	Cycling, Spasticity Reduction	2	RCT	4–12	25	I-III	Bilateral	Quads, HS, GS, TA	4	5	30
Gait											
Chan et al. (2004)	Gait	4	SSRD	4–11	12	-	Bilateral, Unilateral	GS	4	3	15
Damiano et al. (2013)	Gait	3	PT	8–19	14	I-II	Bilateral, Unilateral	TA	40	7	360
Gonçalves et al. (2019)	Gait	4	SSRD	4–7	4	I-II	Unilateral	GS	8	3	50
Johnston et al. (2004)	Gait	3	PT	6–12	17	II-IV	Bilateral	Hip Add., Gluteals, Quads, HS, GS, TA	4	5	≤60

(Continued on following page)

TABLE 2 (*Continued*) Articles reviewed reporting level of evidence, participant characteristics, NMES intervention, and outcomes measures.

Intervention/ Authors (year)	NMES Intervention	Evidence Level	Study Design	Age (years)	Sample Size	GMFCS Level	Limbs	Muscle	NMES Duration (weeks)	Frequency of use (days/ week)	Session duration (min)
Pool et al. (2014) (Pool et al., 2014)	Gait	4	SSRD	5–18	12	I-II	Unilateral	TA	8	6	≥60
Pool et al. (2015)	Gait, Spasticity Reduction	2	RCT	5–18	32	I-II	Unilateral	TA	8	6	≥240
Pool et al. (2016)	Gait	2	RCT	5–18	32	I-II	Unilateral	TA	8	6	≥240
Prosser et al. (2012)	Gait	3	PT	7–19	19	I-II	Unilateral	TA	12	6	30–360
Robinson et al. (2015)	Gait	4	CR	57	1	-	Bilateral	HS, TA	6	5	480
van der Linden et al. (2003)	Gait	2	RCT	5–14	22	-	Bilateral, Unilateral	Gluteals	8	6	30–60
van der Linden et al. (2008)	Gait	2	RCT	4–15	14	-	Bilateral, Unilateral	Quads, TA	10	6	60
Spasticity Reduction											
AlAbdulwahab and Al-Gabbani, 2010	Spasticity Reduction	3	RCT	7–12	42	-	Bilateral	Hip Add	1	7	3 × 15
Daichman et al. (2003)	Strengthening, Spasticity Reduction	4	CR	13	1	-	Bilateral	Quads	6	3–4	5–15
Karabay et al. (2015)	Strengthening, Spasticity Reduction	3	PCS	3–14	28	I-V	Bilateral	GS, TA	4	5	30
Khalili and Hajihassanie, (2008)	Strengthening, Spasticity Reduction	2	RCT	11–14	11	-	Bilateral	Quads	4	3	30
Özen et al. (2021) (Özen et al., 2021)	Cycling, Spasticity Reduction	2	RCT	4–12	25	I-III	Bilateral	Quads, HS, GS, TA	4	5	30
Pool et al. (2015)	Gait, Spasticity Reduction	2	RCT	5–18	32	I-II	Unilateral	TA	8	6	≥240
Rajalaxmi et al. (2017)	Strengthening, Spasticity Reduction	3	PT	5–10	30	-	Bilateral	TA	8	5	15–20

Level of Evidence (Howick, 2011).
Study design abbreviations: Case Report (CR) Case Series (CS), Pilot Study (PS), Prospective Trial (PT), Prospective Controlled Study (PCS), Randomized Controlled Trial (RCT), Single Subject Research Design (SSRD).
Muscle abbreviations: Gluteus Maximus and/or Medius (Gluteals), Quadriceps (Quads), Tibialis Anterior (TA), Gastrocnemius & Soleus (GS), Hamstrings (HS).
CDE, outcome measures abbreviations: Refer to Table 1.
Other outcome measure abbreviations: Physiological Cost Index (PCI), Selective Motor Control (SMC), Australian Spasticity Assessment Scale (ASAS), Activities-specific Balance Confidence scale (ABC), Tinetti Performance Oriented Mobility Assessment (POMA).

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TABLE 3 Articles reviewed reporting NMES parameters.

Authors (year)	NMES frequency (Hz)	NMES intensity (mA)	NMES pulse width (μs)	NMES Timing [on/off] (sec)	NMES ramp [up/ Down] (sec)	NMES Waveform	NMES mode
AlAbdulwahab and Al-Gabbani, (2010)	100	Until tingling sensation	250	-	-		Constant
Armstrong et al. (2020)	40–50	Tolerance	200–250	-	-	-	-
Arya et al. (2012)	20–40	Tolerance	200	14/5	3	Biphasic	Alternate
Chan et al. (2004)	30–35	Visible muscle contraction	-	-	-	-	Manually triggered during stance
Daichman et al. (2003)	35	Tetanic contraction	300	10/50	2	-	-
Damiano et al. (2013)	25	-	25–50	-	-	Asymmetric, Biphasic	Timed with gait
Gonçalves et al. (2019)	26–30	17–33	300	-	-	Symmetric	Manually triggered during activities
Greve and Colvin, (2021)	35	9.75–32.5	200–350	5–10/10–30	1–2	Symmetric, Biphasic	Synchronous
Johnston et al. (2004)	20	20	200	2–4/0	1–3	Asymmetric, Biphasic	-
Johnston and Wainwright, (2011)	33	40–80	250	-	-	-	-
Karabay et al. (2015)	25	20–30	250	10/12	-	-	-
Kerr et al. (2006) (Kerr et al., 2006)	35	Tolerance	300	7/12	2/1	-	-
Khalili and Hajihassanie, (2008)	30	Visible muscle contraction	400	4/4	0.5	-	-
Mukhopadhyay et al. (2017)	40	0–30	200	-	-	Biphasic	-
Nunes et al. (2008)	50	28–44	250	5/10	-	-	-
Özen et al. (2021)	30–45	100	250–300	-	7/2	Biphasic	-
Pool et al. (2014)	33	Tolerance	300	-	-	Asymmetric, Biphasic	-
Pool et al. (2015)	33	-	25–100	-	-	Asymmetric, Biphasic	-
Pool et al. (2016)	33	-	25–100	-	-	Asymmetric, Biphasic	-
Prosser et al. (2012)	16.7–33	-	25–300	-	-	Asymmetric, Biphasic	Timed with gait
Qi et al. (2018)	-	Visible muscle contraction	-	-	-	-	Constant
Rajalaxmi et al. (2017)	-	-	-	-	-		-
Robinson et al. (2015)	30–40	Tolerance	200–300	-	-	Symmetric, Biphasic	Timed with gait
Stackhouse et al. (2007)	50	20	5–200	15/45	3		Alternate
van der Linden et al. (2003)	10–30	-	75–100	5/10–15	0.8	Asymmetric, Biphasic	-
van der Linden et al. (2008)	10–40	20–70	3–350	6/10–14	0.8	Asymmetric, Biphasic	Triggered during gait

3.1.2 Neuromuscular electrical stimulation-assisted cycling

Three studies reported NMES-assisted cycling for exercise, where multichannel NMES was applied using surface electrodes while the participant rode an indoor tricycle or stationary bicycle. One case report (Johnston and Wainwright, 2011) and two RCTs (Armstrong et al., 2020; Özen et al., 2021) reported on multichannel NMES used to target multiple muscles during cycling, including the gluteals, quadriceps, hamstrings, gastrocnemius, and/or anterior tibialis. NMES was applied during cycling alone or in addition to interventions, such as ROM, strengthening, and balance.

TABLE 4 Articles reviewed reporting NINDS common data elements (CDE) and other outcome measures.

Authors (year)	CDE Outcome measures	Change in CDE outcome measures relative to control	Other Outcome measures	Change in other outcome measures relative to control
AlAbdulwahab and Al-Gabbani, (2010)	WS	WS ↑ ($p < 0.021$), Step length ↑ ($p < 0.008$)	Visual observations of knee positions	Visual observations of knee positions (improved) ↑
	SAGV	SAGV ↑ (improved)		
	MAS	MAS ↓ (hip adduction spasticity decreased $p < 0.001$)		
Armstrong et al. (2020)	GMFM	GMFM ↑ ($p < 0.001$)	Sit to Stand	
	PEDI-CAT	PEDI-CAT (no change)		
	PEM-CY	PEM-CY (no change)		
	COPM	COPM ↑ ($p < 0.001$)		
Arya et al. (2012)	WS	WS: 7.83 m/min ($p < 0.01$) ↑	Physiological Cost Index (PCI)	PCI: 1.83 ($p < 0.001$) ↓
	SAGV	Cadence: 23.33 steps/m ($p < 0.01$) ↑		EMG (no change)
	GMFM	GMFM (no significant difference)		
Chan et al. (2004)	IGA	GMFM ↑ ($p < 0.003$)	-	-
	GMFM	IGA ↑ (Improved ankle power $p = 0.015$)		
Daichman et al. (2003)	SAGV	SAGV (walking velocity, step length, and cadence) ↑	Range of motion (ROM)	ROM ↑ (popliteal angle decreased from 40 to 35°)
	PEDI	PEDI ↑	Dynamometry	Dynamometry (quads strength ↑ from 16.3 N to 33.7 N)
	MAS	MAS (no significant difference)		
Damiano et al. (2013)	US	TA (US) CSA ↑	-	-
	IGA	IGA (no change)		
Gonçalves et al. (2019) (Gonçalves et al., 2019)	WS	WS ↑, GMFM ↑	-	-
	GMFM			
Greve and Colvin, (2021)	6MWT	6MWT ↑ (above MCID)	-	-
	GMFM	GMFM ↑ (above MCID)		
	FMS	FMS ↑		
Johnston et al. (2004)	SAGV	SAGV (Walking velocity, step length, and cadence ↑ [$p < 0.05$])	ROM	ROM ↑ ($p < 0.05$)
	GMFM	GMFM ↑ ($p < 0.05$)	VO2/kg/m	VO2/kg/m (no change)
Johnston and Wainwright, (2011)	6MWT	6MWT (didn't meet MDC)	ROM	Dynamometry (22% quads and 18.5% HS strength ↑)
	TUG	TUG ↓ (from 11.9 to 9.0 s)	Dynamometry	
	SAGV	SAGV	Bioimpedance monitor	
	COPM	COPM ↑ - barefoot gait speed of 0.09 m/s and in step length of 0.03–0.05 m (likely not clinically meaningful)	McGill-Melzack Pain Questionnaire	
Karabay et al. (2015) (	US	US (CSA) ↑ (TA from 238.7 to 282.0 mm^2, $p < 0.001$; GS from 207.9 to 229.5 mm^2, $p < 0.008$)	ROM	ROM (no change)
	MAS	MAS (no change)		
Kerr et al. (2006)	GMFM	GMFM (no change)	Dynamometer	Dynamometer (no change)
	LAQ	LAS (from LAQ-CP) ↓ (placebo: 39.98, TES: 33.98, $p < 0.05$)		
Khalili and Hajihassanie, (2008)	MAS	MAS ↓ (2.0 compared to 1.2 in the control group, $p = 0.046$)	ROM	ROM ↑ (from 9 to 13°, $p = 0.04$)
Mukhopadhyay et al. (2017)	WS	WS ↑ (17.67%)	PCI	PCI ↓ (19.7%)
	SAGV	SAGV ↑ step length ↑ (4.08%)		
	GMFM	cadence ↑ (16.17%)		
		GMFM ↑ (2.1%)		
Nunes et al. (2008)	GMFM	GMFM ↑ (group 1: from 94.28% to 97.14% $p < 0.05$, group 2: from 95.23% to 98.09% $p < 0.05$)	ROM	ROM ↑ (group 1: active and passive ankle dorsiflexion $p = 0.05$, group 2: passive ankle dorsiflexion $p < 0.05$)
				TA muscle strength of ↑ (manual)

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TABLE 4 (*Continued*) Articles reviewed reporting NINDS common data elements (CDE) and other outcome measures.

Authors (year)	CDE Outcome measures	Change in CDE outcome measures relative to control	Other Outcome measures	Change in other outcome measures relative to control
Özen et al. (2021)	6MWT GMFM	6MWT ↑ GMFM ↑	Visual Gait Analysis	Visual Gait Analysis ↑ (improvement in ankle dorsiflexion and foot contact)
	WeeFIM	WeeFIM ↑		
	MAS	MAS ↓		
	Tardieu Scale	Tardieu Scale ↓		
Pool et al. (2014)	OGS	OGS (no change)	ROM	ROM ↑ ($p < 0.01$)
			Dynamometry	Dynamometry ↑ ($p < 0.01$)
			Australian Spasticity Assessment Scale (ASAS)	ASAS ↓ ($p < 0.01$)
			SMC dorsiflexion grade (Boyd and Graham, 1999)	SMC dorsiflexion grade ↑
				Self-reported Toe Drag ↓ ($p = 0.02$) and Falls ↓ ($p < 0.01$)
Pool et al. (2015)	IGA	IGA ↑:	ASAS	ASAS ↓ (p = 0.038)
	Tardieu Scale	- ankle angle ↑ (mean difference 11.9°, 95% CI 6.8°–17.1°, $p < 0.001$)	Community Balance and Mobility Scale	Community Balance and Mobility Scale ↑ (mean difference 8.3,
		- stance ↑ (mean difference 0.27, 95% CI 0.05–0.49, $p = 0.011$)	4-Square Step Test	95% CI 3.2–13.4; $p < 0.001$),
		- step length ↑ (mean difference 0.06, 95% CI 0.003–0.126, $p = 0.035$)		4-Square Step Test (no significant change, $p = 0.182$),
		Tardieu Scale ↑ (dynamic ankle dorsiflexion range mean difference 6.9°, 95% CI 0.4°–13.6°, $p = 0.035$)		Self-report Toe Drag ($p = 0.002$) and Falls ↓ (toe dragging: $p = 0.002$, falling: $p = 0.022$)
Pool et al. (2016)	MRI	MRI ↑ (TA muscle volume, $p = 0.039$)	Dynamometry	Dynamometry:
	SCALE	SCALE ↑ (mean difference 0.81, 95% CI 0.3–1.32, $p < 0.001$)		- TA strength ↑ ($p = 0.002$)
				- Ankle SMC ↑ (median difference 0.5, IQR 0–1, $p = 0.048$)
Prosser et al. (2012)	IGA	IGA ↑ (mean and peak dorsiflexion during swing and at foot-floor contact)	-	-
		WS (no change)		
Qi et al. (2018)	WS	WS ↑ (0.72 m/s vs. 0.57 m/s, $p < 0.05$)	Comprehensive Spasticity Scale score	Comprehensive Spasticity Scale score ↓ (7.4 vs. 9.4, $p < 0.05$)
	GMFM	GMFM ↑ (71 vs. 58, $p < 0.05$)		
Rajalaxmi et al. (2017)	MAS	MAS ↓ ($p < 0.001$)	ROM	ROM ↑ (AROM of dorsiflexors, $p < 0.001$; PROM, $p < 0.001$)
			Cadence	Cadence ↑
Robinson et al. (2015)	OGS	OGS ↑ (from 12/22 to 19/22 [right], 14/22 to 21/22 [left])	Activity-specific Balance Confidence (ABC) Scale	ABC ↑ (from 32.8% to 48.1%),
			Performance Oriented Mobility Assessment (POMA)	POMA ↑ (from 12/28 to 15/28),
			Dynamic Gait Index	Dynamic Gait Index ↑ (from 6/24 to 14/24)
Stackhouse et al. (2007)	MRI	MRI ↑ (CSA of Quads +4.42 cm^2, $p = 0.023$)	Dynamometry	Dynamometry ↑ (MVIC ↑ from 81.8% to 118.9%, voluntary muscle activation of Quads ↑, +0.057, $p = 0.084$)
	WS	WS ↑ ($p = 0.028$)		
	IGA	IGA		
van der Linden et al. (2003)	IGA	IGA (no change)	Myometer	Myometer ↑ (strength, not significant)
	GMFM	GMFM ↑ (not significant)	ROM	ROM (no change)
			Parent Questionnaire	Parent Questionnaire (64% of the parents thought that the treatment made a difference to their child)
van der Linden et al. (2008)	IGA	IGA ↑ ($p < 0.01$)	Functional Assessment Questionnaire	Functional Assessment Questionnaire
		WS ↓ (0.03 m/s, $p < 0.05$)		

Common data elements (CDE) by the national institute of neurological disorders and stroke (NINDS).

NMES intervention dosage ranged from 30 min, 3–5 times per week for 4–12 weeks.

Three studies using NMES-assisted cycling reported boosting gross motor skills, walking distance, and speed (Johnston and Wainwright, 2011; Armstrong et al., 2020; Özen et al., 2021). Two studies (Armstrong et al., 2020; Özen et al., 2021) reported improvement in gross motor skills assessed with the GMFM. Studies also reported an increase in walking distance assessed with 6MWT (Johnston and Wainwright, 2011; Özen et al., 2021) and speed assessed using the TUG (Johnston and Wainwright, 2011). NMES was well-tolerated in one study (Özen et al., 2021) and variable in two studies (Johnston and Wainwright, 2011; Armstrong et al., 2020). See Tables 2, 3, 4 for details of each study's NMES application and CDE outcomes.

3.2 Neuromuscular electrical stimulation-assisted gait

Table 2 reports the results of NMES-assisted gait, which includes interventions using NMES during gait for treadmill or overground walking with a known therapeutic dosage.

Eleven studies reported NMES-assisted gait for strengthening and improving gait pattern, including one case report (Robinson et al., 2015), three single-subject research design studies (SSRD) (Chan et al., 2004; Pool et al., 2014; Gonçalves et al., 2019), three prospective trials (Johnston et al., 2004; Prosser et al., 2012; Damiano et al., 2013), and four RCTs (Pool et al., 2016; 2015, van der Linden et al., 2003, 2008). Various NMES devices were used, including surface electrodes for non-wearable units targeting the gluteals, quadriceps, gastrocnemius, and tibialis anterior. Wearable units targeted hip adductors, gluteus maximus and medius, quadriceps, tibialis anterior, and gastrocnemius. NMES was applied during walking overground or performing functional task training. Only one study applied NMES while on a treadmill (Chan et al., 2004). NMES dosage ranged from 15 min to 8 h per day, 3–7 days per week for 4–40 weeks. See Table 3 for details of each study's NMES application and parameters.

The eleven studies that investigated NMES-assisted gait found improved muscle structure, strength, SMC, gross motor skills, and gait (van der Linden et al., 2003, 2008; Chan et al., 2004; Johnston et al., 2004; Prosser et al., 2012; Damiano et al., 2013; Pool et al., 2016, 2015, 2014; Robinson et al., 2015; Gonçalves et al., 2019). NMES-assisted gait resulted in increased muscle volume of tibialis anterior as assessed on MRIs (Pool et al., 2016), increased tibialis anterior CSA as assessed on ultrasound (Damiano et al., 2013), increased strength as assessed by dynamometers (Pool et al., 2016, 2014), improved SMC as assessed by SCALE (Pool et al., 2016), improved gross motor skills as assessed by GMFM (van der Linden et al., 2003; Chan et al., 2004; Johnston et al., 2004; Gonçalves et al., 2019), and improved gait as assessed by kinematics, kinetics, and temporal-spatial parameters (Chan et al., 2004; Johnston et al., 2004; van der Linden et al., 2008; Prosser et al., 2012; Pool et al., 2015; Robinson et al., 2015). Compliance was reported to be high for NMES intervention (Chan et al., 2004; Prosser et al., 2012; Pool et al., 2016, 2015). Tolerance was reported as ranging from good (Damiano et al., 2013; Pool et al., 2014) to variable (van der Linden et al., 2003, 2008). See Table 4 for CDE outcome measures and results for each NMES-assisted gait study.

3.3 Neuromuscular electrical stimulation for spasticity reduction

Seven studies reported on the effects of NMES on spasticity. One case report (Daichman et al., 2003), one prospective controlled study (Karabay et al., 2015), one prospective trial (Rajalaxmi et al., 2017), and four RCTs (Khalili and Hajihassanie, 2008; AlAbdulwahab and Al-Gabbani, 2010; Pool et al., 2015; Özen et al., 2021). The targeted muscles for NMES included hip adductors, quadriceps, hamstrings, gastrocnemius, and tibialis anterior. NMES was applied to the antagonist muscle during exercises, including ROM, balance, strengthening, and gait training (Daichman et al., 2003; Khalili and Hajihassanie, 2008; Pool et al., 2015; Rajalaxmi et al., 2017; Özen et al., 2021). TENS was applied to the antagonist muscle during ROM and gait training exercises (AlAbdulwahab and Al-Gabbani, 2010). In addition, NMES-assisted strengthening and NMES-assisted gait were investigated (Pool et al., 2015; Özen et al., 2021). The dosage varied between 5 and 240 min per session, 3–7 days per week for 1–8 weeks.

Among the seven studies of NMES for spasticity reduction, five studies reported reduced spasticity in the antagonistic muscle when using electrical stimulation (Khalili and Hajihassanie, 2008; AlAbdulwahab and Al-Gabbani, 2010; Pool et al., 2015; Rajalaxmi et al., 2017; Özen et al., 2021). Study results included decreased resistance of the hip adductors (AlAbdulwahab and Al-Gabbani, 2010), hamstrings (Khalili and Hajihassanie, 2008; Özen et al., 2021), and gastrocnemius muscles (Pool et al., 2015; Rajalaxmi et al., 2017; Özen et al., 2021) assessed by the Modified Ashworth Scale (MAS) or Tardieu Scale; while two studies found no change in spasticity (Daichman et al., 2003; Karabay et al., 2015). Application and results of NMES-assisted spasticity reduction can be found in Tables 2, 3, 4.

3.4 Additional literature

Our search identified seven studies reviewing NMES as an intervention for individuals with CP, including reviews (Khamis et al., 2018; Wright M. et al., 2012), scoping reviews (Mooney and Rose, 2019; Walhain et al., 2021), and systematic reviews with meta-analysis (Salazar et al., 2019) and without meta-analysis (Chiu and Ada, 2014; Moll et al., 2017). These reviews explicitly focused on the effects of NMES on muscle morphology (Walhain et al., 2021), gait (Mooney and Rose, 2019, p. 2; Wright P. A. et al., 2012), gross motor function (Salazar et al., 2019), ankle dorsiflexion (Moll et al., 2017), activities (Chiu and Ada, 2014), and improvement in gait deviations when using FES (Khamis et al., 2018). None of the listed reviews were specific to our scoping review looking at the NMES application as a lower extremity exercise for individuals with spastic CP.

4 Discussion

The findings of this scoping review indicate that NMES applied to strengthening exercise, gait, and spasticity reduction demonstrate potential benefits for improving muscle physiology, neuromuscular impairments, gait patterns, and functional mobility in individuals with spastic CP. The twenty-six intervention publications, dating from 2003 to 2021, included a total of 558 individuals aged 3–57 years with CP, GMFCS levels I-IV with unilateral or bilateral involvement. The dosage of NMES intervention varied by study, as noted in Table 2. In addition, while using NMES, the exercise activities varied and included ROM, strengthening (i.e., isometric contractions, progressive resistance exercises, cycling), positioning, functional tasks, and gait. NMES included both wearable and non-wearable devices with surface electrodes, with the exception of two studies that utilized implanted electrodes (Johnston et al., 2004; Stackhouse et al., 2007).

The NMES parameters utilized in these studies included frequencies between 10 and 50 Hz, stimulation intensities between 4 and 100 mA, with typical values below 40 mA, and pulse width between 3 and 350 μs, as shown in Table 3. The most substantial variation was in pulse width, which could be attributed to individual preferences and tolerances and to the sequence of adjusting NMES parameters during treatment. Although pulse width affects muscle force production, currently, there is no evidence suggesting the range of optimal pulse width, therefore, more studies are needed. Clinical experience suggests that electrode size and adherence to the skin and pulse width contribute most to NMES comfort level.

4.1 Neuromuscular electrical stimulation-assisted strengthening

NMES-assisted strengthening was found to increase strength, WS, walking distance, gross motor skills, and functional mobility. Three studies reported that NMES applied during exercise provided better outcomes than exercise alone (Khalili and Hajihassanie, 2008; Arya et al., 2012; Qi et al., 2018). This may be attributed to increased sensory attention to task and motor learning. Weaker muscles are likely to gain more from NMES strengthening than stronger muscles. Physical therapy, as well as surgical preparation and recovery, provide opportunities to initiate NMES strengthening of weakened muscles. Clinical expertise suggests that voluntary contraction is an important element of strengthening and motor control versus NMES stimulation alone. The results of this scoping review found further evidence that supports the use of NMES-assisted strengthening as a clinical treatment for individuals with spastic CP. Future studies need to study the impact of NMES-assisted strengthening on biological aspects of muscle physiology and chronic health conditions in individuals with spastic CP.

Another benefit to muscle strengthening is increasing overall muscle-tendon length across the joint, which may improve ROM (Zhou et al., 2017). Increasing muscle fiber diameter through strengthening theoretically increases overall muscle-tendon length due to the diagonal muscle fiber pennation angle relative to the axis of the bone (Zhou et al., 2017). Several studies identified that muscle CSA was increased with NMES-assisted strengthening, which likely would translate to increased overall muscle-tendon length and improved ROM (Stackhouse et al., 2007; Karabay et al., 2015). Future studies need to examine the impact of NMES-assisted strengthening on overall muscle-tendon length and joint ROM.

4.2 Neuromuscular electrical stimulation-assisted gait

NMES-assisted gait was found to improve strength, motor control, gait pattern, and temporal-spatial parameters. Similar to NMES-assisted strengthening, the repetitive movement of walking on a treadmill combined with NMES was found to have an advantage over treadmill gait or NMES alone for improving ankle power and gross motor skills of standing and walking (Chan et al., 2004). Furthermore, another study suggested that intensive use of NMES-assisted gait in home and community settings may facilitate motor learning (Pool et al., 2014). The results of this scoping review further strengthens the evidence to support NMES-assisted gait as a clinical treatment for individuals with spastic CP. Wearable single-channel NMES units are widely available and allow for home and community use to improve foot clearance in swing; however wearable multi-channel units are not widely available. Wearable multi-channel units are needed to treat gait abnormalities other than limited foot clearance in swing. Further research and development are needed in this area.

4.3 Neuromuscular electrical stimulation for spasticity reduction

NMES was also found to reduce spasticity, as assessed by Tardieu or MAS in five of seven studies reviewed; one study used

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TENS (AlAbdulwahab and Al-Gabbani, 2010), and four studies used NMES (Khalili and Hajihassanie, 2008; Pool et al., 2015; Rajalaxmi et al., 2017; Özen et al., 2021). Corticospinal tract injury results in a loss of descending neural signal activation and inhibition. Muscle spasticity is a neuromuscular impairment that results from loss of inhibition. Further research needs to investigate the potential inhibitory effects of NMES and how to optimize spasticity reduction and duration of treatment effects. The location of ideal electrode placement along the lumbar spine, over relevant dermatomes, directly over spastic muscle, or to elicit antagonist inhibition requires further research.

4.4 Limitations and future research

Limitations of this scoping review include the exclusion of some NMES-related studies that did not meet inclusion criteria due to NMES treatment duration of fewer than 4 weeks, the absence of an exercise component, technology development trials for NMES-assisted gait on a treadmill (Zahradka et al., 2021) or robotics (Shideler et al., 2020). These limitations may have eliminated some evidence in the field. However, with respect to treatment duration, a recent publication recommended at least 8–20 weeks of exercise training to facilitate meaningful changes in muscle structure and improve function in individuals with CP (Moreau and Lieber, 2022). This suggests that 8–20 weeks of exercise duration may be required, and therefore, it is possible that some of the studies in our review lacked the proper dosage to produce a meaningful change. While 11 out of 26 studies in this scoping review were RCTs, further studies with larger sample sizes and more consistent protocols using CDE outcome measures are needed to move the field forward.

This scoping review indicates that further research is needed to determine optimal NMES protocols and dosage using sensitive CDE outcome measures. Furthermore, device development of wearable NMES units that can be easily applied for NMES-assisted strengthening, gait, and spasticity reduction is needed for individuals with spastic CP. Understanding the relationship between NMES strength training and functional results, as well as the optimal NMES protocol and dosage, requires research with a larger sample size and longer treatment duration (i.e., 8–20 weeks). Identifying changes in neuromuscular impairments of weakness, short-muscle tendon unit, spasticity, and impaired SMC as well as motor learning, and utilizing CDEs with careful attention to minimal clinically important differences will allow us to better comprehend the therapeutic effects of NMES. Finally, advancing new NMES technology, such as wireless multichannel NMES devices and hybrid robotic and exoskeleton NMES systems, will provide evidence-based, clinically feasible interventions for individuals with CP to improve functional mobility.

5 Conclusion

Findings from this scoping review provide evidence that supports the use of NMES-assisted strengthening with therapeutic exercise and cycling, NMES-assisted gait, and NMES for spasticity reduction to improve mobility in individuals with spastic CP, based on validated CDE outcome measures. Wearable and non-wearable units were utilized with surface or implanted electrodes targeting the gluteals, hip adductors, hamstrings, quadriceps, gastrocnemius, and tibialis anterior to augment exercise and mobility. NMES was found to improve muscle structure, strength, gross motor skills, gait kinematics, WS, and walking distance and reduce spasticity. Clinicians can consider NMES to be an effective treatment for individuals with spastic CP. Additional research is needed to further investigate optimal parameters, dosage, and impact of NMES on neuromuscular impairments and functional mobility in individuals with spastic CP.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Progressive resistance training for children with cerebral palsy: A randomized controlled trial evaluating the effects on muscle strength and morphology

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Children with spastic cerebral palsy often present with muscle weakness, resulting from neural impairments and muscular alterations. While progressive resistance training (PRT) improves muscle weakness, the effects on muscle morphology remain inconclusive. This investigation evaluated the effects of a PRT program on lower limb muscle strength, morphology and gross motor function. Forty-nine children with spastic cerebral palsy were randomized by minimization. The intervention group (nparticipants = 26, age: 8.3 ± 2.0 years, Gross Motor Function Classification System [GMFCS] level I/II/III: 17/5/4, nlegs = 41) received a 12-week PRT program, consisting of 3-4 sessions per week, with exercises performed in 3 sets of 10 repetitions, aiming at 60%–80% of the 1-repetition maximum. Training sessions were performed under supervision with the physiotherapist and at home. The control group (nparticipants = 22, age: 8.5 ± 2.1 year, GMFCS level I/II/III: 14/5/3, nlegs = 36) continued usual care including regular physiotherapy and use of orthotics. We assessed pre- and post-training knee extension, knee flexion and plantar flexion isometric strength, rectus femoris, semitendinosus and medial gastrocnemius muscle morphology, as well as functional strength, gross motor function and walking capacity. Data processing was performed blinded. Linear mixed models were applied to evaluate the difference in evolution over time between the control and intervention group (interaction-effect) and within each group (time-effect). The α-level was set at $p = 0.01$. Knee flexion strength and unilateral heel raises showed a significant interaction-effect ($p \leq 0.008$), with improvements in the intervention group ($p \leq 0.001$). Moreover, significant time-effects were seen for knee extension and plantar flexion isometric strength, rectus femoris and medial gastrocnemius MV, sit-to-stand and lateral step-up in the intervention group ($p \leq 0.004$). Echo-intensity, muscle lengths and gross motor function showed limited to no changes. PRT improved strength and MV in the intervention group, whereby strength parameters significantly or close to significantly differed from the control group. Although, relative improvements in strength were larger than improvements in MV, important effects were seen on the maintenance of muscle size relative to skeletal growth. In conclusion, this study proved the effectiveness of a home-based, physiotherapy supervised, PRT program to improve isometric and functional muscle strength in children with SCP without negative effects on muscle properties or any serious adverse events.

Clinical Trial Registration: ClinicalTrials.gov, identifier NCT03863197.

KEYWORDS

spastic cerebral palsy, progressive resistance training, muscle morphology, lower extremity, isometric muscle strength, functional muscle strength, ultrasonography

1 Introduction

Cerebral palsy (CP) is one of the main causes of childhood-onset physical disability (Rosenbaum et al., 2007). When classified according to neuromuscular presentation, spastic CP (SCP) is the largest subcategory, whereas a topographical classification further divides SCP in unilateral and bilateral involvement (Surveillance of Cerebral Palsy in Europe, 2002). CP is caused by an injury in the developing brain and the primary neuromotor symptoms are related to upper motor neuron damage, including muscle weakness, spasticity, reduced selective motor control (SMC), and a lack of balance and coordination (Graham et al., 2016). These neuromotor symptoms can lead to secondary musculoskeletal symptoms like reduced joint range of motion, altered muscle growth and bony deformities, which may further influence muscle weakness (Graham et al., 2016). Altogether, these neuromotor symptoms lead to limitations in activities and participation (Rosenbaum et al., 2007).

The initial brain injury in children with SCP leads to an altered neural drive to skeletal muscles and subsequent alterations in movement and muscle activation patterns (Clowry, 2007; Gough and Shortland, 2012). Consequently, skeletal muscle tissue of children with SCP shows a lack of both longitudinal and cross-sectional fiber growth starting in the postnatal period and evolving into childhood (Handsfield et al., 2016; Herskind et al., 2016; Willerslev-Olsen et al., 2018). Decreased muscle size is reported both in proxy measures of fiber width like anatomical CSA, muscle thickness and muscle volume (MV) (Moreau et al., 2010; Noble et al., 2014b; Handsfield et al., 2016; Schless et al., 2017; Hanssen et al., 2021), as well as in proxy measures of fiber length like muscle length (ML) and fascicle length (Matthiasdottir et al., 2014; Schless et al., 2017; Hanssen et al., 2021). Additionally, the quality of muscle tissue is reduced due to increases in fatty and fibrillar tissue in the muscle, resulting in an increased proportion of the MV comprising non-contractile material (Noble et al., 2014a; Pitcher et al., 2015; Obst et al., 2017; Schless et al., 2019).

Muscle morphology has been considered as the primary determinant of force production and the combination of reduced muscle size and quality leads to muscle weakness in children with SCP (Lieber and Friden, 2000). However, while general decreases in muscle size of 18%–50% have been described in ambulant children with SCP (Moreau et al., 2010; Noble et al., 2014b; Handsfield et al., 2016; Schless et al., 2017; Massaad et al., 2019; Hanssen et al., 2021), muscle weakness was found to be more profoundly present, specifically in lower limb muscles, with deficits up to 80% (Wiley and Damiano, 1998; Goudriaan et al., 2018; Darras et al., 2021; Hanssen et al., 2021). We recently showed that the contribution of this decreased muscle size to muscle weakness was 23%–57% for muscle groups around the knee and ankle joint, however, with high variability between children (Hanssen et al., 2021). The remaining part of muscle weakness may result from other muscular changes not directly reflected in muscle size, such as altered fascicle length and pennation angle, as well as from the neural ability to fully recruit motor units and selectively activate the muscle. In children with SCP, the latter presents as an inability to maximally activate agonists and an increased antagonist co-contraction (Elder et al., 2003; Mockford and Caulton, 2010).

Since skeletal muscle tissue is adaptive to mechanical load, one of the best treatment options for muscle weakness is progressive resistance training (PRT) (Faigenbaum and Myer, 2010). Initial strength improvements through PRT result from neural adaptations (Sale, 1988; Tesch, 1988), but PRT can eventually elicit significant adaptations in muscle mass in healthy adults, also referred to as muscle hypertrophy (Franchi et al., 2014; Schoenfeld et al., 2017a). Training results are influenced by the manipulation of training variables (American College of Sports Medicine, 2009), and the recommendations for pediatric training variables focusing on muscle strength include a frequency of 2–3 times per week, with 1-3 sets, using loads that correspond to a repetition range of a

6–15 repetition maximum with qualified instruction and close supervision (Faigenbaum and Myer, 2010; Lloyd et al., 2014).

The effects of PRT have been extensively studied in the SCP population. Recent reviews indicated positive effects of PRT on muscle weakness, however the results on gross motor function and gait speed remain inconclusive (Ryan et al., 2017; Liang et al., 2021; Merino-Andrés et al., 2021). Moreover, the quality of evidence is often rated as low to very low (Ryan et al., 2017). The studies evaluating the underlying mechanisms to increased muscle strength, focusing on muscle morphology, are rather limited. A review by Gillett et al. (2016) found 6 studies showing preliminary evidence that PRT leads to muscle hypertrophy in children and adolescents with CP (Gillett et al., 2016). However, two recent investigations indicated limited to no effects on muscle size outcomes after PRT in children and adolescents with CP (Kruse et al., 2019; Ryan et al., 2020) and an additional review also reported inconsistent evidence with only low-to-moderate quality investigations (Walhain et al., 2020). On the other hand, in young adults, aged 15–30 years, significant increases in plantar flexor MV have been found after 12 weeks of combined anaerobic and strength training (Gillett et al., 2018), and Cho and Lee (2020) reported an increased rectus femoris CSA and quadriceps thickness in young children with SCP after 6 weeks of functional PRT. It remains challenging to generalize these findings, due to the lack of robust designs and variation in included age range, the type of training used, the duration of the training program, the muscle group(s) trained, the assessments used for muscle strength and size, and the training location (Gillett et al., 2016; Walhain et al., 2020; Moreau and Lieber, 2022).

Previous investigations used prospective cohort studies or randomized controlled trials (RCTs) comparing 2 different exercise intervention programs with each other, without a usual care control group (Stackhouse et al., 2007; McNee et al., 2009; Moreau et al., 2013; Williams et al., 2013; Lee et al., 2015; Kruse et al., 2019). So far, 3 RCTs have been performed comparing the effects of PRT with a usual care control group assessed at identical time points, 2 in adolescents and young adults focusing on the plantar flexors (Gillett et al., 2018; Ryan et al., 2020) and 1 in children focusing solely on the knee extensors (Cho and Lee, 2020). One of these RCTs in adolescents found no effects of PRT, in contrast to the other 2 (Ryan et al., 2020). Assessing the effects of PRT on muscle strength, size and function, next to a usual care control group, for several muscle groups, will improve our understanding of the adaptive potential of skeletal muscle in children with SCP and the mechanisms underpinning strength or functional improvements.

Therefore, the primary goal of this investigation was to evaluate the effects of a 12-week PRT program on muscle strength and muscle size of the lower limbs in children with SCP, in comparison to a usual care control group. Secondary, the effects on muscle length and quality, as well as on gross motor function and walking capacity, were assessed. We hypothesized an increase in isometric strength and MV in the intervention group compared to the control group, with unchanged intrinsic muscle quality in both groups. With part of the strength increases resulting from neural adaptations, the increases in muscle strength were expected to be larger than the increases in muscle size. We further expected ML to increase similarly in both groups due to general growth, and improved functional strength in the intervention group, whilst gross motor function and walking capacity were expected to remain unchanged.

2 Materials and methods

A waitlist RCT was conducted to define the effects of a PRT program for the knee extensor, knee flexor and plantar flexor muscle groups. A minimization technique was used to divide participants in an intervention group, performing a 12-week PRT program and a waitlist control group, continuing usual care for 12 weeks first. The data of the waitlist control group were only included as control data, the results of the delayed intervention have not been included because this was out of the scope of the current investigation.

2.1 Participants

Participants were recruited across Flanders in Belgium, through the CP reference center of the University Hospitals Leuven, pediatric physiotherapists, and special needs schools between August 2018 and February 2021. Written informed consent was obtained from the children's parents or legal guardian prior to the first assessment. The study was registered at Clinicaltrials.gov (NCT03863197) and was approved by local medical ethical committees of University Hospitals Leuven (s59945) and Ghent (EC/2017/0526). The inclusion criteria for participation were 1) a diagnosis of SCP, 2) age at baseline between 5 and 11 years and 3) level of I, II or III on the gross motor function classification system (GMFCS) (Palisano et al., 2008). Exclusion criteria were 1) botulinum neuro-toxin A injections and/or lower leg casts in the past 6 months, 2) lower limb bony surgery in the past 2 years, 3) lower limb muscular surgery or selective dorsal rhizotomy at any time point, 4) inability to communicate in Dutch or English and 5) inability to understand instructions and cooperate during assessments and training.

2.2 Study design

After enrollment and prior to the first assessment, participants were assigned to the intervention or the control group through randomization by minimization. MinimPy was used to randomize the participants based on age (2 levels:

<8 years and >8 years) and GMFCS score (3 levels: I, II and III) (Saghaei and Saghaei, 2011). The allocation ratio was 1:1 and probability was set at 0.75. The biased coin minimization was used as probability method and marginal balance as distance measure. The global Covid-19 pandemic led to a forced stop of the investigation in March 2020, with recommencement after several months. Since drop-outs could not be administered in MinimPy, group assignment after recommencement was performed manually by an independent researcher to prevent skewness in the balance of the 2 groups, whereby the same minimization procedure, based on age and GMFCS level, was applied.

Assessments were planned in the University Hospitals and special needs schools, at baseline (PRE) and after the 12-week control or intervention period (POST). Training and assessments were always conducted on different days. Participants in the intervention group started training within 2 weeks after the baseline assessment. For both groups, the POST assessments were performed within 1 week after the 12-week period. Blinding was not completely possible since participants and trainers were aware of group allocation. Assessors were aware of group allocation during assessments but data was anonymized before processing and analyses. The participants were PRE and POST assessed by the same assessors and PRE and POST data was processed by the same processer.

Before the start of the trial, piloting for the feasibility of the measurements and parameter extraction was done through prior and parallel investigations. The exercises used during the training were piloted through iterations with strength and conditioning specialists to ensure correct exercise selection and also with senior pediatric physiotherapists and their patients to ensure the applicability in the targeted population of children with SCP.

2.3 Sample size

At trial commencement in 2018, no data were available on an RCT investigating changes in muscle size after PRT in a population of children with SCP. Therefore, effect sizes (d) of systematic reviews and meta-analyses reporting muscle strength outcomes after PRT were used. Reported effect sizes were moderate (d = 0.53) (Ryan et al., 2017) and large (d = 1.050 and d = 1.105) (Park and Kim, 2014). Based on a large effect size of d = 0.8 with the probability of making a type I error set equal to or less than 1% ($p \leq 0.01$) and a power of 80% an independent samples t-test with common standard deviation required 39 independent observations per group to compare the evolution over time between the intervention and control groups. To account for the possibility of clustered legs in bilaterally affected participants a design effect (Killip et al., 2004) was calculated resulting in an estimated sample size of clustered observations per group with following formulas:

$$Design\ effect = 1 + \rho * (m - 1)$$

where ρ is the intraclass correlation and m the cluster size, and,

$$\begin{aligned} Estimated\ sample\ size\ of\ clustered\ legs &= estimated\ sample\ size\ of\ independent \\ &\quad observations * design\ effect \\ &= m * number\ of\ participants. \end{aligned}$$

With a cluster size of m = 2 (2 legs per bilaterally affected participant) and an intraclass correlation coefficient of $\rho = 0.1$, based on literature of general health parameters (Adams et al., 2004), the estimated design effect was 1.1, resulting in 43 clustered legs, or 22 bilaterally affected participants per group. A group including both uni- and bilaterally affected children would require a sample size between 39 and 43.

2.4 Intervention

Participants assigned to the control group continued their usual care. Participants assigned to the intervention group undertook 3 or 4 PRT sessions per week (alternating), on non-consecutive days, for 12 weeks, resulting in a total of 42 scheduled sessions. The PRT program was explained during a visit to the physiotherapist(s) and parent(s). After a familiarization phase of up to 3 sessions, the official PRT started. At least 1, but up to 3, sessions per week were performed under the supervision of the physiotherapist(s). The remaining sessions were completed at home under the supervision of a parent or guardian. The patient-specific PRT program was created and communicated through the online software platform Skill-Up (www.Skill-up.com) and each PRT session was logged in a training diary. Throughout the 12-week period, the PRT program was supervised through phone calls, e-mails, and targeted visits to check adherence and progress exercises by trainers with a background in human movement sciences (BH and NP). Participants in the intervention group were invited for an interim assessment after 6 weeks, which was also used as an additional moment to evaluate and adjust the intensity of the training program. The results of this interim assessment are not included in the current study.

The PRT program, targeting strength and hypertrophy of knee extensors, knee flexors and plantar flexors, was prescribed in close consultation with the personal physiotherapist(s) to ensure feasibility for each participant. It was recommended to begin the sessions with a 5-min dynamic warm-up and end with a 5-min cool-down. Depending on the participants' abilities, the PRT started with 1-3 functional multi-joint exercises, followed by 2-3 single-joint exercises targeting the specific muscle groups, all performed without orthotics. Examples of used exercises are presented in Supplementary Table S1. Following international guidelines for youth resistance training of the National Strength and Conditioning Association, as well as CP-specific recommendations, the initial exercises started at a training volume of 3 sets of 10 repetitions, aiming at an exercise intensity of 60%–80% of the estimated 1-repetition maximum, with a rest period in between sets of at least 1 min (Faigenbaum et al., 2009; Verschuren et al., 2011; Lloyd et al., 2014; Verschuren et al., 2016). The most difficult exercise that could be performed, with the maximal load that could be lifted, for the defined number of repetitions and sets was defined through trial and error (Moreau, 2020). Throughout the training program, exercise difficulty was increased. Thereto, physiotherapists were encouraged to regularly test the difficulty of the exercises, i.e., at least biweekly, by asking a maximum performance in the last set, based on exercise execution and fatigue. The intensity was modified by the trainers or the physiotherapist(s) if the last set exceeded 15 well-executed repetitions. Exercise modification options were, depending on the exercise, addition of weight in a weighted vest (0.5 kg increments up to 10 kg), use of a stronger resistance band (5 colors ranging from light to very heavy), increase of ankle weight (1.0, 1.5, or 2.0 kg), or selection of a more challenging exercise. The number of sets and repetitions performed, modifications or compensations, perceived fatigue at the end of the session and potential adverse events were noted in the training diary.

2.5 Assessments and outcome measures

2.5.1 Participant characteristics

Age, body mass and height were recorded for the participants at the PRE- and POST-assessment. Usual care and treatment history were requested at the PRE-assessment using standardized in-house questionnaires. A routine clinical examination regarding the investigated muscle groups was performed, including passive joint range of motion, spasticity, manual muscle testing and SMC, based on standard clinical scales (Matthews, 1977; Bohannon and Smith, 1987; Boyd, 1999; Gage et al., 2009). These clinical examination parameters were used to define the most affected leg for bilaterally affected children. If both sides were equally affected, the right leg was used. Lower limb SMC was assessed with the selective control assessment of the lower extremity total limb score (Fowler et al., 2009). Assessments were commonly performed in the same order, starting with clinical examination and muscle morphology, followed by isometric and functional strength and lastly gross motor function and walking capacity. In some exceptions, such as time and space limitations when assessing in schools, this order could be modified. An overview of the clinimetric properties of each assessment can be found in Supplementary Table S2.

2.5.2 Isometric strength assessments

Knee extensor, knee flexor and plantar flexor maximum voluntary isometric contractions were collected with a fixed dynamometer in a previously described, custom-designed chair (Goudriaan et al., 2018; Verreydt et al., 2022). The dynamometer was positioned at 75% of the lower leg and foot length, and the lever arm distance was measured between this position and the joint axis. After a test trial, the aim was to collect 3 well executed maximum voluntary isometric contractions with a duration of 3–5 s. Standardized verbal encouragement and visual feedback were provided throughout the isometric contraction. The protocol included periods of rests of at least 10 s between repeated assessments and of at least 2 min between different muscle groups. Peak force was extracted from each trial with a custom-written MATLAB script and maximal joint torque (in Nm) was calculated by multiplying peak force with the lever arm and taking the average of the 3 trials. Knee and plantar flexion maximal voluntary isometric contractions were corrected for gravity by subtracting the gravitational torque in rest from the outcomes. Maximal joint torque was divided by body weight to obtain normalized maximal joint torque (Nm/kg).

2.5.3 Three-dimensional freehand ultrasonography

A previously described (Hanssen et al., 2021) and validated (Cenni et al., 2016) 3-dimensional (3-D) freehand ultrasonography technique was used to evaluate muscle morphology, combining a 2-dimensional B-mode ultrasonography device (Telemed-Echoblaster 128 Ext-1Z, with a 5.9 cm 10 MHz linear ultrasound transducer, Telemed, Ltd., Lithuania) with a motion tracking system (Optitrack V120:Trio, NaturalPoint, Inc., Corvallis, Oregon, United States). Ultrasound settings were kept constant throughout the study period at a frequency of 8 MHz, with a focus of 3 cm, a gain of 64%, a dynamic range of 56 dB and unaltered time-gain compensation. Depth could vary between 5 and 7 cm, adjusted to muscle size. The m. rectus femoris was scanned in supine position with a triangular cushion underneath the calf, providing approximately 25 degrees of knee and hip flexion. The m. semitendinosus and m. medial gastrocnemius were scanned in prone position with a triangular cushion underneath the shank, providing 25 degrees of knee flexion and an unconstrained ankle angle. STRADWIN software (version 6.0; Mechanical Engineering, Cambridge University, Cambridge, United Kingdom) was used for data acquisition, generation of 3-D datasets, and data processing. Experienced processers drew equally spaced transverse plane segmentations throughout the 3-D datasets, which were interpolated with an automatic cubic planimetry technique resulting in the MV (in mL) (Treece et al., 1999). ML (in mm) was defined by calculating the linear distance between muscle origin and muscle tendon junction. Both MV and ML were normalized to fibula length to correct for skeletal growth (mL/cm and cm/cm). The echo-intensity (EI) from ultrasound images was used as an indication of intrinsic muscle quality, with higher EI-values representing an increased ratio of non-contractile vs. contractile tissue (Pitcher et al., 2015; Young et al., 2015). EI (expressed in arbitrary units) was computed as the average value throughout the interpolated reconstruction of the muscle.

2.5.4 Functional strength assessments

Endurance functional strength was assessed with 30-s maximum repetition tests including bi- and unilateral heel raise, sit-to-stand, and lateral step-up, as previously described (Van Tittelboom et al., 2021). Participants completed as many repetitions as possible in 30 s. Each test was repeated 2 to 3 times and the average was taken as final score. Explosive strength was evaluated with a standing long jump, with both feet together, which was also repeated 3 times and the scores were averaged. The use of orthoses was not allowed, as the PRT program was also performed without orthoses.

2.5.5 Gross motor function and walking capacity

Gross motor function was evaluated with the Gross Motor Function Measure-Item Set (Brunton and Bartlett, 2011) and the Gross Motor Ability Estimator 2 was used to estimate the final score. The 1-min walk test, performed on an indoor 20-m track, was used to assess walking capacity (McDowell et al., 2009; Chrysagis et al., 2014). The participant was instructed to walk as fast as possible without running and the distance covered in 1 min was recorded. Both assessments were performed without orthoses, but a kay-walker was allowed for the 1-min walk test for children classified as GMFCS-level III.

2.6 Statistics

Descriptive statistics for each group were summarized using means and standard deviations. Linear mixed models were applied to evaluate the difference in evolution over time between the control and intervention group (time*group interaction-effect) and between PRE and POST within each group (time-effect). The random effects in these models can correct for the correlation between repeated observations within the same subject. Moreover, in the case of missing values that are completely at random or at random, linear mixed models provide valid inferences for missing observations. A covariance structure for repeated measurements to model longitudinal dependencies within the participant was applied with a random intercept for participant (legs are nested within participants). A full-factorial time*group mean model adjusted for age and GMFCS level, with a compound symmetry covariance matrix was used, unless an unstructured covariance matrix resulted in a better fit (Akaike information criterion decrease of >2). Adjustment for age (categorical variable: <8 years and >8 years) and GMFCS level was included as these were used to allocate the children to the control or intervention group. The primary analyses were performed on all affected legs of all participants (both legs of bilateral affected children and the affected leg of unilateral affected children), also including available data of participants who dropped out. To determine if the inclusion of all affected legs, the change in randomization from program-driven to manual and the participants who dropped out influenced the results, sensitivity analyses were performed on the most affected legs of the participants that were originally randomized before onset of the pandemic as well as on the most affected legs of the participants who participated in the POST assessments after the intervention or control period. The α-level was adjusted to $p \leq 0.01$ since multiple parameters were evaluated for most research questions, with a maximum of 5 parameters (functional strength). All analyses were performed with SPSS (Version 28, SPSS Inc., Chicago, Illinois). The mean difference scores were compared with the known standard error of measurements and minimal detectable changes as presented in Supplementary Table S2. Presented relative changes indicate the mean difference as a percentage of the baseline values. There were some missing data due to 3DfUS reconstructions that could not be (fully) analyzed because of technical errors, isometric and functional strength tests that could not be assessed due to inability of the participant and missing anthropometric information.

3 Results

3.1 Participants

The participant flow chart for recruitment, allocation and drop-out, following CONSORT guidelines, is presented in Figure 1. Eventually, 49 children participated in this investigation, of whom 41 were randomized by minimization in the MinimPy software and 8 were added after the enforced stop due to Covid-19 pandemic in March 2020. The main reasons for refusal to participate in the study were time and distance constraints or the child being in a challenging period regarding school or home situation. Initially, 20 children were allocated to the control group, of whom 17 completed the POST-assessments. Twenty-one children were allocated to the intervention group, and 15 completed the intervention and participated in the POST-assessments. Of the 8 additional children included post Covid-19 regulations, 2 were manually allocated to the control group and 6 to the intervention group, with a drop-out of 2 children in the latter. Drop-outs in the control group were due to: 1) inability to perform the POST-assessments in time due to medical reasons ($n = 1$); 2) a clinically prescribed botulinum neurotoxin-A injection during the control period ($n = 1$) and 3) Covid-19 regulations ($n = 1$). Drop-outs in the intervention group were due to 1) a lack of cooperation during the assessments ($n = 1$); 2) cancellation of appointments due to Covid, eventually leading to loss of contact ($n = 1$); 3) a clinically prescribed botulinum neurotoxin-A injection during the intervention period ($n = 1$); 4) Covid-19 regulations ($n = 3$).

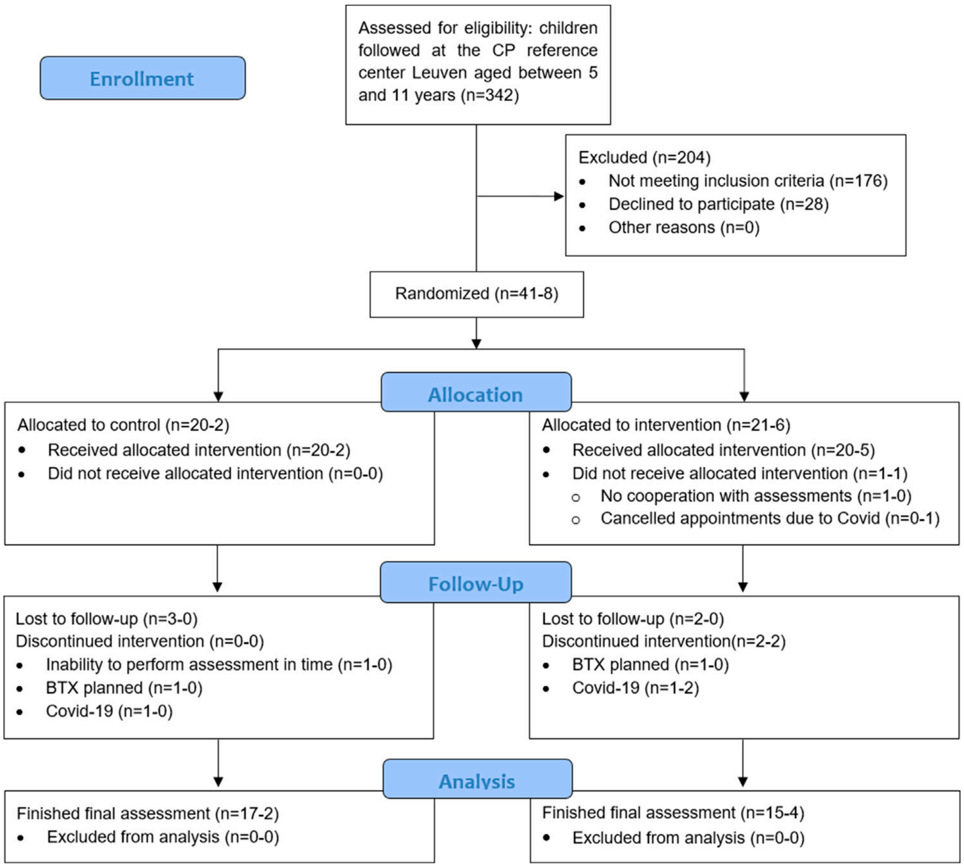

FIGURE 1
All children aged 5–11 years old were extracted from the clinical database of the CP reference center Leuven (*n* = 342) and screened based on gross motor function classification system level and type of CP. The scheduled appointments at the children's hospital and gait laboratory were monthly checked to further screen potential participants based on the exclusion criteria (±10% eligible every month, part of the *n* = 342). Additionally, pediatric physiotherapists at private practices and special needs schools were consulted for potential participants resulting in 6 of the 49 participants not being followed up in Leuven. The first number, before the hyphen, represents the participants that were randomized by minimization by Minim-Py before the forced stop of the study due to the global Covid-19 pandemic, the number after the hyphen represents the participants who were manually minimized afterwards.
*Included in primary analyses: control group=22 and intervention group=26 (1 randomized child did not participate in baseline assessments).
Included in sensitivity analyses:
- Randomized: control group=20 and intervention group=20 (1 randomized child did not participate in baseline assessments).
- Finished: control group=19 and intervention group = 19.

BTX, botulinum neurotoxin type A; CP, cerebral palsy.

Patient characteristics for the primary analyses on all affected legs of all participants in both groups are presented in Table 1, and for both sensitivity analyses in Supplementary Table S3. At baseline the control group (n = 22) had an average age 8.5 ± 2.1 years, with a weight of 28.3 ± 7.1 kg and a height of 128.6 ± 11.2 cm. In this group 14 children were classified as GMFCS level I, 5 as GMFCS level II and 3 as GMFCS level 3. Eight children were unilaterally affected and 14 bilaterally, resulting in 36 assessed legs. Average fibula length of all assessed legs was 27.6 ± 3.5 cm and selective control assessment of the lower limb score was 7.1 ± 2.6. For the intervention group (n = 26) the average age was 8.3 ± 2.0 years, with an average weight of 27.7 ± 8.1 kg and 127.3 ± 14.0 cm. Seventeen children were classified as GMFCS level I, 5 as GMFCS level II and 4 as GMFCS level 3. Eleven children were unilaterally affected and 15 bilaterally, resulting in 41 assessed legs. Fibula length was on average 27.3 ± 3.6 cm and the selective control assessment of the lower limb score was 7.0 ± 2.1. One participant was randomized but never assessed due to repeated cancellations, therefore the total number of participants in the primary analyses is 48 ($n_{participants}$ = 48, $n_{affected\ legs}$ = 77).

TABLE 1 Descriptive statistics of patient characteristics for all participants (or legs) included in the primary analyses.

	CON (n=22)	INT (n=26)
	Frequencies (%)	Frequencies (%)
GMFCS		
Level I	14 (63.6)	17 (65.4)
Level II	5 (22.7)	5 (19.2)
Level III	3 (13.6)	4 (15.4)
Age group		
<8 years	11 (50.0)	12 (46.2)
>8 years	11 (50.0)	14 (53.8)
Involvement		
Unilateral	8 (36.4)	11 (42.3)
Bilateral	14 (63.6)	15 (57.7)
Gender		
Boy	16 (72.7)	14 (53.8)
Girl	6 (27.3)	12 (46.2)
	Mean ± SD	Mean ± SD
Age (years)	8.5 ± 2.1	8.3 ± 2.0
Weight (kg)	28.3 ± 7.1	27.7 ± 8.1
Height (cm)	128.6 ± 11.2	127.3 ± 14.0
	CON (n=36)	INT (n=41)
	Mean ± SD	Mean ± SD
Fibula (mm)	27.6 ± 3.5	27.3 ± 3.6
SCALE	7.1 ± 2.6	7.0 ± 2.1

Total participants in control group = 22 and in intervention group = 26. Total legs in control group = 36 and in intervention group = 41.
Abbreviations: CON, control group; GMFCS, gross motor functional classification system; INT, intervention group; N, number; SCALE, selective control assessment of the lower extremity; SD, standard deviation.
Units: cm, centimeter; kg, kilogram; mm, millimeter.

3.2 Training program and usual care

The median number of performed training sessions was 35 (83% adherence), ranging from 24 to 42 (57%–100% adherence). The PRT part of the training sessions, without warm-up and cool-down, lasted between 25 and 45 min. Fatigue scores at the end of each training session showed a wide variability between and within participants, ranging from 0 to 10, with a median of 3 out of 10. However, physiotherapists and parents often mentioned a discrepancy between reported fatigue by the child and perceived fatigue based on exercise performance. Reported adverse events were muscle cramp or pain, joint pain and general discomfort from the weighted vest. No adverse events were reported that led to missed training sessions or required medical treatment. In case of pain during or shortly after the exercises, individual exercise intensity was modified by reducing resistance or changing the exercise, followed by exercise progression once pain had disappeared.

Usual care consisted of the use of orthoses and regular physical therapy including, among others, stretching, muscle strengthening and gait training. Regular physical therapy ranged from 1 to 4 sessions per week. Although usual care involved general strength exercises, no physiotherapist reported PRT as part of usual care, whereby PRT was defined as performing several sets of each exercise with gradually increasing load.

3.3 Primary analyses

Baseline data for the primary analyses on all affected legs of all participants in both groups are presented in Table 2. The mean differences of the mixed model analyses are presented in Figure 2 for the morphological parameters and in Figure 3 for the strength and functional parameters, supported by the estimated marginal means of the PRE- and POST-assessments in Supplementary Tables S5, S6. Isometric muscle strength showed a significant interaction-effect for knee flexion (p = 0.008), whilst knee extension and plantar flexion were close to significance ($p \le 0.015$). In the intervention group, all muscle groups showed a significant time-effect, indicating an increase in isometric muscle strength (knee flexion: Δ = 6.0Nm (3.3–8.7), p=<0.001, knee extension: Δ = 2.5Nm (0.8–4.2), p = 0.004, plantar flexion: Δ = 3.6Nm (2.2–5.0), $p < 0.001$). The results for normalized isometric muscle strength were similar, with a significant interaction-effect for knee flexion (p = 0.005) and significant time-effects in the intervention group for knee flexion (Δ = 0.19Nm/kg (0.11–0.27), $p < 0.001$) and plantar flexion (Δ = 0.13Nm/kg (0.08–0.18), $p < 0.001$) whilst knee extension was close to being significant (Δ = 0.07Nm/kg (0.01–0.13), p = 0.032).

For MV, no significant interaction-effects were present, however, the increase in rectus femoris and medial gastrocnemius MV showed a significant time effect in the intervention group (rectus femoris: Δ = 3.7 ml (1.9–5.5), $p <$ 0.001, medial gastrocnemius: Δ = 2.0 ml (0.9–3.1), $p < 0.001$). In the control group, the increase of rectus femoris MV was close to significant (Δ = 1.6 ml (–0.1–3.4), p = 0.069). No interaction-effects were found for ML and EI. In both groups a significant or close to significant time-effect was found for rectus femoris ML (CON: Δ = 5.5 mm (1.8–9.3), p = 0.005, INT: Δ = 3.9 mm (0.0–7.7), p = 0.050) and medial gastrocnemius ML (CON: Δ = 2.4 mm (0.3–4.4), p = 0.025, INT: Δ = 3.5 mm (1.4–5.6), p = 0.002), indicating increased ML. For ML of the semitendinosus and EI of all 3 muscles, no significant time-effects were found.

Regarding normalized morphological parameters, mean differences of the mixed model analyses are presented in Figure 4 and estimated marginal means of the PRE- and POST-assessment are included in Supplementary Table S7,

TABLE 2 Descriptive statistics of observed data at baseline for all participants, with all affected sides for unilaterally tested parameters.

		CON		INT	
		n	Mean ± SD	n	Mean ± SD
Isometric strength	KE (Nm)	36	16.6 ± 11.1	39	14.3 ± 9.5
	KF (Nm)	36	13.7 ± 11.3	39	8.1 ± 8.2
	PF (Nm)	35	7.9 ± 5.9	39	5.6 ± 3.7
Muscle volume	RF (mL)	35	70.5 ± 24.1	41	63.8 ± 27.0
	ST (mL)	31	48.9 ± 16.5	38	48.3 ± 18.4
	MG (mL)	35	48.2 ± 28.3	41	42.1 ± 19.0
Muscle length	RF (mm)	33	225.6 ± 31.5	40	222.3 ± 34.9
	ST (mm)	31	217.0 ± 34.6	35	211.6 ± 27.0
	MG (mm)	34	154.4 ± 31.6	41	150.8 ± 24.3
Muscle quality	RF (AU)	35	140.8 ± 15.4	41	140.5 ± 17.7
	ST (AU)	31	138.7 ± 16.0	38	134.4 ± 19.3
	MG (AU)	35	161.3 ± 12.5	41	162.5 ± 14.0
Functional strength	STS (n)	21	13.0 ± 5.1	25	14.4 ± 4.9
	LSU (n)	34	17.1 ± 8.7	38	16.0 ± 6.5
	BHR (n)	22	23.8 ± 10.4	22	24.0 ± 9.3
	UHR (n)	27	20.7 ± 10.8	27	15.1 ± 9.4
	SLJ (cm)	16	84.1 ± 30.1	19	75.9 ± 28.3
Walking capacity	1MWT (m)	21	77.6 ± 24.2	22	76.9 ± 20.5
Gross motor function	GMFM (%)	18	81.0 ± 12.6	25	79.6 ± 14.5

Complete dataset: participants in control group = 22 and in intervention group = 26. Total legs in control group = 36 and in intervention group = 41.
Abbreviations: 1MWT, 1-min walk test; BHR, bilateral heel raise; CON, control group; GMFM, gross motor function measure; INT, intervention group; KE, knee extension; KF, knee flexion; LSU, lateral step-up; MG, medial gastrocnemius; PF, plantar flexion; RF, rectus femoris; SD, standard deviation; SLJ, standing long jump; ST, semitendinosus; STS, sit to stand; UHR, unilateral heel raise.
Units: AU, arbitrary units on 8-bit greyscale; cm, centimeter; m, meter; mL, milliliter; mm, millimeter; n, number; Nm, Newton meter.

showing close to significant interaction-effects were present for normalized MV of the rectus femoris (p = 0.041) and medial gastrocnemius (0.074), With a significant or close to significant time-effect in the intervention group (rectus femoris: Δ = 0.08 ml/cm, (0.02–0.14), p = 0.007), medial gastrocnemius: Δ = 0.04 ml/cm, (−0.01–0.08), p = 0.085) and absent time-effects in the control group (rectus femoris: Δ = 0.00 ml/cm, (−0.06–0.06), p = 0.941), medial gastrocnemius: Δ = −0.02 ml/cm, (-0.05–0.02), p = 0.450). For normalized ML no interaction-nor time-effects were found, with mean differences in both groups around 0 cm/cm.

The endurance functional strength assessments indicated significant interaction-effects for unilateral heel raise (p < 0.001), and was close to significance for sit-to-stand and lateral step-up ($p \leq$ 0.076), all with significant time-effects in the intervention group indicating an increase in number of repetitions (unilateral heel raise: Δ = 9.1 (5.7–12.4), p < 0.001, sit-to-stand: Δ = 2.7 (1.2–4.1), p < 0.001, lateral step-up: Δ = 2.7 (1.4–3.9), p < 0.001). The bilateral heel raise improved significantly in both groups [CON: 3.6 (1.1–6.0), p = 0.005, INT: 4.5 (1.9–7.1), p = 0.001]. Explosive functional strength, walking capacity and gross motor function showed no significant interaction-effects, but the time-effects of both the 1-min walk test and the standing long jump in the intervention group were close to significance (1-min walk test: 5.6 m (0.9–10.4), p = 0.022, standing long jump: 5.8 cm (−0.2–11.8), p = 0.056).

3.4 Sensitivity analyses

Baseline data for the sensitivity analyses are presented in Supplementary Table S4. The results of the sensitivity analyses for morphological parameters are presented in Supplementary Table S5 and results of strength and functional parameters in Supplementary Table S6, together with the results of the primary analyses. The analyses on only the most affected legs, both in the randomized and the finished group, resulted in similar coefficients and mean differences and showed no clinically relevant differences in comparison to the primary analyses including all affected legs of all participants. However, the sensitivity analyses mostly resulted in higher p-values due to

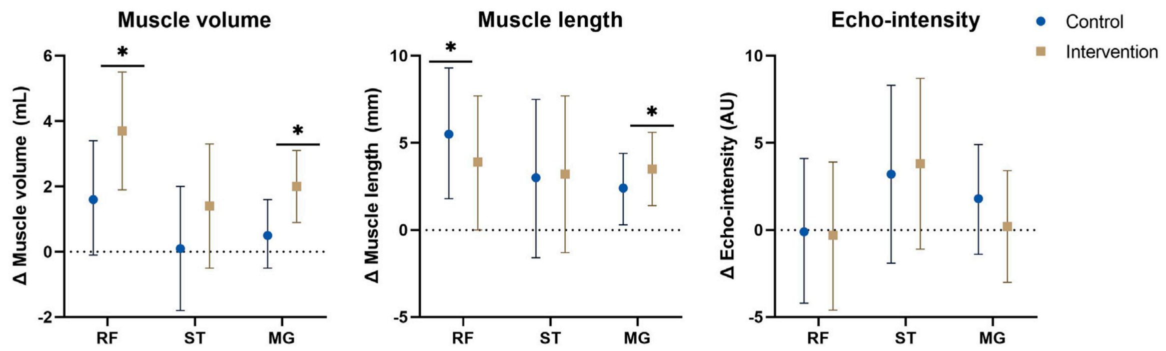

FIGURE 2
Estimated marginal mean differences with 95% confidence interval of mixed model analyses for muscle morphology with results for within and between analyses including all participants and all affected legs. *: significant time-effect at $p \leq 0.01$. Abbreviations: Δ, change; MG, medial gastrocnemius; RF, rectus femoris; ST, semitendinosus. Units: AU, arbitrary units; mL, milliliter; mm, millimeter.

the lower power. Both analyses indicated that including all affected legs instead of one, most affected, leg per child did not impact the results. The analyses on all randomized children showed that the change in randomization by minimization from program-driven to manual did not influence the main results, whereas the analyses on all children who finished the intervention or control group showed that the drop-out of participants due to varying reasons (see 3.1 Participants) did not impact the results.

4 Discussion

This study described the effects of a 12-week PRT program on muscle strength and muscle size of the lower limbs, as well as on gross motor function and walking capacity, in children with SCP, in comparison to a usual care control group. Below, we first discussed the effects of the PRT program on isometric strength, muscle morphology, and functional outcomes in relation to the literature, followed by an overview of potential explanations for the observed lack of muscle hypertrophy response, the study limitations and the final conclusion.

4.1 Training effect on isometric strength

The PRT program resulted in significant improvements in muscle strength in the intervention group for all trained muscle groups. This distinguished the intervention group significantly from the control group for knee flexion, and close to significantly for knee extension and plantar flexion. Overall changes were a significant 22% increase for knee extension, 97% for knee flexion and 77% for plantar flexion maximal joint torque in the intervention group, in comparison to non-significant changes of −3%, 8%, and 16% in the control group, respectively. These increases in the intervention group are in line with or larger than a previously reported average increase of 27% for targeted muscles after PRT for adolescents and young adults with SCP (Taylor et al., 2013) and increases around 10% in children with SCP (Lee et al., 2008; Scholtes et al., 2010), as well as with previous systematic reviews and meta-analyses reporting moderate to strong effects of PRT on muscle strength covering both children and adults with CP (Park and Kim, 2014; Ryan et al., 2017). The less pronounced improvement in knee extension maximal joint torque, in comparison to plantar flexion and knee flexion, might be explained because knee extension was already more targeted in usual care or by the position in which the knee extension strength was evaluated (Goudriaan et al., 2018). For children with limited knee extension range of motion and short spastic hamstring muscles, the current positioning of 30° knee flexion was close to the end of their active range of motion. PRT on the contrary focused on exercises throughout a larger range of motion (e.g., from 90° to knee extension, see Supplementary Table S1).

4.2 Training effect on muscle morphology

For MV, no significant interaction-effects were found, indicating no significant differences in cross-sectional muscle growth between the intervention and control group. However, muscle size increases were more than twice as large in the intervention group in comparison to the control group. The only previously performed RCT in pre-pubertal children with SCP found significant interaction-effects for rectus femoris CSA and quadriceps MT after a functional PRT (Cho and Lee, 2020). Similarly, Gillett et al. found significant increases ranging from 7.5% to 9.6% for plantar flexor MV in adolescents and adults with SCP following a 12-week functional and anaerobic strength training program, without changes in the control group (Gillett et al., 2018). On the other hand, Ryan et al. found no

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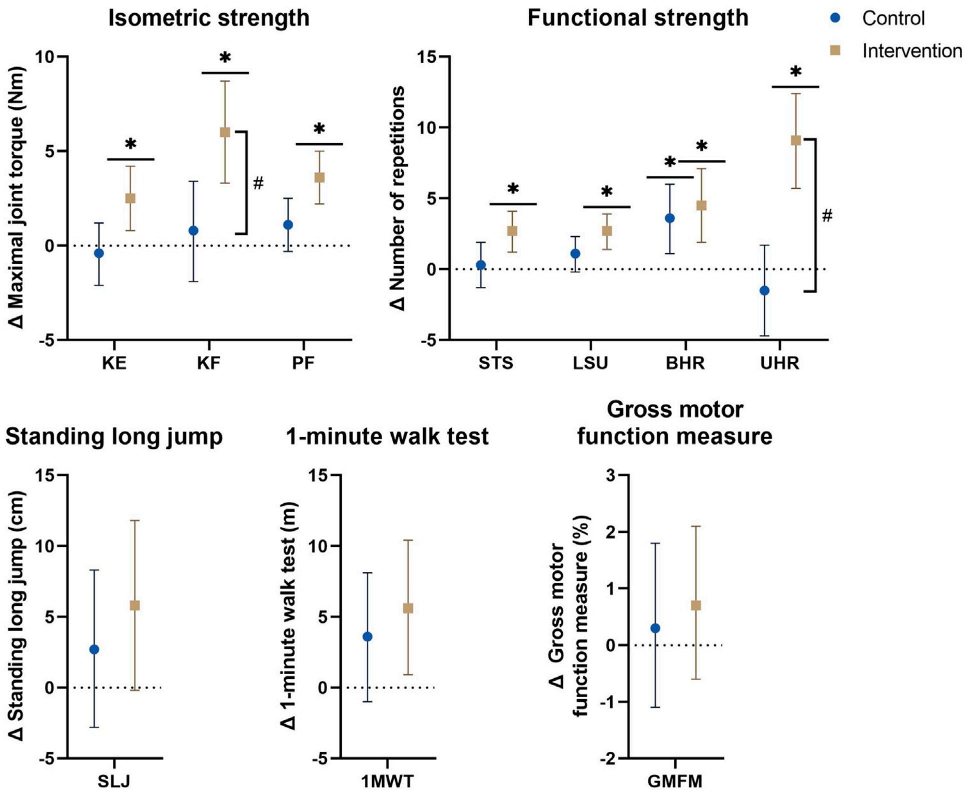

FIGURE 3
Estimated marginal mean differences with 95% confidence interval of mixed model analyses for strength and functional parameters with results for within and between analyses including all participants and all affected legs for bilaterally tested parameters. #: significant time*group interaction-effect at $p \le 0.01$. *: significant time-effect at $p \le 0.01$. Abbreviations: Δ, hange; 1MWT, 1-minute walk test; BHR, bilateral heel raise; GMFM, gross motor function measure; KE, knee extension; KF, knee flexion; LSU, lateral step-up; PF, plantar flexion; SLJ, standing long jump; STS, sit-to-stand; UHR, unilateral heel raise. Units: Cm, centimeter; M, meter; Nm, Newton-meter.

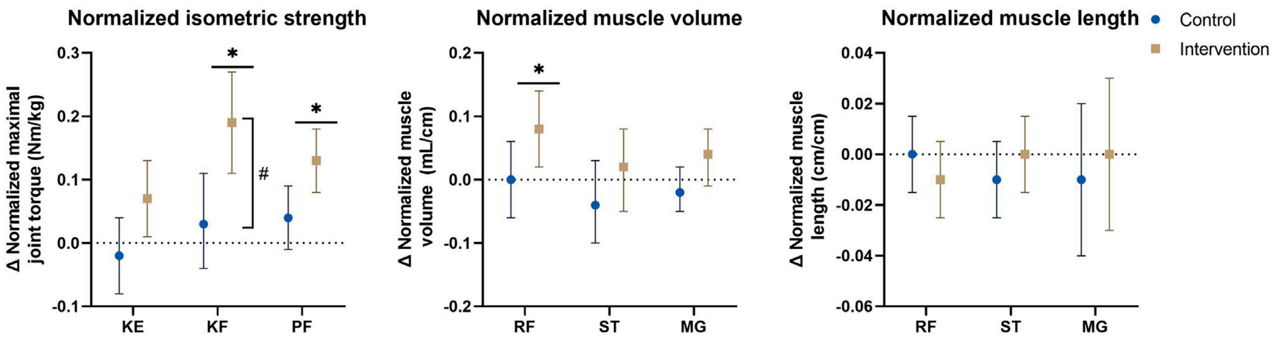

FIGURE 4
Estimated marginal mean differences with 95% confidence interval of mixed model analyses for normalized muscle morphology and isometric strength parameters with results for within and between analyses including all participants and all affected legs. #: significant time*group interaction-effect at $p \le 0.01$. *: significant time-effect at $p \le 0.01$. Abbreviations: Δ, change; KE, knee extension; KF, knee flexion; MG, medial gastrocnemius; PF, plantar flexion; RF, rectus femoris; ST, semitendinosus. Units: Cm/cm, centimeter/centimeter; mL/cm, milliliter per centimeter; Nm/kg, Newton-meter per kilogram.

significant difference in the MV changes of the medial gastrocnemius in a comparison of a 10-week PRT program of the plantar flexors with usual care in 10–19 year old children and adolescents with SCP (Ryan et al., 2020).

The children in the intervention group showed significant improvements for MV of the rectus femoris (6.3%) and medial gastrocnemius (5.3%). This is much lower than the 23.1% MV increase observed for the medial gastrocnemius after 10 weeks plantar flexor training (McNee et al., 2009). It should be noted that the latter study did not include a control group, and the reported effects were larger than improvements seen in healthy adults after PRT (Schoenfeld et al., 2017b). While Lee et al. (2015) found increases in both quadriceps muscle thickness and rectus femoris CSA after 6 weeks of progressive functional training, Kruse et al. (2019) only found an increase in vastus lateralis but not rectus femoris and medial gastrocnemius muscle thickness after 8 weeks of PRT. Once the results of the current study were normalized to fibula length, mean differences in the control group became negative (ranging from 0.0 to −2.4%). In the intervention group on the other hand the results remained positive (1.2–3.7%), although only significant for the rectus femoris and close to significant for the medial gastrocnemius. The PRT program might provide possibilities to overcome the limited cross-sectional muscle growth in relation to skeletal growth seen in SCP, but with effects that were too small to be statistically significant from the control group.

In the same line as for MV, ML showed no significant interaction-effects, but increased similarly in both groups. When ML was normalized to tibia length, the mean differences in both groups were close to 0, indicating that ML followed skeletal growth. PRT had no positive nor negative effect on longitudinal muscle growth. Together with previous literature stating that PRT did not increase muscle tone or spasticity, this finding counters the notion of a potential negative influence of PRT on muscle properties for persons with spasticity (Fowler et al., 2001; Damiano et al., 2008; Scholtes et al., 2010; Stubbs and Diong, 2015; Cho and Lee, 2020). EI, on the other hand, remained unchanged for all muscles, suggesting an unaltered ratio of contractile and non-contractile muscle tissue in both groups. However, the larger standard error of measurement for EI warns us to interpret this parameter with caution (Supplementary Table S2). Only Gillett et al. (2018) estimated muscle quality after a PRT program in SCP and reported no significant difference in medial gastrocnemius intramuscular fat fraction based on MRI assessment between the intervention and control group. More specific assessments of the ratio of contractile and non-contractile muscle tissue should be used in future research to determine any changes after PRT.

4.3 Training effects on functional outcomes

Unilateral heel raise showed significant interaction-effects, with an improvement of 82% in the intervention group, which is in line with the results of McNee et al. (2009). Sit-to-stand and lateral step-up were close to significant for their interaction-effects and showed significant increases in the intervention group of 22% and 18%, respectively, while bilateral heel raise improved significantly in both the control and intervention group, by 17% and 22%, respectively. Scholtes et al. (2010) reported no effects on sit-to-stand and lateral step-up after a 12-week functional PRT, whereas Lee et al. (2008) found significant improvements in both sit-to-stand and lateral step-up following a 5-week training program, but only sit-to-stand was significantly different from the control group, and Gillett et al. (2018) found an overall improvement of 50% for the combination of lateral step-up, sit-to-stand and lunges in an adolescent and adult population after a combined strength and anaerobic training program. The absence of significant interaction-effects for the sit-to-stand, lateral step-up and bilateral heel raise in the current study might have different causes. First, the sit-to-stand had a smaller sample size in comparison to the unilateral tested exercises. Second, the lateral step-up and bilateral heel raise tasks require a smaller part of the maximal strength than the unilateral heel raise and sit-to-stand, respectively, and reflect a combination of balance, agility, spatial and temporal accuracy with strength endurance (Aertssen et al., 2016). Moreover, unilateral heel raises and sit-to-stand exercises were more often prescribed in the training program as they targeted the 60%–80% of 1-repetition maximum better than bilateral heel raises and lateral step-ups, which were often not intense enough. Improvements might also be related to a learning effect, which may explain improvements found in the control group.

Despite some within-group time-effects following PRT, explosive strength (evaluated with the standing long jump), walking capacity and gross motor function, did not differ between the groups. It should be noted that these outcomes were not specifically trained in the PRT program. Earlier investigations found a comparable lack of translation of PRT to gross motor function and mobility improvements (Scholtes et al., 2012; Taylor et al., 2013; Liang et al., 2021; Merino-Andrés et al., 2021). This highlights the principle of specificity of training and the need to adequately chose the type of training for the predetermined outcomes (Baker et al., 1994). A more comprehensive, functional training program might be needed to improve this carry-over (Faigenbaum and Myer, 2010). For example, training programs incorporating a power component, like the functional power training of Van Vulpen et al. (2017), and the functional and anaerobic training of Gillett et al. (2018), have shown to improve walking capacity.

4.4 The challenge of comparing progressive resistance training studies

There were some inconsistencies and discrepancies between the current investigation and previous muscle morphology studies

(Stackhouse et al., 2007; McNee et al., 2009; Moreau et al., 2013; Williams et al., 2013; Lee et al., 2015; Gillett et al., 2018; Kruse et al., 2019; Cho and Lee, 2020; Ryan et al., 2020). First, the age of the included participants differed between studies. In previous investigations on morphological changes after PRT in patients with SCP, the ages ranged from 5 to 28 years. The current investigation can be situated at the lower end of this range. While the intervention study in older adolescents and adults showed significant increases in muscle size following PRT (Gillett et al., 2018), the results in children and younger adolescents showed inconsistencies, ranging from no to large improvements. Secondly, the training features also varied across investigations. The duration of the training program ranged from 6 to 12 weeks. While some investigations found morphological changes after 6 weeks of PRT (Lee et al., 2015; Cho and Lee, 2020), one other study did not find such effects after 10 weeks of training (Ryan et al., 2020). The applied progressive resistance training in previous studies was either isometric, analytic or functional, whereby one previous investigation combined this resistance training with anaerobic training. The training settings in previous studies were a gymnasium or rehabilitation center, at the physiotherapist, at home or a combination of these. Previous studies that applied fully home-based or combined home-based and physiotherapy-supervised interventions found limited to no results on muscle strength or hypertrophy (Kruse et al., 2019; Ryan et al., 2020), which is in contrast with the results of the current investigation. A gymnasium or rehabilitation center may provide better opportunities to maintain intensity, especially in older and more functional participants, while well-supervised home-based interventions might be practically more feasible for the parents and children. Third, inclusion criteria related to previous treatments should also be considered when comparing results of different studies. Indeed, previous studies differed regarding the timing since the last botulinum neuro-toxin A injections, as well as regarding previous lower limb bony or muscular surgery. In line with this, other differences between previous studies include the trained and investigated muscle groups, as well as the outcome parameters to define muscle size alterations, including muscle thickness, anatomical cross-sectional area and volumes of single muscles or muscle groups. Whether all muscle groups respond similarly to PRT remains to be further explored. Overall, it is challenging to generalize findings from different previous studies and define possible mechanisms regarding muscle size increases after PRT in SCP.

4.5 Comparison to measurement errors

Accurate assessment of morphological and functional parameters is critical both for defining the training program variables, like exercise selection, number of sets and repetitions, as well as to evaluate the efficacy of training programs (Noorduyn et al., 2011; Verschuren et al., 2011; Aertssen et al., 2018). An overview of the clinimetric properties of the used assessments (i.e., absolute and relative standard error of measurements and minimal detectable change) has been included as Supplementary Table S2. Only the improvements in knee flexion and plantar flexion isometric strength, and unilateral heel raise in the intervention group were close to or larger than their defined minimal detectable changes. Knee extension isometric strength, sit-to-stand, bilateral heel raise and standing long jump were close to or larger than their defined standard error of measurements. No morphological results were larger than the minimal detectable changes, but rectus femoris MV improvement in the intervention group as well as rectus femoris and medial gastrocnemius ML increases in both groups were close to or larger than their standard error of measurements (Noorduyn et al., 2011; Verschuren et al., 2011; Aertssen et al., 2018). The sensitivity of the applied methods and the nature of assessing children with neuromotor impairments made it difficult to detect smaller changes in some parameters. Future research should continue the search for sensitive assessments, adapted to the population and the intended intervention.

4.6 Potential explanations for the lack of muscle hypertrophy

Overall, the 12-week PRT program led to increased lower limb muscle strength, however, with a limited concurrent change in muscle morphology. Potential explanations for these limited muscular adaptations include a lack of mechanical injury necessary for muscle hypertrophy and a deficient hypertrophic response to the mechanical injury. Specifically, to elicit muscle hypertrophy, a net positive protein balance or anabolic state is needed where protein synthesis is larger than protein breakdown (Glass, 2005; McCarthy and Esser, 2010). This protein balance can be influenced by training and nutrition, by hormonal status and the cellular environment.

4.6.1 Training stimulus

The applied PRT program was meant to provide an external training stimulus promoting the post-exercise physiological cascade and shifting the protein balance towards synthesis (Schoenfeld, 2010). The duration, volume and intensity of the PRT program were based on international guidelines for youth resistance training (Faigenbaum et al., 2009; Lloyd et al., 2014) and CP-specific training guidelines (Verschuren et al., 2011; Verschuren and Peterson, 2016). With the first weeks of training resulting in merely neural adaptations (Sale, 1988; Tesch, 1988), 12 weeks might have been too short to elicit larger adaptations in muscle mass or muscle composition. Moreover, the PRT program should result in a progressive overload, resulting from both training frequency and intensity (American College of Sports Medicine, 2009). Throughout the training period, a frequency of 3–4 training sessions per week was prescribed, taking into account expected missed training sessions due to sickness, holidays, and school trips (Scholtes et al., 2010). The median of performed training sessions was 35, representing an averaged frequency of approximately to 3 sessions per week, however with a wide range from 24 to 42. Although in adult populations an increase from 2 to 3 training sessions per week was not found to improve hypertrophy outcomes, this dose-response relationship is yet to be determined in the SCP population (Schoenfeld et al., 2016). Moreover, defining baseline strength as well as the intensity for a specific exercise remain challenging in a pediatric population. Though specific guidelines were set, the common fear for overload as well as eliciting unfavorable increases in muscle stiffness or spasticity due to PRT among physiotherapists (Bobath and Bobath, 1984) might have led to an underdosage of training intensity. Yet, to train at a sufficient intensity, it is also important to recruit as many muscle fibers as possible and expose them to the exercise stimulus (Wernbom et al., 2007). Voluntary muscle activation is decreased in children with SCP in comparison to typically developing children (Elder et al., 2003; Stackhouse et al., 2005; Mockford and Caulton, 2010) and research has indicated a limitation in the recruitment of higher-threshold motor units and in the activation of lower-threshold motor units to the same rate as typically developing children (Rose and McGill, 2005). Therefore the voluntary muscle contractions might not have produced sufficiently large forces in every participant to induce the mechanical injury necessary for muscle hypertrophy. Finally, due to the specific goals of this intervention, the training program variables and targeted muscle groups were fixed to match these goals. While, exercise selection was patient-specific, it was not possible to include patient-specific goals or outcomes. Although we tried to make the program as child-friendly as possible, mainly through the training diary which included motivational quotes, coloring pages and a training timeline where stickers could be attached after every training session, some physiotherapists and parents reported motivational issues, which may also have resulted in a limited training stimulus in some sessions. In the translation to clinical practice, the inclusion of patient specific goals or outcomes, combined with more interaction during training, e.g., through an online application or group training sessions, might promote participant motivation, as has been applied before in training studies for children with CP (Scholtes et al., 2010; Vulpen et al., 2017).

4.6.2 Nutrition

Nutritional components influencing the protein balance include total calorie intake, with a specific emphasis on protein intake, as well as nutritional supplements like Vitamin-D or calcium (Verschuren et al., 2018). Although previous investigations found no difference in protein intake between typically developing children and children with SCP (Grammatikopoulou et al., 2009; Kalra et al., 2015), the timing of protein intake appears to be highest towards the evening instead of evenly balanced throughout the day (Anker-Van Der Wel et al., 2019). Moreover, it is still unclear whether children with SCP have the same protein requirements, as well as protein uptake as their typically developing peers (Verschuren et al., 2018). Especially during intensive rehabilitation programs, like PRT, the notion has been raised that protein requirements might be higher (Verschuren and Peterson, 2016). Although nutritional interventions, whether or not combined with exercise interventions, are rather limited in SCP, a recent investigation supplementing the essential amino acid leucine found both increased muscle strength (25.4%) and size (3.6%) after 10 weeks (Theis et al., 2021). Other nutritional supplements considered often in the elderly, preventing or treating sarcopenia, include Vitamin D or calcium (Verschuren et al., 2018). Research into the effects of dietary modifications and nutritional supplementations and their interaction with exercise interventions are necessary to elucidate their effects on the protein balance and consequently muscle hypertrophy in the CP population.

4.6.3 Age

An additional reason for this lack of muscle hypertrophy can be found in the age of the participants, who were all pre-pubertal or early-pubertal. In a young, developing population, the adaptations should exceed the muscular strength and size increases related to growth and maturation alone. While the knowledge of the trajectory of muscle growth in children with SCP is rather limited (Verschuren et al., 2018; Williams et al., 2020), the current investigation showed non-statistically significant but clinically important negative changes in MV normalized to tibia length in the usual care control group, indicating limited cross-sectional muscle growth in relation to skeletal growth. Therefore, this population with SCP might first have to overcome this process of relative decline in muscle size before muscle growth can happen, emphasizing the importance to look at muscle size normalized to skeletal growth to determine training effects in this population. Moreover, research in typically developing children showed that strength increases during childhood, before puberty, are mainly related to the maturation of the central nervous system and therefore to improved motor unit recruitment, firing frequency, synchronization and neural myelination rather than muscular changes (Ramsay et al., 1990; Granacher et al., 2011; Lloyd et al., 2014). Strength gains later in life, during adolescence and beyond, are a combination of these neural improvements together with structural and architectural muscular changes (Fukunaga et al., 1992; Lillegard et al., 1997). The latter are a result of increased hormonal concentrations, including growth hormone, insulin-like growth factor and testosterone. Therefore, the timing of PRT in relation to the pubertal status might have to be taken into account if muscle strength improvement with concurrent muscle hypertrophy is the intended goal.

4.6.4 Cellular environment

Additionally, the question should be raised whether the cellular environment of muscles in SCP has the same capacity for muscle repair, adaptation and growth as in typically developing muscles. A major factor in the post-exercise physiological cascade are satellite cells, leading to muscle regeneration from the initial mechanical injury (Murach et al., 2021). These cells are usually in a quiescent state, laying in the periphery of the muscle fiber but are triggered by external factors like exercise and injury (Snijders et al., 2015). In SCP muscles, a decreased number of satellite cells has been observed in comparison to typically developing muscles (Smith et al., 2013; von Walden et al., 2018). The influence of altered cytokine expression and extracellular matrix remodeling by fibroblasts on the complex process of muscle repair and growth, together with the alterations in satellite cell concentration and efficacy, are to be further explored in SCP muscles (Handsfield et al., 2022).

4.6.5 Variability of training response

Ultimately, the response to training was quite variable. SCP is known as a very heterogeneous disorder, stemming from a range of possible brain lesions differing in timing, location and extent, and resulting in a similarly varied presentation of clinical symptoms and functional impairments (Himmelmann and Uvebrant, 2011). For example on the impairment level, muscle weakness, muscle size and the contribution of muscle size deficits to muscle weakness showed inter-individual variation (Hanssen et al., 2021). Moreover, in adult populations, PRT has been shown to cause a wide range of responses (Hubal et al., 2005; Ahtiainen et al., 2016; Bonafiglia et al., 2021). Therefore, it might be interesting for future research to identify which child might respond well to PRT based on baseline characteristics like age, gender, SMC, functional ability, topographical distribution, strength or muscle size deficits.

4.7 Limitations

The first limitation was the sample size and drop-outs due to Covid regulations and for other reasons. The final group size was 22 individuals, or 36 legs, in the control group and 26 individuals, or 41 legs, in the intervention group. This was just below the estimated sample size of 39–43 legs. Therefore, we were slightly underpowered for isometric and functional strength outcomes. This may explain the many interaction-effects that could be considered borderline significant. A second limitation is the inclusion of GMFCS levels, with an underrepresentation of GMFCS level II and III. The unequal distribution was mainly caused by the inclusion criteria related to previous treatments and cognitive abilities. Thirdly, strength and muscle size deficits were not used as inclusion criterium and participants with mild deficits might have had limited possibilities for improvement. On the other hand, the level of SMC was also not used as an exclusion criterium, which may have led to limitations in active and isolated contraction of the targeted muscle groups in some more affected participants. Fourth, dietary intake was not evaluated during the intervention and a lack of overall energy or protein intake could have impacted muscle hypertrophy. Finally, although the improvements in muscle strength with limited concurrent changes in muscle morphology point towards neural improvements, the exact underlying neural mechanisms were not evaluated and the underlying microscopic muscular changes remain unknown. Future research is required to elucidate both the underlying neuromuscular and cellular mechanisms to PRT, in other age groups (e.g., mid or post-puberty) with a follow-up period to evaluate the long term influence of training and detraining.

5 Conclusion

This study proved the effectiveness of a home-based, physiotherapy supervised PRT program to improve isometric and functional muscle strength in children with SCP without negative effects on muscle properties or any serious adverse events. Moreover, smaller but important effects were seen on maintaining or increasing muscle size. This is an accessible and applicable type of treatment for individuals with SCP. The carry-over of isometric and functional strength gains to gross motor function and walking ability was limited, highlighting the principal of specificity of training. However, the achieved strength gains could be further used to improve activity and participation in a well-planned and periodized rehabilitation program matching type of training to the training goal. Finally, the response to training remained quite variable, indicating the need to identify the baseline characteristics of responders and non-responders to PRT.

Ethics statement

The studies involving human participants were reviewed and approved by the local medical ethical committees of University Hospitals Leuven (s59945) and Ghent (EC/2017/0526). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

Conceptualization: KD, CVB, BH, NP, and NDB. Data curation: BH, NP, NDB, AV, and LP. Formal analysis: BH, AV, and ED. Funding acquisition: KD, CVB, GM, and AVC. Methodology: BH, NP, KD, and NDB. Resources: KD and CVB. Supervision: KD, CVB, GM, and AVC. Writing—original draft: BH. Writing—review and editing: BH, NP, NDB, AV, LP, GM, AVC, ED, CVB, and KD.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphys.2022.911162/full#supplementary-material

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Instrumented strength assessment in typically developing children and children with a neural or neuromuscular disorder: A reliability, validity and responsiveness study

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The aim of this study was to determine the clinimetric properties, i.e., reliability, validity and responsiveness of an instrumented strength assessment in typically developing (TD) children and children with cerebral palsy (CP) and Duchenne muscular dystrophy (DMD). Force (N), torque (Nm) and normalized torque (Nm/kg) were defined for maximal voluntary isometric contractions (MVICs) of the lower limb muscles using a pre-established protocol. Intraclass correlation coefficient (ICC), standard error of measurement (SEM) and minimal detectable change (MDC) of TD children (n = 14), children with CP (n = 11) and DMD (n = 11) were used to evaluate intra-rater reliability for the three cohorts and the inter-rater intersession as well as inter-rater intrasession reliability for TD children. Construct validity was assessed by comparing MVICs in TD children (n = 28) to children with CP (n = 26) and to children with DMD (n = 30), using the Kruskal Wallis and post-hoc Mann-Whitney U tests. Responsiveness was investigated by assessing changes in MVICs following a strength intervention in CP (n = 26) and a 1 and 2 year follow-up study in DMD (n = 13 and n = 6, respectively), using the Wilcoxon Signed-Rank test. The overall intra-rater reliability, was classified as good to excellent for 65.1%, moderate for 27.0% and poor for 7.9% of the measures (47.6%, 76.2%, and 66.7% good-excellent; 28.6%, 23.8%, and 33.7% moderate; 23.8%, 0%, and 0% poor in TD, CP, and DMD, respectively), while ICC values for TD children were slightly lower for inter-rater intrasession reliability (38.1% good-excellent, 33.3% moderate and 26.6% poor) and for inter-rater intersession reliability (47.6% good-excellent, 23.8% moderate and 28.6% poor). Children with CP and DMD were significantly weaker than TD children ($p < 0.001$) and the majority of these strength differences exceeded the MDC. Children with CP significantly improved strength after training, with changes that exceeded the SEMs, whereas only limited strength decreases over time were observed in the DMD cohort. In conclusion, the investigated instrumented strength assessment was sufficiently reliable to confirm known-group validity for both cohorts and could detect the responsiveness of children with CP after a strength intervention. However, more research is necessary to determine the responsiveness of this assessment in children with DMD regarding their natural decline.

KEYWORDS

cerebral palsy, Duchenne musclar dystrophy, muscle weakness, instrumented strength assessment, clinimetric properties, reliability, validity, responsiveness

1 Introduction

Muscle weakness is a common symptom in childhood onset disorders like cerebral palsy (CP) and Duchenne muscular dystrophy (DMD), despite its different etiology in both patient groups (Sussman, 2002; Odding et al., 2006). CP is primarily a neurological disease, where the loss of muscle strength is related to neurological factors, namely lower motor drive and altered recruitment patterns. However, secondary impairments caused by the initial brain lesion lead to, among others, altered muscle structure, also contributing to muscle weakness (Hoffman et al., 1988; Sussman, 2002; Mockford and Caulton, 2010). DMD on the other hand, a genetic dystrophy, is classified as a neuromuscular disease, but the origin of the muscle weakness is solely found in the muscular system (Sussman, 2002).

CP is the most common neurological disorder in children, with a prevalence of 2–3 per 1,000 live births (Surveillance of cerebral palsy in Europe: a collaboration of cerebral palsy surveys and registers. Surveillance of Cerebral Palsy in Europe (SCPE)., 2000). Muscle weakness is one of the primary symptoms that is caused by an upper motor neuron lesion occurring in the developing fetal or infant brain (Odding et al., 2006; The Definition and Classification of Cerebral Palsy, 2007). Dallmeijer et al. (2017) described lower limb strength for children with CP in comparison to typically developing (TD) children using handheld dynamometry (HHD) and showed that hip flexion (HF) was most affected, with a reduction of 63%–82%, followed by hip abduction (HA, 47%–76%), knee extension (KE, 56%–68%), knee flexion (KF, 36%–68%) and plantar flexion (PF, 37%–57%) (Dallmeijer et al., 2017).

DMD is a progressive X-linked muscular disease, affecting 2–3 per 10,000 new-born boys (Sussman, 2002). The protein dystrophin, important for muscle cell stability, is deficient due to a mutation in the gene encoding for this protein (Hoffman et al., 1988; Sussman, 2002; Birnkrant et al., 2018). The quick deteriorating muscle dystrophy results in progressive loss of muscle strength and alterations in posture and gait (Sutherland, 1981; Pasternak et al., 1995; Sussman, 2002). First symptoms occur before the age of 5 years, with an early effect on the proximal muscles and eventually resulting in a general muscle impairment (Hoffman et al., 1988; Baumann, 2003). Children with DMD lose ambulation between the age of 7.1 and 18.6 years (mean age: 12.7 years) (Goemans et al., 2021). Mathur et al. (2010) showed that dorsiflexion (DF), PF and KE muscle strength was 67%, 67%, and 71% of TD children, respectively, in boys with DMD (Mathur et al., 2010). Longitudinal analyses in DMD revealed that before the age of 7.5 years KE and KF isometric and isokinetic muscle strength still increased, however to a lesser extent than in TD (Lerario et al., 2012). After the age of 7.5 years, strength in these muscle groups decreased, with a more pronounced decrement after the age of 9 years (Lerario et al., 2012).

While DMD has an intrinsic progressive character, children with CP present with persisting, non-progressive brain damage and variable muscle weakness (Sussman, 2002; The Definition and Classification of Cerebral Palsy, 2007). Consequently, muscle strength training is often included in the treatment protocol of CP, whereas in children with DMD, other modalities, like pharmacological interventions, are considered more useful (Manzur et al., 2008; Scholtes et al., 2008; Vulpen et al., 2017). While several studies suggested the effectiveness of strength training in children with CP (Ryan et al., 2017), valid quantitative measures of muscle strength are considered essential to define the intensity of the strength training program, to monitor adjustments and to properly assess the effects of strength training (Van Vulpen et al., 2013). In children with DMD, the natural history of the disease, including the age at which they lose ambulation, might be altered with promising novel therapeutic strategies. However, demonstrating the benefits of these novel drugs in DMD has shown to be very challenging with the current assessment methods (Goemans et al., 2014). To delineate the natural history of the disease and the potential effect of novel therapies in children with DMD, a reliable and valid assessment method is needed.

A wide range of instruments can be used to assess muscle strength in pediatric populations. While functional testing, such as heel raises and squatting, recently gained popularity, in a clinical setting, the Medical Research Council (MRC) scale is most often used due to its simplicity and all-round applicability. It examines the dynamic strength over the joint range of motion per muscle group of the patient by grading it on an ordinal scale from zero to five. Although this assessment is useful to determine the influence of muscle weakness on a patient's daily life abilities, it has a subjective character and has questionable inter-rater reliability (Pfister et al., 2018). Isokinetic dynamometry is considered the most valid method to assess muscle strength in adults, due to its dynamic nature, allowing quantification at relevant joint velocity and over relevant joint range of motion (Dallmeijer et al., 2011; El Mhandi and Bethoux, 2013). Yet, this method was found to be challenging in young children or children with distinct muscle weakness and its high costs and large size make it less useful in clinical settings (El Mhandi and Bethoux, 2013). In previous studies, a HHD was often used to assess muscle strength in pediatric populations. In these assessments, participants were asked to perform maximal voluntary isometric contractions (MVICs) against the HHD (Physio and Galea, 2007; Verschuren et al., 2008). Although this method is found to be more reliable than the MRC scale, the strength assessment can be influenced by the assessor (Physio and Galea, 2007; Verschuren et al., 2008; Hébert et al., 2011). Ideally, every assessor should generate the same force while holding the HHD in the test procedure matched to the participant's force to ensure a true isometric contraction (Physio and Galea, 2007; Hébert et al., 2011). Moreover, when the child is not thoroughly fixated, the obtained results can be influenced by compensation mechanisms (Dallmeijer et al., 2011; Hébert et al., 2011; Goudriaan et al., 2018a). An additional limitation is the static nature of the measurement, limiting its outcome to the unchanged specific joint angle in which strength was assessed, which may not be representative for muscle use in dynamic conditions (Dallmeijer et al., 2011). To eliminate the two other main limitations of HHD, i.e., influence of the strength of the assessor and compensations of the subject, Goudriaan et al. (2018a) developed a new isometric strength assessment protocol. This latter protocol is the main focus of the current study and is further referred to as the 'instrumented strength assessment'. During this assessment, MVICs were performed in a custom-made chair, i.e., an external frame on which the HHD could be attached. The child was fixated in the chair.

Reliability, validity and responsiveness, which are essential clinimetric properties (Feinstein, 1987; De Vet et al., 2003), were only partly defined for this instrumented strength assessment. The reliability was assessed in TD children for DF, PF, KE, and KF strength, and was found to be moderately reliable in this population, with 13 out of 16 ICCs being higher than 0.500 (Goudriaan et al., 2018a). Construct validity was investigated in both TD and CP children for the ankle and knee joint by associating joint strength with gait parameters. However, clinimetric properties are not randomly transferable from adults to children or from TD children to children with a neural or neuromuscular disorder (De Vet et al., 2003; Jerosch-Herold, 2005; Clark et al., 2017). Associated disabilities such as spasticity and cognitive deficits may influence the test performance of the child (Physio and Galea, 2007). It is therefore important to determine clinimetric properties per specific pediatric clinical population, such as CP and DMD (Clark et al., 2017). Moreover, the responsiveness of this assessment, comparing changes following interventions with reliability indices, are still absent.

The overall aim of the current study was to comprehensively determine the reliability, validity, and responsiveness of the instrumented strength assessment in TD children, as well as in children with CP and DMD in muscle groups around the ankle (DF and PF), knee (KE and KF), and hip [HA, hip extension (HE) and HF]. To achieve this overall aim, the current study was divided into three parts. Part one aimed at determining the intra- and inter-rater reliability of the instrumented strength assessment using the intraclass correlation coefficient (ICC) and the standard error of measurement (SEM) as relative and absolute reliability index, respectively (Goudriaan et al., 2018a). While the intra-rater reliability was assessed in the three cohorts, inter-rater reliability was only assessed in the TD cohort. It was hypothesized that intra-rater reliability of the strength assessment for lower limb muscle groups is good (ICC>0.750) for TD children, as well as for children with CP and DMD, with a tendency of higher reliability in TD children because the performance of muscle strength assessments in children with CP and DMD is expected to be more challenging and thus less consistent (Koo and Li, 2016). Part two aimed to evaluate the construct validity of this instrument through the evaluation of the known-group validity by comparing TD, CP, and DMD cohorts, using the SEM and minimal detectable change (MDC) as a reference value. It was hypothesized that the SEM and MDC values resulting from the reliability analysis are sufficiently small to distinguish strength assessments between pathological and TD populations. Part three aimed to evaluate the responsiveness of the instrumented strength assessment by comparing the SEM and MDC values to change over time during a strength intervention in children with CP and during the natural decline in children with DMD. It was hypothesized that the

TABLE 1 Overview of the in- and exclusion criteria for the reliability analysis.

	Inclusion criteria	Exclusion criteria
TD	- Age between five and 18 years old	- History of orthopedic impairments of the lower limb - Neurological disorders - Known cognitive or behavioral disorders
CP	- Age between five and 18 years old - Confirmed diagnosis of spastic CP - GMFCS I-III	- Less than 6 months post-BTX - Less than 12 months post-surgery - Inability to understand the test procedure
DMD	- Age between five and 18 years old - Diagnosis of DMD *via* immune-histochemistry, muscle biopsy and/or mutation of the dystrophin gene - Ambulant and able to walk independently for at least 100 m	- Cognitive and behavioral disorders preventing accurate measurements - History of lower limb surgery - Clinical picture of Becker muscular dystrophy - Genetic diagnosis predicting a milder phenotype, such as in frame deletions

Abbreviations in alphabetical order: BTX, botulinum toxin infiltration; CP, cerebral palsy; DMD, Duchenne muscular dystrophy; GMFCS, gross motor function classification system; m, meter; TD, typically developing.

SEM and MDC values are small enough to define changes over time related to strength training in CP or to the natural evolution in DMD.

2 Materials and methods

The methods are described per study part. This study was approved by the ethical commission of KU Leuven (Ethical Committee UZ Leuven/KU Leuven; S59945, S61324, and S63340) and Ghent University (EC/2017/1674) under the Declaration of Helsinki. Participants' parents/caregivers signed a written informed consent prior to participation. Children above the age of 12 were asked to sign an assent as well.

2.1 Part one: reliability of the instrumented strength assessment

2.1.1 Participants

Prior to the study, the sample size was determined based on the approximations of Walter et al. (1998). Corresponding to the ICC-range reported by Goudriaan et al. (2018a), the minimal ICC-value (ρ0) and maximal ICC-value (ρ1) was set at 0.500 (fair to good) and 0.900 (excellent), respectively. Taking into account an alpha of 0.05 and a power of 0.80, a minimal sample size of nine children was necessary in each reliability analysis (inter- and intra-rater) (Walter et al., 1998). To foresee drop-out during the study, the number of participants recruited was larger than the calculated sample size. The final cohorts of 15 TD, 11 CP, and 11 DMD participants were recruited based on predefined inclusion and exclusion criteria, listed in Table 1. For the children with DMD, chronic treatment with corticosteroids and participation in clinical trials were permitted.

2.1.2 Study design

First, the intra-rater reliability of DF, PF, KE, KF, HA, HE, and HF MVICs was investigated for the three cohorts, TD, DMD, and CP, and was defined by measuring all children twice by the same assessor with an interval of 1–2 weeks. An interval of 1–2 weeks was set to avoid the influence of recall and to avoid further deterioration of muscle weakness in the DMD population and progression of the clinical picture in the CP population. Second, the inter-rater reliability in an intrasession condition was defined for the same muscle groups by performing a second measurement by another assessor 45 min after the first measurement, on the first test day. Third, the inter-rater intersession reliability was defined by comparing this second measurement performed on the first test day with the data collected during the second session. The inter-rater reliability, both intersession and intrasession, was limited to the TD cohort to reduce the test load for the pathological cohorts. Assessors were a well-trained senior human movement scientist and pediatric physiotherapist, and two final year master students in pediatric physical therapy who received training to perform the instrumented strength assessment (1 day of general explanation, 2 days of practice and assisted with 10 measurements). After this initial training, the students collected the inter-rater and intra-rater reliability assessments in the TD cohort, whereby the data collection during the first and second assessments on the first test day was supervised by the human movement scientist or pediatric

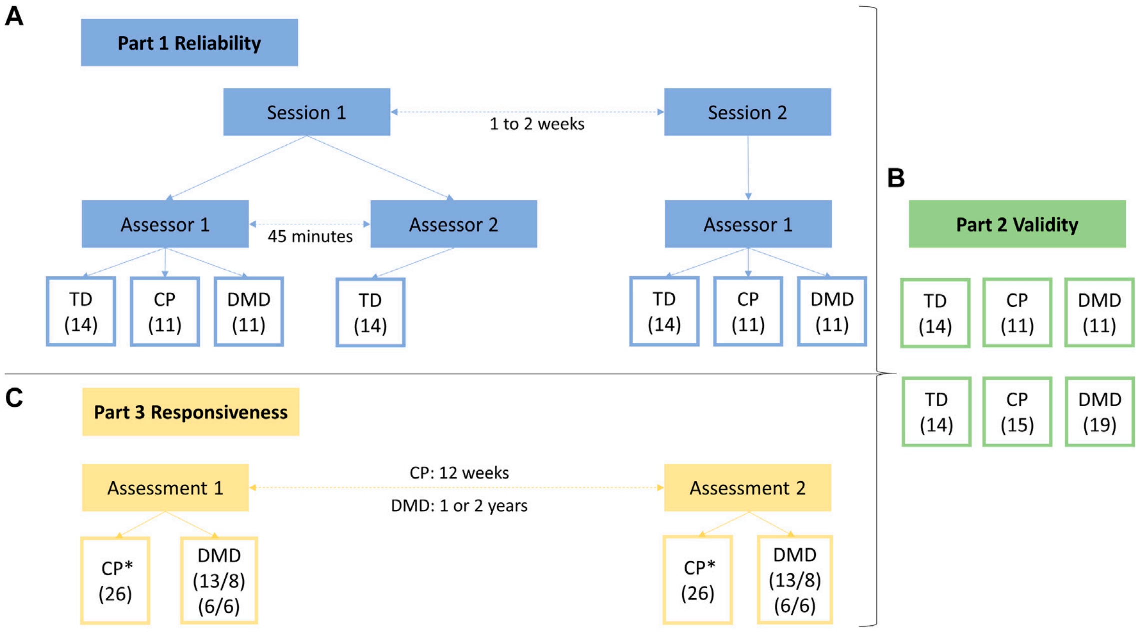

FIGURE 1
Study design of all three parts of the study. Part one represents the reliability study **(A)**, including (1) the intra-rater reliability, with data from session 1—assessor 1 and from session 2—assessor 1, (2) the inter-rater intrasession reliability, with data from session 1—assessor 1 and from session 1—assessor 2 and (3) the inter-rater intersession reliability, with data from session 1—assessor 2 and from session 2—assessor 1. Part two represents the validity study **(B)**, based on the data of the children included in the reliability study complemented with data of additional participants. Part three represents the responsiveness study **(C)**, based on (1) data of a strength training program in children with CP (* indicating that the hip joint was not assessed) and (2) data of the natural decline of the children with DMD. Abbreviations in alphabetic order: CP, cerebral palsy; DMD, Duchenne muscular dystrophy; TD, typically developing.

FIGURE 2
Custom-made chair used for assessment of maximal voluntary isometric contractions. The chair and handheld dynamometer are positioned to assess knee extension strength **(A)**. Further, the whole measurement set-up is shown with the laptop placed in front of the child to give visual feedback. Close-up on the position of the handheld dynamometer for knee flexion strength **(B)**. Close-up on the position of the handheld dynamometer for dorsiflexion strength **(C)**.

physiotherapist, while the third assessment during the second session was collected without supervision. All assessments for the intra-rater reliability in the CP and DMD cohort were collected by the senior human movement scientist or pediatric physiotherapist. Figure 1A shows an overview of the study design. Data was collected unilaterally for all children. The side was randomly selected for the TD children and the most affected side was selected for the children with CP and DMD, while the evaluated limb was randomly selected in case of a symmetrical clinical picture. In all cohorts, the same limb was evaluated in each measurement session.

2.1.3 Data collection

Anthropometric data, including height and weight, was obtained during the first measurement session. Muscle strength was defined by performing MVICs using a HHD (MicroFet, Hogan Health Industries, West Jordan, UT United States) in a standardized manner, as introduced by Goudriaan et al. (2018a). Thereby, a custom-made chair was used, fixating the hip joint in 60° flexion, the knee joint in 30° flexion and the ankle joint in a neutral position. A visual impression of the measurement set-up is given in Figure 2. When positioned in the chair, segment lengths of the lower limb (hip: trochanter major—knee joint space; knee: proximal border of fibula head—distal border of lateral malleolus; ankle: distal border (dorsal point) of lateral malleolus—distal metatarsal II, projected on the lateral border of the foot) were measured. The HHD was placed at 75% of the segment length to standardize the lever arms. At each measurement session, the segment lengths and lever arms were determined by the assessor performing the measurement. Compensations were minimized by fixating the child in the chair using a waistbelt, two thigh straps and performing the MVICs crossing their arms in front of their chest. During the assessments of DF, PF, HE, and HF, the heel was fixated in a heel cuff. Influence of gravitational force during the MVICs of PF, KF, and HE was ruled out by performing a separate passive trial and subtracting it from the actual MVICs outcomes (Boiteau et al., 1995). The children were asked to perform a test trial, followed by three well executed actual trials with a duration of 3–5 s. If compensations were observed, i.e. obvious contractions in other muscles than the tested muscle, an additional trial was performed after verbal instructions to correctly perform the MVIC and avoid compensations. Between each trial, a resting period of at least 10 s was provided. In case of observed signs of fatigue, the recovery period was prolonged until the participant was ready. When transitioning to the measurements of a different joint, a resting period of at least 30 s was provided. The children received both consistent verbal encouragement by the assessor and visual feedback of the ongoing trial as well as previous trials of that assessment.

2.1.4 Data analysis

All data was analyzed using a custom-written Matlab (The Mathworks Inc., Natick, M.A., R2019a) script. At first, the strength data was resampled to 100 Hz. The maximal force (in Newton [N]) per MVIC trial was extracted. The average of the maximal force from the representative MVICs was calculated for each muscle group. By multiplying the average maximal force with the lever arm and dividing it by the body weight, the mean torque (in Newton meter [Nm]) and mean torque normalized to body weight (in Newton meter per kilogram body weight [Nm/kg]) were calculated, respectively. Hereby, torque and normalized torque were considered the primary outcomes. The force was described as secondary outcome, as it may help to understand the observed torque values.

2.1.5 Statistical analysis

To determine the inter- and intra-rater reliability, the ICCs for MVICs were calculated in SPSS (SPSS Inc., Chicago, IL version 27). ICC (2,1) with a 95% confidence interval (CI) was calculated using a two-way random model based on a single-rater with absolute-agreement. Bland-Altman plots were created and checked to determine any systematic bias. Based on visual inspection of these plots, two assessors independently checked for outliers, i.e., a participant from which the difference between the two assessments exceeded 2 standard deviations. In case outliers were caused by a processing error, the MVICs were reprocessed. In addition, one TD participant (all MVICs), the PF MVICs of one participant with CP and the HA MVICs of one participant with DMD were outliers and were excluded for further analysis because of the following reasons: an exceptional more advanced maturity compared to other participants, a compensation during the assessment that was discovered by a deviating selectivity score [assessed during standard clinical examination with the Selective Control Assessment of the Lower Extremity (Fowler et al., 2009)] and missing data of the first assessment, respectively. Following Koo and Li (2016), an ICC ≤ 0.500 resembled poor reliability, 0.501–0.750 a moderate, 0.751–0.900 a good and >0.900 an excellent reliability (Koo and Li, 2016). The SEM was calculated by taking the square root of the mean square error, which is the within group mean square value in the two-way random model. If the SEM is low, the reliability is high, which is associated with an ICC approaching one. In addition, the MDC score was calculated using the SEM obtained in the two-way ANOVA by $SEM*1.96*\sqrt{2}$. Both SEM and MDC were also expressed as a percentage of the median of the averaged scores from each assessment per participant, SEM% and MDC%, respectively.

2.2 Part two: validity of the instrumented strength assessment

2.2.1 Participants

The required sample size was estimated based on previous research (Goudriaan et al., 2018a; Vandekerckhove et al., 2020). The Wilcoxon effect sizes r (Fritz et al., 2012) of the differences in muscle strength between CP and TD were calculated from the available data of Goudriaan et al. (2018a) and ranged between 0.55 and 0.80 (Goudriaan et al., 2018a). Vandekerckhove et al. (2020) reported similar Wilcoxon effect sizes r ranging between 0.65 and 0.79 for differences in muscle strength between DMD and TD (Vandekerckhove et al., 2020). Taking into account a Cohen's D effect size of 1.3, which corresponds to the smallest Wilcoxon effect size r (0.55) reported in previous studies, an α error probability of 0.0036 (to correct for the comparison of 14 parameters) and a power of 0.95, a minimal sample size of 26 for each cohort was required. Therefore, the children from the reliability study were supplemented with 14 additional TD children, 15 additional children with CP and 19 additional children with DMD. These additional data were collected as part of ongoing studies, i.e., a natural history in children with DMD, and databases within a larger project for the TD and CP cohort. For the TD cohort, the assessors of these additional data were trained final year master students in pediatric physical therapy, and for the CP and DMD cohort the assessors were the well-trained senior human movement scientist and pediatric physiotherapist. In total, the TD, CP and DMD cohort included 28, 26, and 30 children, respectively. The same inclusion and exclusion criteria were applied as specified in part one (Table 1).

2.2.2 Study design

Part two of the study investigated the construct validity of the instrumented strength assessment for MVICs for all measured muscle groups including all three cohorts, i.e., TD, CP, and DMD. First, the validity was assessed by investigating differences between the TD children and the two clinical cohorts, using unpaired comparison analysis. Second, differences between the median data of TD and CP and between the median data of TD and DMD were compared with the SEM and MDC values of the CP and DMD cohort, respectively. These SEM and MDC values were obtained in part one of the study. Figure 1B shows an overview of the study design.

2.2.3 Data collection

Idem part one.

2.2.4 Data analysis

Idem part one.

2.2.5 Statistical analysis

First, since the data was not normally distributed, the non-parametric Kruskal Wallis test was used to compare the three different cohorts, indicating whether a difference between the TD, CP, and DMD cohort was found. In case of significant results in the Kruskal Wallis test, a post-hoc Mann-Whitney U (MWU) test was conducted to locate these differences. To correct for the comparison of 14 primary parameters, i.e., torque and normalized torque of seven muscle groups, the significance threshold was set to $\alpha = 0.0036$, according to the Bonferroni correction (Sidak, 1967). Critical p-values ranging between 0.0036 and 0.05 were discussed as tendencies. Second, the absolute differences between the median data of TD and CP and between the median data of TD and DMD were calculated for torque and normalized torque, as well as for force, per muscle group. To explore the relevance of these differences, we compared the absolute differences to the absolute SEM and MDC values of the CP and DMD cohort. This comparison was visualized, in the absence of additional statistical testing, and indicated the ability of the instrumented strength assessment to distinguish between a TD cohort and clinical cohorts. To be able to interpret the measurement error in relation to the extent of weakness, the relative differences between the median data of TD and CP and between the median data of TD and DMD (i.e., the absolute difference relative to the median TD scores) were also compared with the SEM% and MDC% values of the CP and DMD cohort, respectively.

2.3 Part three: responsiveness of the instrumented strength assessment

2.3.1 Participants

In part three of the study, only children with CP and DMD who participated in ongoing follow-up studies, were included. Due to the lack of previously reported follow-up studies using the same instrumented strength assessment and the explorative nature of our ongoing studies, the required sample size could not be calculated *a priori*. Hence, all available data from the ongoing studies were checked to determine if they could be included in part three of the current study. The assessors of these data were the well-trained senior human movement scientist and pediatric physiotherapist for the CP and DMD cohort. The inclusion and exclusion criteria of these subjects were the same as in part one of this study (Table 1). A maximum age of 12 years was an additional inclusion criterion for the children with CP (defined by the design of the ongoing study). This resulted in a total of 26 children with CP. Even though DMD is a progressive disorder, natural history studies have shown that children with DMD present maturational improvements before the age of 7 years, followed by a period of stability, and finally entering in a more rapid decline (Mcdonald et al., 2013b; Goemans et al., 2016; Jumah et al., 2019). In addition, increases in muscle strength before the age of 7.5 years have previously been reported (Lerario et al., 2012). Therefore, two additional inclusion criteria were used for children with DMD: 1) age > 7.5 years old and 2) an observed motor decline indicated by a decrease in 6 min walking test (6 MWT) > 8% of the 6 MWT at the first measurement, which corresponds to the minimal clinically important difference previously reported (Mcdonald et al., 2013a). This way, we ensured that the included DMD patients were in "decline." Two DMD groups, with a follow-up

TABLE 2 Intra-rater intersession reliability results of the TD children as well as children with CP and DMD included in the reliability study.

	TD: Intra-rater intersession reliability (A1-A3)				CP: Intra-rater intersession reliability (A1-A2)				DMD: Intra-rater intersession reliability (A1-A2)			
	Median (IQR)				Median (IQR)				Median (IQR)			
Number	14				11				11			
Age (years)	10.5 (4.0)				15.2 (4.4)				12.2 (2.2)			
Weight (kg)	34.0 (14.5)				51.3 (15.0)				42.8 (14.7)			
Height (cm)	141.5 (15.0)				151.0 (24.7)				128.9 (6.6)			
GMFCS	—				I: 1 II: 6 III:4				—			
	Median (IQR)	ICC (95%CI)	SEM	MDC	Median (IQR)	ICC (95%CI)	SEM	MDC	Median (IQR)	ICC (95%CI)	SEM	MDC
Primary parameter: Torque (Nm)												
Dorsiflexion	10.7 (3.2)	0.914 (0.760–0.971)	1.8	4.9	3.5 (2.5)	0.840 (0.504–0.955)	0.9	2.4	3.7 (3.1)	0.745 (0.307–0.924)	0.8	2.3
Plantar flexion	17.5 (7.9)	0.626 (0.194–0.860)	3.7	10.4	6.6 (4.3)	0.743 (0.193–0.936)	2.0	5.6	8.6 (5.0)	0.743 (0.277–0.924)	1.8	4.9
Knee extension	43.2 (21.8)	0.874 (0.657–0.957)	8.7	24.1	13.4 (18.3)	0.935 (0.779–0.982)	3.0	8.3	15.2 (10.8)	0.915 (0.728–0.976)	2.7	7.4
Knee flexion	27.9 (19.2)	0.911 (0.751–0.971)	3.5	9.6	16 (16.8)	0.719 (0.276–0.914)	5.6	15.6	14.6 (7.3)	0.833 (0.508–0.952)	1.7	4.8
Hip abduction	33.9 (18.8)	0.892 (0.704–0.982)	4.7	13.1	9.4 (4.3)	0.860 (0.582–0.960)	3.2	9.0	16.4 (7.0)	0.728 (0.201–0.926)	2.8	7.7
Hip extension	38.2 (25.3)	0.768 (0.420–0.919)	9.1	25.2	22.7 (31.3)	0.947 (0.795–0.986)	3.6	10.0	20.7 (18.1)	0.863 (0.576–0.960)	3.6	10.1
Hip flexion	58.2 (43.0)	0.622 (0.180–0.859)	17.1	47.3	31.2 (24.7)	0.870 (0.585–0.963)	7.6	21.0	30.5 (15.2)	0.797 (0.352–0.943)	4.1	11.4
Primary parameter: Normalized torque (Nm/kg)												
Dorsiflexion	0.29 (0.05)	0.750 (0.400–0.911)	0.03	0.09	0.08 (0.08)	0.790 (0.414–0.938)	0.03	0.09	0.11 (0.08)	0.760 (0.354–0.928)	0.03	0.09
Plantar flexion	0.44 (0.25)	0.713 (0.333–0.896)	0.10	0.29	0.14 (0.16)	0.797 (0.337–0.950)	0.05	0.15	0.24 (0.19)	0.804 (0.414–0.944)	0.05	0.15
Knee extension	1.30 (0.39)	0.462 (−0.046–0.786)	0.23	0.65	0.3 (0.38)	0.931 (0.761–0.981)	0.05	0.15	0.41 (0.28)	0.905 (0.699–0.973)	0.08	0.21
Knee flexion	0.81 (0.24)	0.862 (0.621–0.954)	0.08	0.21	0.35 (0.42)	0.562 (-0.059–0.862)	0.19	0.52	0.38 (0.19)	0.889 (0.657–0.968)	0.04	0.12
Hip abduction	0.96 (0.22)	0.343 (-0.220–0.730)	0.14	0.40	0.25 (0.24)	0.898 (0.680–0.971)	0.05	0.15	0.44 (0.2)	0.750 (0.262–0.932)	0.08	0.23
Hip extension	1.11 (0.31)	0.121 (−0.429–0.600)	0.22	0.60	0.45 (0.5)	0.946 (0.781–0.986)	0.06	0.18	0.54 (0.46)	0.857 (0.563–0.959)	0.12	0.33
Hip flexion	1.75 (0.38)	0.088 (−0.419–0.568)	0.40	1.12	0.86 (0.71)	0.884 (0.627–0.967)	0.15	0.41	0.81 (0.33)	0.816 (0.434–0.947)	0.12	0.34
Secondary parameter: Force (N)												
Dorsiflexion	104.9 (36.4)	0.922 (0.774–0.974)	13.6	37.7	35.7 (26.1)	0.787 (0.378–0.938)	9.3	25.7	47.8 (35.4)	0.674 (0.199–0.899)	10.6	29.5
Plantar flexion	171.5 (90.3)	0.652 (0.202–0.874)	38.7	107.4	71.7 (46.1)	0.721 (0.149–0.930)	21.2	58.9	103.6 (82.6)	0.775 (0.360–0.934)	23.2	64.3
Knee extension	177.5 (58.7)	0.779 (0.445–0.923)	34.7	96.1	59.5 (59.4)	0.919 (0.729–0.978)	11.0	30.4	79.5 (68.1)	0.909 (0.712–0.974)	13.6	37.8

(Continued on following page)

TABLE 2 (*Continued*) Intra-rater intersession reliability results of the TD children as well as children with CP and DMD included in the reliability study.

Secondary parameter: Force (N)												
Knee flexion	116.8 (56.1)	0.890 (0.690–0.963)	12.2	33.8	69.8 (53.2)	0.621 (0.110–0.879)	22.2	61.6	69.2 (38.9)	0.844 (0.531–0.955)	9.4	26.0
Hip abduction	126.4 (38.7)	0.785 (0.446–0.926)	18.5	51.2	35.6 (13.1)	0.846 (0.549–0.956)	10.7	29.7	66.5 (24.1)	0.750 (0.246–0.932)	12.0	33.2
Hip extension	143.5 (43.3)	0.585 (0.124–0.843)	33.7	93.3	90.9 (98.3)	0.939 (0.770–0.984)	12.3	34.2	97.9 (74.9)	0.865 (0.583–0.961)	15.3	42.4
Hip flexion	229.9 (125.1)	0.453 (−0.027–0.778)	54.6	151.4	128.5 (69.4)	0.838 (0.505–0.954)	26.5	73.3	134.7 (44.7)	0.749 (0.233–0.929)	16.9	46.9

Abbreviations in alphabetical order: A1, assessment one; A2, assessment two; A3, assessment three; CI, confidence interval; cm, centimeter; CP, cerebral palsy; DMD, Duchenne muscular dystrophy; GMFCS, gross motor function classification system; ICC, intraclass correlation coefficient; IQR, interquartile range; kg, kilogram; MDC, minimal detectable change; N, Newton; Nm, Newton meters; Nm/kg, Newton meters per kilogram; SEM, standard error of measurement; TD, typical developing; Green, excellent to good reliability; Blue, moderate reliability; Red, poor reliability.

interval of 1 year and 2 years, were created. The first group (1-year interval) consisted of 13 pairs of measurements from eight children with DMD. Six of these 13 children with DMD were included in the second group (2-year interval).

2.3.2 Study design

The responsiveness of the instrumented strength assessment was defined by investigating differences in MVICs between two measurement sessions, within the CP and DMD cohort. The enrolled children with CP were involved in a strength intervention study that consisted of a 12-week, partially home-based, intervention for the lower limb muscles acting around the ankle and knee. Hence, the hip joint was not included for the responsiveness assessment in children with CP. The strength intervention followed the guidelines of progressive resistance training, prescribing three to four training sessions per week (Verschuren et al., 2011), of which one to three sessions were performed under the supervision of the physiotherapist and the remaining ones at home. The training program consisted of one to three multi-joint exercises, followed by two to three single-joint exercises targeting KE, KF, and PF. Exercises were performed in three sets of ten repetitions, to match an estimated effort of 60%–80% of the 1-repetition maximum, and were gradually progressed. The instrumented strength assessment was performed at baseline and at the end of the intervention. The enrolled children with DMD were involved in a follow-up study that described the natural decline of muscle strength of the ankle, knee and hip muscles over time. Data after 1 year and after 2 years were analyzed. Figure 1C shows an overview of the study design.

2.3.3 Data collection

Idem part one.

2.3.4 Data analysis

Idem part one.

2.3.5 Statistical analysis.

First, Wilcoxon Signed-Rank tests were performed to investigate differences in MVICs between two measurement sessions, i.e., to evaluate whether muscle strength increased in children with CP and decreased in the boys with DMD. The significant threshold was set to 0.0063, to correct for the comparison of eight parameters, in the CP cohort. In the DMD cohort, the significant threshold was set to 0.0036, to correct for the comparison of 14 parameters. p-values ranging between the significant thresholds and 0.05 are described as trends. Second, the absolute difference between the MVICs of the two measurements per participant was calculated. The median of all absolute differences was compared with the absolute SEMs and MDCs determined in part one. This comparison was visualized, in the absence of additional statistical testing, and indicated the ability of the instrumented strength assessment to detect the responsiveness in the CP and DMD cohort. The relative difference was calculated as absolute difference between the MVICs of two measurements relative to the MVIC of the first measurement per participant. The median of all relative differences was compared to the SEM% and MDC% from part one.

3 Results

In the results section, only the primary parameters are described. The results on the secondary parameters can be found in the corresponding tables.

3.1 Part one: reliability

Subject characteristics and median values for the MVICs for the three cohorts of the reliability study are presented in Tables 2 and 3.

Table 2 shows the ICC, SEM and MDC values of the intra-rater reliability, while the SEM% and MDC% are provided in

TABLE 3 Inter-rater intrasession and intersession reliability results for the TD children included in the reliability study.

	TD: Inter-rater intrasession reliability (A1-A2)				TD: Inter-rater intersession reliability (A2-A3)			
	Frequency or median (IQR)				Frequency or median (IQR)			
Number	14				14			
Age (years)	10.5 (4.0)				10.5 (4.0)			
Weight (kg)	34.0 (14.5)				34.0 (14.5)			
Height (cm)	141.5 (15.0)				141.5 (15.0)			
	Median (IQR)	ICC (95%CI)	SEM	MDC	Median (IQR)	ICC (95%CI)	SEM	MDC
Primary parameter: Torque (Nm)								
Dorsiflexion	10.1 (4.7)	0.936 (0.817–0.979)	1.4	4.0	9.9 (4.3)	0.925 (0.761–0.976)	1.5	4.2
Plantar flexion	14.3 (7.6)	0.234 (-0.365–0.676)	6.2	17.2	16.4 (7.2)	0.397 (-0.122–0.753)	5.3	14.8
Knee extension	40.1 (24.4)	0.936 (0.536–0.984)	4.4	12.3	38.3 (16.5)	0.867 (0.646–0.955)	9.1	25.2
Knee flexion	27.8 (18.7)	0.877 (0.660–0.959)	4.9	13.5	27.1 (16.4)	0.791 (0.469–0.928)	5.9	16.4
Hip abduction	33.6 (17.5)	0.900 (0.723–0.967)	4.8	13.4	32.3 (20.3)	0.874 (0.662–0.957)	5.4	14.9
Hip extension	42.3 (23.7)	0.735 (0.344–0.907)	10.6	29.5	38.0 (20.0)	0.863 (0.628–0.954)	7.9	22.0
Hip flexion	57.7 (36.1)	0.714 (0.297–0.900)	12.9	35.7	56.7 (40.2)	0.787 (0.465–0.926)	10.9	30.1
Primary parameter: Normalized torque (Nm/kg)								
Dorsiflexion	0.26 (0.08)	0.758 (0.398–0.916)	0.03	0.09	0.29 (0.09)	0.757 (0.398–0.915)	0.03	0.09
Plantar flexion	0.44 (0.23)	0.296 (-0.287–0.708)	0.14	0.39	0.47 (0.23)	0.332 (-0.157–0.712)	0.14	0.38
Knee extension	1.11 (0.45)	0.417 (-0.054–0.756)	0.30	0.84	1.18 (0.45)	0.389 (-0.098–0.744)	0.30	0.85
Knee flexion	0.78 (0.31)	0.659 (0.204–0.878)	0.14	0.38	0.78 (0.22)	0.622 (0.140–0.862)	0.14	0.40
Hip abduction	0.91 (0.35)	0.701 (0.307–0.892)	0.12	0.33	0.92 (0.22)	0.502 (0.018–0.803)	0.16	0.45
Hip extension	1.17 (0.34)	0.222 (-0.366–0.668)	0.25	0.71	1.07 (0.31)	0.360 (-0.220–0.742)	0.22	0.61
Hip flexion	1.67 (0.36)	0.209 (-0.226–0.624)	0.33	0.92	1.61 (0.45)	0.344 (-0.219–0.731)	0.30	0.82
Secondary parameter: Force (N)								
Dorsiflexion	101.4 (42.5)	0.899 (0.723–0.966)	13.7	38.1	97.7 (42.1)	0.674 (0.199–0.899)	14.8	41.1
Plantar flexion	147.6 (80.8)	0.171 (-0.411–0.637)	57.9	160.5	162.6 (73.9)	0.214 (-0.330–0.655)	50.7	140.5
Knee extension	174.4 (91.3)	0.903 (0.090–0.979)	12.9	35.8	164.6 (52.6)	0.832 (0.556–0.943)	29.6	81.7
Knee flexion	111.1 (63.5)	0.750 (0.375–0.913)	21.3	59.0	115.2 (62.8)	0.678 (0.239–0.885)	23.5	65.1
Hip abduction	125.4 (56.6)	0.849 (0.604–0.948)	16.8	46.5	118.5 (39.8)	0.782 (0.455–0.924)	21.1	58.6
Hip extension	156.0 (52.6)	0.645 (0.185–0.871)	35.9	99.5	138.1 (54.3)	0.773 (0.422–0.920)	28.0	77.6
Hip flexion	221.2 (100.5)	0.538 (0.055–0.822)	42.6	118.0	219.4 (91.6)	0.694 (0.270–0.891)	35.3	97.8

Abbreviations in alphabetical order: A1, assessment one; A2, assessment two; A3, assessment three; CI, confidence interval; cm, centimeter; ICC, intraclass correlation coefficient; IQR, interquartile range; kg, kilogram; MDC, minimal detectable change; N, newton; Nm, newton meters; Nm/kg, newton meters per kilogram; SEM, standard error of measurement; TD, typically developing; Green, excellent to good reliability; Blue, moderate reliability; Red, poor reliability.

Supplementary Table S1. Taking the results of the three cohorts into account, 65.1% of the parameters were classified as good to excellent, 27.0% as moderate and 7.9% as poor reliability. In the TD cohort, 47.6% of the parameters were classified as good to excellent, 28.6% as moderate and 23.8% as poor reliability. The ICCs for torque were all classified as good to excellent, except for PF and HF, which were classified as moderate. Normalized torques indicated the lowest reliability, whereby all ICCs around the hip were classified as poor, while ICCs around the knee and ankle were moderate to good, except for KE which showed a poor reliability. In the CP cohort, 76.2% of the parameters were classified as good to excellent and 23.8% as moderate reliability. For torque, ICCs were all classified as good to excellent, except for PF and KF, which were classified as moderate. The ICCs of the normalized torques were all

TABLE 4 Subject characteristics and median torque, normalized torque and force of the TD, CP, and DMD cohorts and statistical results of the comparison of the three cohorts, included in the validity study.

	TD	CP	DMD	Kruskal–wallis test
Subject information	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**	***p*-value**
Number of participants	28	26	30	
Age (years)	10.9 (2.8)	12.0 (4.0)	10.6 (4.2)	$p = 0.057$
Weight (kg)	36.2 (11.8)	42.8 (26.1)	31.9 (20.6)	$p = 0.136$
Height (cm)	144.7 (15.0)	144.5 (18.3)°	125.4 (17.9)*	$p < 0.001$
GMFCS-level	—	I:2 II:16 III:8	—	
Primary parameter: Torque (Nm)				
Dorsiflexion	10.1 (4.6)	1.8 (2.4)*	3.7 (2.4)*	$p < 0.001$
Plantar flexion	16.2 (7.9)	4.7 (5.0)*	9.5 (6.7)*	$p < 0.001$
Knee extension	38.1 (25.1)	12.2 (10.8)*	16.5 (10.9)*	$p < 0.001$
Knee flexion	29.6 (17.1)	11.8 (9.0)*	9.3 (7.8)*	$p < 0.001$
Hip abduction	26.5 (20.2)	8.5 (7.2)*	11.8 (9.8)*	$p < 0.001$
Hip extension	38.5 (18.2)	17.2 (9.1)*°	7.6 (7.3)*	$p < 0.001$
Hip flexion	51.4 (27.3)	25.9 (14.7)*	26.7 (11.0)*	$p < 0.001$
Primary parameter: Normalized torque (Nm/kg)				
Dorsiflexion	0.33 (0.21)	0.05 (0.05)*°	0.12 (0.08)*	$p < 0.001$
Plantar flexion	0.52 (0.47)	0.15 (0.19)*°	0.27 (0.27)*	$p < 0.001$
Knee extension	1.18 (0.44)	0.37 (0.39)*	0.50 (0.32)*	$p < 0.001$
Knee flexion	0.89 (0.33	0.30 (0.26)*	0.33 (0.26)*	$p < 0.001$
Hip abduction	0.90 (0.34)	0.20 (0.21)*°	0.44 (0.27)*	$p < 0.001$
Hip extension	1.25 (0.54)	0.39 (0.36)*°	0.24 (0.32)*	$p < 0.001$
Hip flexion	1.43 (0.64)	0.65 (0.56)*	0.90 (0.53)*	$p < 0.001$
Secondary parameter: Force (N)				
Dorsiflexion	106.3 (47.7)	20.9 (23.7)*°	42.9 (35.1)*	$p < 0.001$
Plantar flexion	162.0 (88.9)	54.0 (46.0)*°	115.1 (81.3)*	$p < 0.001$
Knee extension	162.4 (74.8)	53.4 (51.1)*	82.3 (48.3)*	$p < 0.001$
Knee flexion	121.8 (67.2)	47.9 (26.5)*	49.0 (34.0)*	$p < 0.001$
Hip abduction	110.5 (52.0)	33.1 (25.8)*°	60.7 (34.2)*	$p < 0.001$
Hip extension	157.3 (42.3)	67.0 (38.4)*°	30.8 (36.5)*	$p < 0.001$
Hip flexion	196.9 (73.7)	100.4 (57.0)*	122.8 (48.5)*	$p < 0.001$

Abbreviations in alphabetic order: cm, centimeter; CP, cerebral palsy; DMD, Duchenne muscular dystrophy; GMFCS, gross motor function classification scale; IQR, interquartile range; kg, kilogram; m, meter; N, Newton; Nm, Newton meter; Nm/kg, Newton meter per kilogram body weight; TD, typically developing. Symbols represent significance according to the Mann Whitney U test with $p < 0.0036$: *TD-CP, *TD-DMD, °CP-DMD.

classified as good to excellent, except for KF, which showed a moderate ICC. In the DMD cohort, 66.7% of the parameters were classified as good to excellent and 33.7% as moderate reliability. For torque, ICCs were all classified as good to excellent, except for DF, PF, and HA, which were classified as moderate. All the ICCs for normalized torque for boys with DMD were good to excellent, except for HA, which showed a moderate ICC.

For the TD cohort, the ICC, SEM, and MDC of the inter-rater intrasession and intra-rater intersession are presented in Table 3, while the SEM% and MDC% are provided in Supplementary Table S1. For the inter-rater intrasession, 38.1% of the ICCs were classified as good to excellent, 33.3% as moderate and 28.6% as poor. For torque, the reliability of all muscle groups was classified as good to excellent, except for HE and HF, which were classified as moderate and PF, which was classified as poor. Concerning the ICCs for

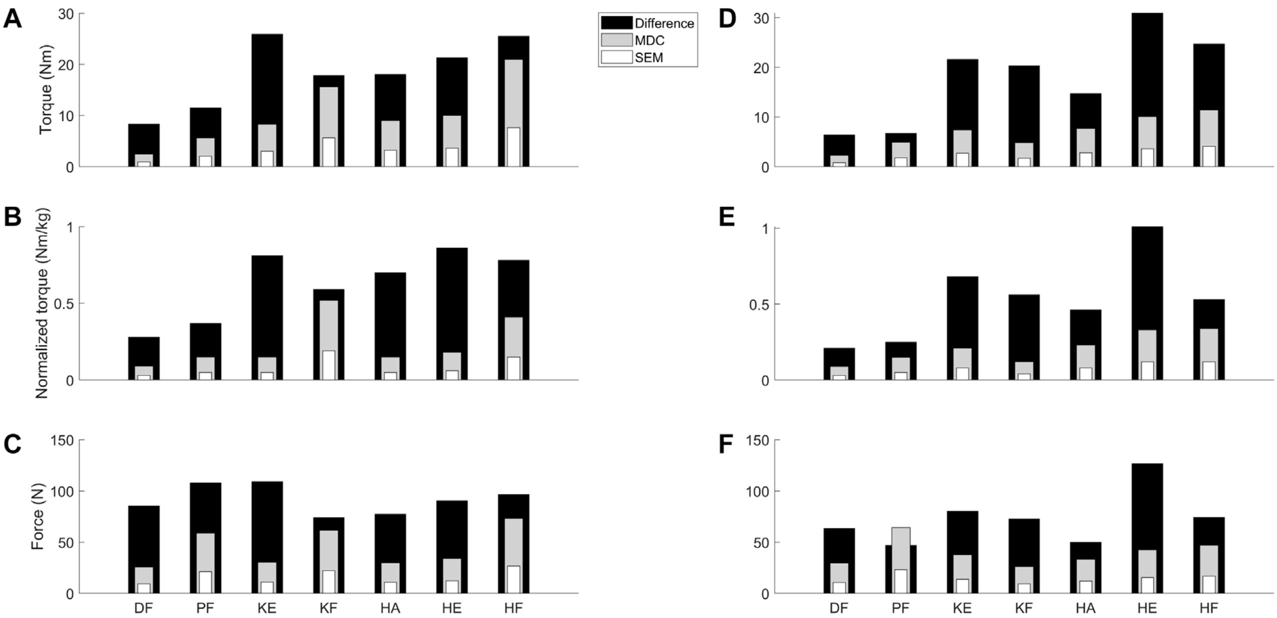

FIGURE 3
Visual representation to compare the absolute SEM (white) and MDC (grey) values as retrieved from the reliability study for the children with CP and DMD with the absolute differences between the median values of TD children and the clinical cohorts (black) from the validity study. Panel A–C visualize the data for torque **(A)**, normalized torque **(B)** and the force **(C)** in the children with CP. Panel D–F visualize the data for the torque **(D)**, normalized torque **(E)** and the force **(F)** in the children with DMD. Abbreviations in alphabetical order: CP, cerebral palsy; DF, dorsiflexion; DMD, Duchenne muscular dystrophy; HA, hip abduction; HE, hip extension; HF, hip flexion; KE, knee extension; KF, knee flexion; MDC, minimal detectable change; N, Newton; Nm, Newton meter; Nm/kg, Newton meter per kilogram body weight; PF, plantar flexion; SEM, standard error of measurement; TD, typically developing.

normalized torques, only for DF, the reliability was classified as good, whereas KF and HA had moderate and PF, KE, HF, and HE had poor reliability. For the inter-rater intersession reliability, 47.6% of the ICCs were classified as good to excellent, 23.8% as moderate and 28.6% as poor. For torque, the ICCs of all muscle groups were classified as good to excellent reliability, except for PF which was classified as poor. Concerning the ICCs for normalized torques, only DF had good reliability, whereas KF and HA had moderate and PF, KE, HF, and HE had poor reliability.

3.2 Part two: validity

The descriptive results of the three cohorts included in the validity study and the median values of the MVICs for the three cohorts are presented in Table 4. The children with CP and DMD were significantly weaker than the TD children for all muscle groups ($p \leq 0.001$), whereas muscle-specific differences were observed between CP and DMD. The children with CP were significantly weaker than the children with DMD in the ankle joint for normalized torque, and for HA normalized torque ($p \leq 0.002$), whereas children with DMD were significantly weaker than the children with CP for HE torque and normalized torque ($p < 0.001$).

The absolute differences between the medians of the TD and CP cohort ranged between 8.3 Nm (DF) and 25.9 Nm (KE) for torque, and between 0.28 Nm/kg (DF) and 0.86 Nm/kg (HE) for normalized torque (Supplementary Table S2). The absolute differences for the CP cohort for torque and normalized torque were all above the absolute SEM and MDC of the CP cohort (Figures 3A–C). The absolute differences between the medians of the TD and DMD cohort ranged between 6.4 Nm (DF) and 30.9 Nm (HE) for torque, and between 0.21 Nm/kg (DF) and 1.01 Nm/kg (HE) for normalized torque (Supplementary Table S2). These absolute differences were all above the absolute SEM and MDC of the DMD cohort, except for PF force (Figures 3D–F). To limit the discussed parameters and outcomes, the comparison of the relative differences with SEM% and MDC% were included in Supplementary Table S2 and Supplementary Figure S1.

3.3 Part three: responsiveness

As descriptive results, the subject characteristics and the median values of the MVICs for the responsiveness study are presented in Table 5 for the CP and in Table 6 for the DMD

TABLE 5 Subject characteristics, median MVICs of the first and second assessment and statistical results after the strength intervention of children with CP included in the responsiveness study.

Subject information			CP Frequency or median (IQR)
Number of participants			26
Age (years)			8.1 (4.5)
Weight (kg)			28.4 (15.2)
Height (cm)			127.8 (24.9)
GMFCS-level			I:17 II:6 III:3
	A1	A2	Wilcoxon Rank test *p*-value
Primary parameter: Torque (Nm)			
Dorsiflexion	2.0 (2.1)	3.2 (2.6)	$p = 0.003$
Plantar flexion	5.1 (5.8)	10.3 (7.3)	$p < 0.001$
Knee extension	12.4 (20.1)	20.0 (17.4)	$p < 0.001$
Knee flexion	8.4 (11.1)	18.4 (15.6)	$p < 0.001$
Primary parameter: Normalized torque (Nm/kg)			
Dorsiflexion	0.08 (0.7)	0.11 (0.12)	$p = 0.003$
Plantar flexion	0.19 (0.16)	0.33 (0.17)	$p < 0.001$
Knee extension	0.44 (0.57)	0.62 (0.42)	$p = 0.003$
Knee flexion	0.32 (0.32)	0.58 (0.39)	$p < 0.001$
Secondary parameter: Force (N)			
Dorsiflexion	24.7 (19.3)	38.0 (29.5)	$p = 0.001$
Plantar flexion	59.4 (56.0)	125.3 (71.6)	$p < 0.001$
Knee extension	62.0 (86.2)	95.7 (68.5)	$p = 0.003$
Knee flexion	40.1 (44.1)	81.7 (61.9)	$p < 0.001$

Abbreviations in alphabetical order: A1, assessment one; A2, assessment two; CP, cerebral palsy; GMFCS, gross motor function classification scale; IQR, interquartile range; kg, kilogram; cm, centimeter; N, Newton; Nm, Newton meter; Nm/kg, Newton meter per kilogram body weight.

cohort. In the CP cohort, the muscle strength increased after the strength intervention in all muscle groups ($p < 0.003$). The DMD cohort showed no statistically significant changes in muscle strength over the observed intervals. However, several trends in decreasing muscle strength appeared ($p < 0.05$).

The medians of the absolute differences observed in the CP cohort ranged between 1.1 Nm (DF) and 7.7 Nm (KF) for torque, and between 0.03 Nm/kg (DF) and 0.22 Nm/kg (KF) for normalized torque between the strength scores before and after training (Supplementary Table S3). All medians of the absolute differences were larger than the absolute SEM, except for KE torque and DF normalized torque, where the medians of the absolute increases were similar to the absolute SEM (Figures 4A–C). However, all medians of the absolute increases were lower than the absolute MDC values. In the DMD cohort, the absolute decreasing trend in HA torque was 1.66 Nm over an interval of 2 years (Supplementary Table S3). For normalized torque, DF, KE, HA, and HF showed trends in medians of the absolute decreases, ranging from 0.02 Nm/kg (DF) to 0.06 Nm/kg (HA) over an interval of 1 year and from 0.05 Nm/kg (DF) to 0.19 Nm/kg (HF) over an interval of 2 years. The detected trends for children with DMD revealed that the medians of the absolute decreases over an interval of 2 years exceeded the absolute SEM of the DMD cohort for normalized torque of DF, KE, HA, and HF (Figures 4D–F). For the other trends in DMD, i.e., DF and HA normalized torque over 1 year, and HA torque over 2 years, the median of the absolute decreases were smaller than the absolute SEM of the DMD cohort. All medians of the absolute decreases observed in boys with DMD were lower than the absolute MDC values. To limit the discussed parameters and outcomes, the relative differences with SEM% and MDC% from the responsiveness study were only included in Supplementary Table S3 and Supplementary Figure S2.

4 Discussion

The overall aim of the current study was to comprehensively determine the clinimetric properties of the instrumented strength assessment in a TD, CP, and DMD cohort for muscle groups around the ankle, knee and hip. To achieve this overall aim, three sub-aims were defined, and the study was divided in three parts, covering the reliability, the construct validity, and the responsiveness of the instrumented strength assessment.

4.1 Part one: reliability

Our hypothesis concerning the first sub-aim was only partly confirmed. Indeed, some strength measurements showed a lower reliability than expected. In general, the instrumented strength assessment showed moderate to excellent reliability in the CP and DMD cohort and poor to excellent reliability in the TD cohort. This difference between the clinical cohorts and the TD cohort may be partly explained by the difference in the assessors' experience, since the human movement scientist and pediatric physiotherapist collected the assessments in the CP and DMD cohort, while the trained master students collected the assessments in the TD cohort. However, it can also be explained by the higher force producing capacity of TD participants, introducing a larger window for variation and resulting in more difficulties to limit

TABLE 6 Subject characteristics, median MVICs of the first and second assessment and statistical results for the 1-year and 2-year follow-up period of boys with DMD included in the responsiveness study.

	DMD 1 year interval			DMD 2 year interval		
	Frequency or median (IQR)			Frequency or median (IQR)		
Number of participants	8 (i.e., 13 pairs of measurements)			6 (i.e., 6 pairs of measurements)		
Age (years)	11.0 (2.8)			9.8 (3.1)		
Weight (kg)	36.7 (10.7)			33.1 (11.0)		
Height (cm)	127.5 (11.0)			126.7 (14.0)		
	A1	A2	Wilcoxon Rank test (*p*-value)	A1	A2	Wilcoxon Rank test (*p*-value)
Primary parameter: Torque (Nm)						
Dorsiflexion	4.7 (1.2)	4.0 (1.7)	$p = 0.087$	4.8 (0.7)	3.7 (1.6)	$p = 0.075$
Plantar flexion	7.2 (5.5)	9.4 (7.5)	$p = 0.701$	7.1 (5.0)	5.9 (4.4)	$p = 0.600$
Knee extension	12.2 (8.9)	10.1 (7.1)	$p = 0.133$	13.2 (11.4)	8.9 (7.4)	$p = 0.075$
Knee flexion	9.6 (6.3)	9.4 (6.6)	$p = 0.507$	10.3 (5.8)	7.6 (5.85)	$p = 0.463$
Hip abduction	12.1 (9.0)	8.9 (5.6)	$p = 0.087$	12.4 (9.7)	9.9 (4.6)	$p = 0.028$
Hip extension	4.3 (6.1)	3.7 (3.6)	$p = 0.345$	4.9 (12.3)	2.7 (7.8)	$p = 0.600$
Hip flexion	24.3 (17.2)	20.5 (18.9)	$p = 0.311$	24.8 (24.5)	19.1 (27.4)	$p = 0.249$
Primary parameter: Normalized torque (Nm/kg)						
Dorsiflexion	0.14 (0.06)	0.10 (0.06)	$p = 0.029$	0.16 (0.04)	0.10 (0.04)	$p = 0.028$
Plantar flexion	0.25 (0.17)	0.23 (0.21)	$p = 0.906$	0.24 (0.16)	0.20 (0.14)	$p = 0.207$
Knee extension	0.34 (0.21)	0.26 (0.19)	$p = 0.092$	0.36 (0.34)	0.23 (0.26)	$p = 0.043$
Knee flexion	0.28 (0.18)	0.24 (0.14)	$p = 0.220$	0.32 (0.10)	0.22 (0.15)	$p = 0.080$
Hip abduction	0.33 (0.24)	0.25 (0.17)	$p = 0.041$	0.40 (0.32)	0.27 (0.15)	$p = 0.028$
Hip extension	0.10 (0.14)	0.10 (0.07)	$p = 0.184$	0.14 (0.35)	0.08 (0.16)	$p = 0.249$
Hip flexion	0.62 (0.50)	0.49 (0.45)	$p = 0.235$	0.75 (0.71)	0.58 (0.76)	$p = 0.043$
Secondary parameter: Force (N)						
Dorsiflexion	55.9 (16.1)	43.3 (15.2)	$p = 0.046$	53.4 (18.2)	39.3 (22.7)	$p = 0.046$
Plantar flexion	93.6 (79.9)	99.4 (85.4)	$p = 0.917$	85.2 (64.9)	71.3 (66.1)	$p = 0.463$
Knee extension	62.1 (47.5)	48.4 (34.7)	$p = 0.075$	65.7 (55.3)	43.4 (81.18)	$p = 0.046$
Knee flexion	48.1 (29.9)	48.0 (28.6)	$p = 0.249$	51.4 (25.9)	37.4 (23.6)	$p = 0.345$
Hip abduction	53.0 (33.4)	37.0 (25.2)	$p = 0.046$	53.4 (34.6)	38.2 (18.4)	$p = 0.028$
Hip extension	16.5 (24.2)	16.0 (13.9)	$p = 0.279$	23.1 (45.5)	10.7 (28.9)	$p = 0.249$
Hip flexion	98.6 (70.5)	90.1 (67.7)	$p = 0.211$	106.3 (94.5)	82.2 (99.2)	$p = 0.173$

Abbreviations in alphabetical order: A1, assessment one; A2, assessment two; DMD, Duchenne muscular dystrophy; IQR, interquartile range; kg, kilogram; cm, centimeter; N, Newton; Nm, Newton meter; Nm/kg, Newton meter per kilogram body weight.

compensations. A slightly lower than expected intra-rater reliability was observed for the torque of PF and HF in TD, of PF and KF in CP and of DF, PF and HA in DMD, which were all classified as moderate. For normalized torque, the reliability of DF and PF in TD, KF in CP and HA in DMD were classified as moderate, while the reliability of KE and measurements of the muscle groups around the hip were classified as poor in the TD cohort. There were no obvious differences between the reliability indices of TD children and the indices of the clinical cohorts. Yet, in both clinical cohorts, a wide range of CIs was observed, which can be attributed to the limited sample size. Hence, caution is

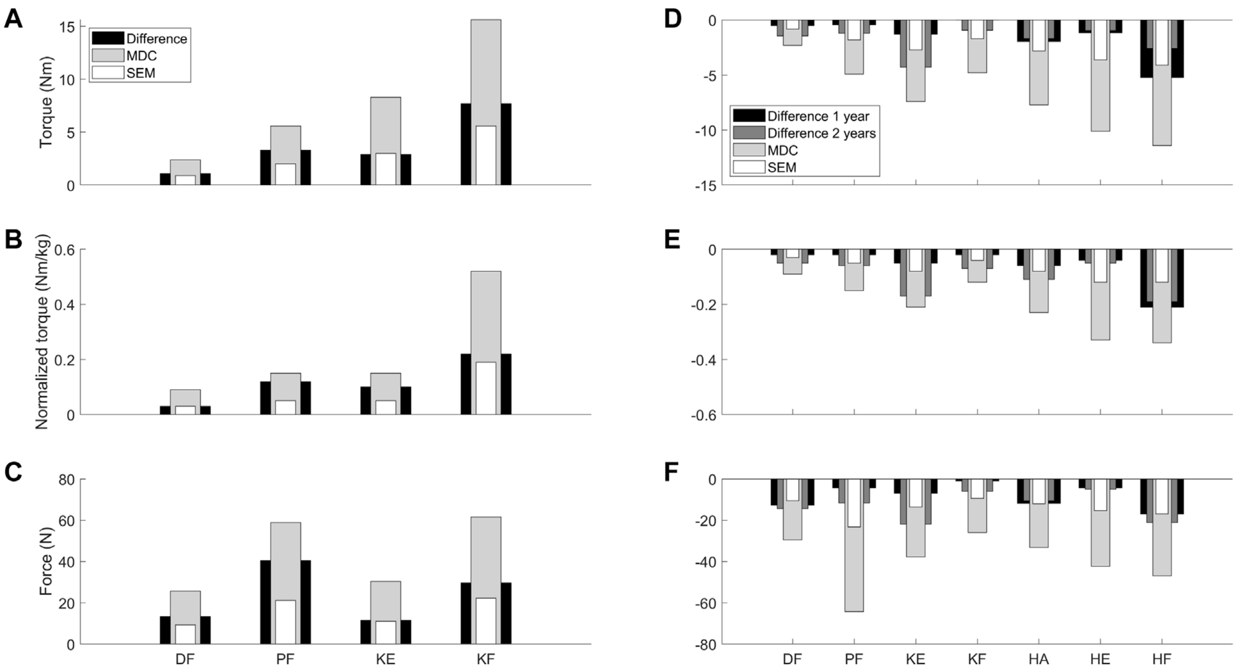

FIGURE 4
Visual representation to compare the absolute SEM (white) and MDC (light grey) values as retrieved from the reliability study for the children with CP and DMD with the median of the absolute differences between the two assessments (black = CP and 1 year interval DMD; dark grey = 2 year interval DMD) from the responsiveness study. Panel **A-C** visualize the data for torque **(A)**, normalized torque **(B)** and the force **(C)** in the children with CP. Panel **D-F** visualize the data for torque **(D)**, normalized torque **(E)** and the force **(F)** in the children with DMD. Abbreviations in alphabetical order: CP, cerebral palsy; DF, dorsiflexion; DMD, Duchenne muscular dystrophy; HA, hip abduction; HE, hip extension; HF, hip flexion; KE, knee extension; KF, knee flexion; MDC, minimal detectable change; N, Newton; Nm, Newton meter; Nm/kg, Newton meter per kilogram body weight; PF, plantar flexion; SEM, standard error of measurement.

needed in the interpretation of the results. In general, proximal muscle groups demonstrated a slightly better reliability than distal muscle groups in both patient groups. These results were in line with the findings in the study of Florence et al. (1992), who investigated the intra-rater reliability of manual muscle testing when assessing muscle strength in children with DMD. The study of Florence et al. (1992) showed a reliability range with ICCs from 0.65 to 0.93, with the proximal muscles presenting higher reliability values (Florence et al., 1992). In the study of Berry et al. (2004), results similar to the current study where found, while their set-up did not include fixation of the HHD. Berry et al. (2004) included 15 children diagnosed with CP to evaluate the intra- and intersession reliability of the HHD, based on bilateral measurements of KE, KF and HA, with a time interval of 4–14 days. Intra-rater ICCs of 0.840 or higher were found, except for the left KF (Berry et al., 2004). The current study confirmed these results for the KE and HA muscles, but not for the KF muscles, which showed a lower ICC value.

The current study results revealed that the inter-rater intrasession ICCs were higher than the intra-rater intersession ICCs in the TD cohort, pointing towards the potential impact of repositioning the child in the set-up and the potential different performance on different test days, which appears to be larger than the impact of different raters. However, the impact of training experience on the applied instrumented strength assessments should be further explored in future studies. Goudriaan et al. (2018a) investigated the intra-rater and inter-rater reliability of the instrumented strength assessment (within one session) and showed higher inter-rater ICCs compared to the intra-rater ICCs, whilst torque showed better ICCs than normalized torque (Goudriaan et al., 2018a). The current study confirmed these results, showing similar ranges of the inter- and intra-rater ICCs in the TD cohort, and added results for the hip joint and two clinical cohorts (Goudriaan et al., 2018a).

In the current study, normalization of TD torque data to body weight resulted in lower ICC-values with wider CIs. This is not surprising, since the variability of normalized torque data was smaller due to the known relationship between strength and body weight, resulting in lower ICC values. Indeed, it is known that the ICC depends on the variability of the data (Florence et al., 1992; Berry et al., 2004). The lower ICC values for PF torque (intra-rater: 0.626, inter-rater—intrasession: 0.234 and inter-rater—intersession: 0.397) could be explained by the complex

TABLE 7 Overview and overall conclusion of the clinimetric properties of the instrumented strength assessment in Typically developing children and children with cerebral palsy and Duchenne muscular dystrophy.

TYPICALLY DEVELOPING CHILDREN					
	Intra-rater reliability	**Inter-rater inter-session**	**Inter-rater intra-session**	**Overall conclusion**	**Advice**
Dorsiflexion	Excellent	Excellent	Excellent	USE +++	Ready to be used.
Plantar flexion	Moderate	Poor	Poor	Limited USE- -	More research needed to optimize assessment standardization
Knee extension	Good	Excellent	Good	USE +++	Ready to be used.
Knee flexion	Excellent	Good	Good	USE +++	Ready to be used.
Hip abduction	Good	Good	Good	USE +++	Ready to be used.
Hip extension	Good	Moderate	Good	USE ++	Ready to be used, with special attention on assessment standardization
Hip flexion	Moderate	Moderate	Good	Partial USE +	Careful use, with special attention on assessment standardization
CHILDREN WITH CEREBRAL PALSY					
	Intra-rater reliability	**Validity**	**Response**	**Overall conclusion**	**Advice**
Dorsiflexion	Good	Excellent	Good	USE +++	Ready to be used
Plantar flexion	Moderate	Excellent	Good	USE ++	Ready to be used, but with special attention on assessment standardization
Knee extension	Excellent	Excellent	Good	USE +++	Ready to be used
Knee flexion	Moderate	Excellent	Good	USE ++	Ready to be used, but with special attention on assessment standardization
Hip abduction	Good	Excellent	Unknown	USE ++	Ready to be used for group comparison. Unknown for response.
Hip extension	Excellent	Excellent	Unknown	USE ++	Ready to be used for group comparison. Unknown for response.
Hip flexion	Good	Excellent	Unknown	USE ++	Ready to be used for group comparison. Unknown for response.
CHILDREN WITH DUCHENNE MUSCULAR DYSTROPHY					
	Intra-rater reliability	**Validity**	**Response**	**Overall conclusion**	**Advice**
Dorsiflexion	Moderate	Excellent	Moderate	Partial USE +	Careful use. More research required to strengthen the evaluation of response.
Plantar flexion	Moderate	Good	Absent	Limited USE +/-	Careful use, with special attention on standardization. Not ready to evaluate response.
Knee extension	Excellent	Excellent	Moderate	USE ++	Ready to be used, but more research is required to strengthen the evaluation of response.
Knee flexion	Good	Excellent	Absent	Partial USE +	Ready to be used for group comparison. Not ready to evaluate response.
Hip abduction	Moderate	Excellent	Moderate	Partial USE +	Careful use. More research required to strengthen the evaluation of response.
Hip extension	Good	Excellent	Absent	Partial USE +	Ready to be used for group comparison. Not ready to evaluate response.
Hip flexion	Good	Excellent	Moderate	USE ++	Ready to be used, but more research required to strengthen the evaluation of response.

The following scoring was applied. Reliability: the reliability of the torque parameters are reported following Koo and Li. (2016): poor: ICC≤ 0.500, moderate: ICC = 0.501–0.750, good: ICC = 0.751–0.900 and excellent: ICC>0.900. Validity or Responsiveness: absent = no significant p-values [p >0.0036 and p>0.0063 (CP, responsiveness)] and no trends (p>0.05); poor = trend (p<0.05) but absolute differences (i.e. absolute difference between median of clinical cohort and TD, cohort for validity and median of all absolute differences between assessment one and two per participant for responsiveness) smaller than SEM, and MDC; moderate = trend (p<0.05) and absolute differences larger than SEM, but smaller than MDC; good = trend (p<0.05) and absolute differences larger than SEM, and MDC, or significant p-value (p<0.0036 and p < 0.0063 (CP, responsiveness)) and absolute differences larger than SEM, but not larger than MDC; excellent = significant p-value [p < 0.0036 and p < 0.0063 (CP, responsiveness)] and absolute differences larger than SEM, and MDC. The overall conclusion was based on a summation of the first three columns of the table (for TD: all reliability assessments and for the clinical cohorts: reliability, validity and responsiveness). First, good and excellent was scored as +, moderate as and poor and absent as – per column and then, summed for the overall conclusion. If the overall conclusion is +++ or ++, the instrumented strength assessment is recommended to be used to assess the strength of the corresponding muscle group. If the overall conclusion is +, partial use is recommended. If the overall conclusion is +/–, –, –– or –––, limited use is recommended. A more detailed advice is described in the last column. Abbreviations in alphabetical order: CP, cerebral palsy; DMD, Duchenne muscular dystrophy; MDC, minimal detectable change; SEM, standard error of measurement; TD, typically developing.

nature of the PF movement. It is likely that children were still able to compensate in the knee and hip joint, knowing that fixating the ankle joint is complex. The results of the secondary parameters were in line with the findings of the primary parameters.

4.2 Part two: validity

Our hypothesis concerning the second sub-aim was confirmed. Significant differences were found for alle muscle groups, indicating that children with CP and DMD are overall weaker than TD children. The torque deficits in the CP cohort ranged from 49.6% for HF to 82.2% for DF (Supplementary Table S2), which is in agreement with previously reported ranges of lower limb muscle weakness (Dallmeijer et al., 2017; Hanssen et al., 2021). In the DMD cohort, the torque deficits ranged from 41.4% for PF to 80.3% for HE (Supplementary Table S2). Similar DF and KF strength deficits were found in previous literature, while the PF strength deficit was smaller in the current study (Mathur et al., 2010; Lerario et al., 2012; Wokke et al., 2014; Goudriaan et al., 2018b; Vandekerckhove et al., 2020). The KE torque deficit from the current study was in agreement with previously reported results from our research group (Goudriaan et al., 2018b; Vandekerckhove et al., 2020). While larger deficits for the KE strength have been found by other research groups using different strength assessments (Mathur et al., 2010; Lerario et al., 2012; Wokke et al., 2014). Following the approach of Buckon et al. (2016), who took the control data of Hébert et al. (2015) into account, the hip torque deficits from the current study were also in agreement with previous findings (Hébert et al., 2015; Buckon et al., 2016). However, statistically significant differences do not automatically prove relevant differences. The latter was evaluated by comparing the absolute differences between the TD and the two clinical cohorts with the absolute SEM and MDC values. The observed absolute differences between the median of the pathological cohorts and TD cohort exceeded the absolute MDC values in every subcategory, except for PF force in the DMD cohort. Overall, these findings prove the construct validity of the instrumented strength assessment. Future research is necessary to expand the findings of the validity part of this study to other clinical populations to strengthen its generalizability. Future studies should also compare the observed between-groups differences to minimally clinical important differences, for example by taking differences in muscle strength between pathological subgroups based on GMFCS-level, based on different gait patterns, or based on participation or quality of life scores as a reference.

4.3 Part three: responsiveness

Our hypothesis concerning the third sub-aim was only partly confirmed, since all absolute differences were smaller than the MDC values in CP and DMD. After strength training, the strength in all muscle groups increased significantly in the children with CP. While most of the absolute increases exceeded the absolute SEM values, they were smaller than the absolute MDC values. Unfortunately, the hip joint was not included in the strength training protocol of the CP children. With this additional proof of the effectiveness of strength training in children with CP and the availability of the clinimetric properties of strength assessments, future studies could expand the protocol to the hip muscle groups, especially since these muscles showed significant weakness (Table 4). For the DMD children, no significant differences in muscle strength could be observed within a time interval of 1 or 2 years. Yet, DF, and HA MVICs tended to decrease over the observed interval (1 and 2 years). In addition, a tendency towards a decrease in KE and HF MVICs was detected, only over an interval of 2 years. The absolute decreases in the DMD cohort were all smaller than the absolute MDC values, however, the absolute decreases in DF, KE, HA, and HF normalized torque over 2 years were larger than the absolute SEM values. This suggests a shortness in sensitivity of the instrumented strength assessment for the DMD cohort when evaluating muscle strength with a time interval of 1 or 2 years. Yet, it should be noted that the sample of boys with DMD was still limited, which may have caused a lack of power. The included sample size in the DMD cohort was limited due to the rarity of the disease combined with the strict inclusion criteria in part three. Moreover, the sample showed a large heterogeneity, e.g., differences in underlying gene mutation (four boys: deletion; two boys: point mutation; one boy: in frameshift mutation and one boy: nonsense mutation), participation in clinical trials (50% participated in clinical trials; one boy: ataluren and three boys: givinostat) and corticosteroids dosage (100% calcort; dosage ranged between 15 and 21 mg), which might partly explain the lack of significant change in the MVICs. Nevertheless, clinical tendencies towards increasing muscle weakness could be observed within the DMD results, ranging from 12.5% (HA torque) to 39% (KE normalized torque) over an interval of 2 years (Supplementary Table S3). McDonald et al. (1995) reported a decrease in KE isometric strength from 50% of control data at 6 years old to 0% at 12 years old (McDonald et al., 1995). This corresponds to a relative decrease in KE muscle strength of 33.3% in 2 years and therefore, is in agreement with the current study. However, careful study of the individual results showed that for the torque and normalized torque parameters, 32% of the measurement pairs over 1 year and 17% of the measurement pairs over 2 years presented increases in muscle strength between the two assessments, suggesting that these children with DMD did not yet lose muscle strength. This is surprising, since the boys with DMD were selected based on an age criterium of 7.5 years and a clinically meaningful decrease in the 6 MWT. The interaction between functional deterioration and strength loss in the natural history of the disease should be further investigated.

4.4 Limitations

In general, strength assessments in pediatric cohorts, especially in children with neurological and neuromuscular diseases, are challenging. While the goal was to obtain three well executed actual trials, not all children with CP or DMD were able to fulfil this task due to fatigue. It must also be noted that the practical applicability of the instrumented strength assessment can be challenging in clinical practice in comparison to the HHD, considering the size of the external structure and the alterations that must be made during the measurements to adapt the instrumented strength assessment to the different muscle groups. On the other hand, all the joint movements can be assessed with the patient in the same position, avoiding excessive repositioning of the patient. In addition, the results revealed that the instrumented strength assessment can be considered reliable in TD children and children with CP and DMD, albeit these limitations. Despite the applied fixations, compensation could not be entirely avoided when performing the MVICs. For example, during PF, co-contraction in knee and hip joint could still be observed, even after verbal instructions, and when performing HF, the waistbelt was not always sufficiently tight to prevent children from moving in the chair. A possible solution might be to replace the waistbelt with a type of safety harness, fixating both the trunk and pelvis and thereby further limiting compensations when producing forces around the hip. Electromyography could be applied to assess muscle activity during MVICs and quantify potential compensations, co-contractions or synergies during MVICs. Another important consideration of the applied study protocol was the measurement of the segment lengths from which the lever arms were calculated. The manual measurement of the segment lengths using a tape measure may be sensitive to errors. It is important to take into account that small errors in these measurements could have influenced the lever arm which was necessary to calculate torque and normalized torque. Furthermore, the applied joint positions did not correspond with common test protocols. Future test positions can be chosen based on the populations, the comparison with other daily life activities and the available reference data.

5 Conclusion

A concluding overview of all investigated clinimetric properties of the instrumented strength assessment and its usability is given in Table 7. The instrumented strength assessment showed moderate to excellent reliability results and proved sufficiently reliable to confirm the known-group validity for both clinical cohorts. The reliability results in the TD cohort indicated the need for further standardization of the strength assessments at the hip and all cohorts indicated this need for assessment of PF strength. Where the instrumented strength assessment was able to detect the responsiveness of children with CP after a strength intervention, more research is necessary to determine the responsiveness of DMD regarding their natural decline. Consequently, as highlighted in the overview in Table 7, the assessment is ready to be used in clinical studies on children with CP, although the responsiveness around the hip joint remains to be determined, whereas further research on the responsiveness of the instrumented strength assessment for boys with DMD is needed. Thereby, the use of a larger sample size, a more homogenous group of children with DMD and a further improvement of the standardization could improve the results. In addition, future research could define the minimal important clinical difference of the assessment as well as transfer the assessment to other pediatric patient populations.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary Material.

Ethics statement

The studies involving human participants were reviewed and approved by ethical commission of KU Leuven (Ethical Committee UZ Leuven/KU Leuven; S59945, S61324, and S63340) and Ghent University (EC/2017/1674). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

Conceptualization was done by IVe, IVa, BH, and KD. IVa, BH, ES, NP, and VvT participated in the data curation. Formal analysis was performed by IVe and IVa. Funding acquisition was acquired via IVa, LDW, NG, and KD. Methodology was developed by IVe, IVa, BH, and KD. KD operated as a resource. BH and KD provided supervision. Visualization was done by IVe, IVa, and BH. Writing of the original draft was done by IVe, IVa, and BH while IVa, BH, ES, NP, VvT, PVdW, LDW, MVdH, NG, AVC, and KD reviewed and edited the manuscript. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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Clinical and school-based intervention strategies for youth obesity prevention: A systematic review

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Introduction: In the last couple of decades, numerous intervention strategies (ISs) have been formulated in school/community or clinical sectors using physical activity (PA) in order to prevent youth obesity because they have been highly effective in addressing this issue. These two sectors have revealed some interesting information in terms of efficient results and best practice mechanisms, but comparisons between them to learn about their functioning have been rare.
Methods: Therefore, the aim of this systematic review was to analyze and synthesize PA ISs from school/community or clinical domains for the period 2013–2017, in French or English, targeting youths aged 5–19 years old through primary, secondary, and tertiary prevention.
Results: In total, 68 full articles were reserved for data extraction and synthesis and 617 were excluded because they did not meet eligibility criteria (61 of 68 were kept for the final analysis). The results identified a number of differences between the studies of the various IS sectors and also a third type of IS, mixed sector. Mixed ISs (clinical and school-community) have a special advantage because they can benefit from the strengths of both school/community-based and clinical-based ISs. Mixed ISs showed the most promising results. This review also highlighted the differences between sectors and their ISs in terms of intervention teams, prevention objectives, duration, materials, and efficiency.
Conclusion: Future studies should focus on establishing a prevention program in a given geographical area involving all stakeholders with their respective skills/knowledge, in the area of decision-making and in the development of ISs, to ensure that the program is the most efficient and best adapted to its environment.

KEYWORDS
obesity, youth, clinical, school, intervention strategies, prevention

1. Introduction

Nowadays, it is well known that obesity is a chronic pathology with multifactorial origins, defined by the World Health Organization (WHO) as an abnormal or excessive fat accumulation that presents a risk to health (e.g., vascular, endocrine) (1, 2). A study reported that in the last four decades, the number of young obese children (aged 5–19) multiplied by 10 worldwide (3). Another study reported that the rate of youth obesity prevalence increased by 47% in the last three decades (4). To help control this disease condition, the WHO made some recommendations [e.g., physical activity (PA); nutrition] (5, 6) to be followed, in order to adopt a healthy lifestyle and reduce health problems and the risk of obesity.

In parallel, it is also known that PA has many health benefits (physical, mental, and social, among others) that can help reduce obesity and maintain a certain weight when combined with nutrition (7). Moreover, the adoption of a healthy lifestyle during childhood or adolescence tends to spill over into adulthood. Nevertheless, 80% of youths aged 13–15 do not follow those PA recommendations (8) and tend to lead a sedentary lifestyle (9). This sedentariness and inactivity could lead to overweight or obesity (10). To address this issue and curb this tendency, intervention strategies (ISs) and programs integrating PA have been developed and implemented in different settings to prevent overweight and obesity (11). According to Gadais (11), ISs are initiatives and programs with thematic content and events that directly or indirectly aim to facilitate people to adopt healthy lifestyles for the benefit of their immediate and future health. When we look closely at the literature on obesity prevention (12), a few different settings emerge, and two of them have been widely studied (13, 14): the clinical setting on how to manage childhood obesity and the school/community setting on how to deal with obesity prevention and the role of the school in such prevention. It is from this perspective that we decided to focus our work on these two promising intervention sectors.

As we suggested earlier and to quote Lydecker et al. (15), "prevention assumes that individuals have some degree of susceptibility to obesity and would benefit from medical and psychosocial interventions to counter that susceptibility" (15). If the degree of susceptibility to obesity varies from one individual to another, prevention must also take place at different levels: primary, secondary, and tertiary. Primary prevention targets every individual without any distinction, for example, advertisements on television that invite people to be active and eat better. Secondary prevention targets subsamples of the population: people at risk of becoming overweight or obese, for example, children in the upper BMI range or who engage in very little physical activity. Tertiary prevention targets specific individuals who are already overweight or obese with complications, in this case, interventions that aim to help people obtain sufficient weight loss to reduce comorbidities (15–17). These three types of interventions are generally implemented in two major sectors: clinical or school and community sectors.

A clinical setting is a place where people are treated (e.g., hospital, health center). In this context, clinical ISs seem to contain better financial resources (e.g., exergaming) (18) and human resources/expertise to act as a source of quality and reliable information (19). Clinical ISs have also shown good results in the fight against childhood obesity (20–22), making it an important contributor in the management of obesity. Nevertheless, not all studies show good results, as prevention does not involve only treatment, which is mostly the last step of prevention, thus making the ISs of the other sector also useful.

The school and community sector can be seen as a place dedicated to learning where children develop their knowledge and skills (e.g., physical, social, cognitive skills). Many authors agree that school is a privileged place for the prevention of obesity (23–25). Indeed, children and adolescents spend most of their time at school and it is "possible to globally reach the population of interest without stigmatizing or discriminating and without being primarily dependent on families" (26). According to these authors, the school/community sector could assume an important role to promote positive change in children's lifestyles, in order to make them adopt a healthy way of life (11, 27). Yet, some studies have demonstrated that school-based obesity prevention interventions with children have produced limited efficacy (28, 29), generally lacking in financial or human resources, among others.

According to the literature, school/community-based ISs and clinical ISs seem to be different because they do not employ the intervention on the same level of childhood obesity prevention. Interestingly, both seem to show promising results in preventing obesity. Therefore, a question arises: Could it be possible to consider a global prevention strategy (primary, secondary, and tertiary levels) to reduce youth obesity prevalence and incidence in the coming years by integrating the best practices from one sector into another? We, therefore, sought to know if there were relevant elements in the ISs from these two sectors that would help formulate effective strategies for the prevention of obesity among young people through mutual enrichment.

The aims of this study were to

(1) prepare an extensive inventory on the recent literature regarding programs and ISs that aimed at preventing youth obesity, from clinical or school-community perspectives;
(2) extract information in order to identify the mechanisms that make programs effective in a clinical or school/community sector;
(3) propose some recommendations from the point of view of both sectors (clinical and school/community) and improve the current ISs for future studies.

2. Methods

To conduct this systematic review, we followed the six steps of the PRISMA (30) for preparing a flow chart (**Figure 1**).

2.1. Phase 1: Identification of studies

In the first phase, an exhaustive search through computerized databases was performed to identify scientific publications targeting youth obesity prevention. Particularly, we used specific search equations to conduct the first overall research. Relevant articles were identified by means of a computerized search through three databases (i.e., SPORTDiscus, PubMed, and ScienceDirect) with different combinations of keywords (e.g., program; obese; physical activity, child) (**Appendix A**) and Equations/Meshterms (**Appendix B**).

2.2. Phase 2: Screening

In phase two, 40 duplicates were eliminated and 685 papers were identified. We started looking for non-systematic reviews and prioritized peer-reviewed articles. Some reports from credible organizations such as government agencies, international agencies, or academic centers were also included in our research (e.g., WHO), but none of them were finally considered.

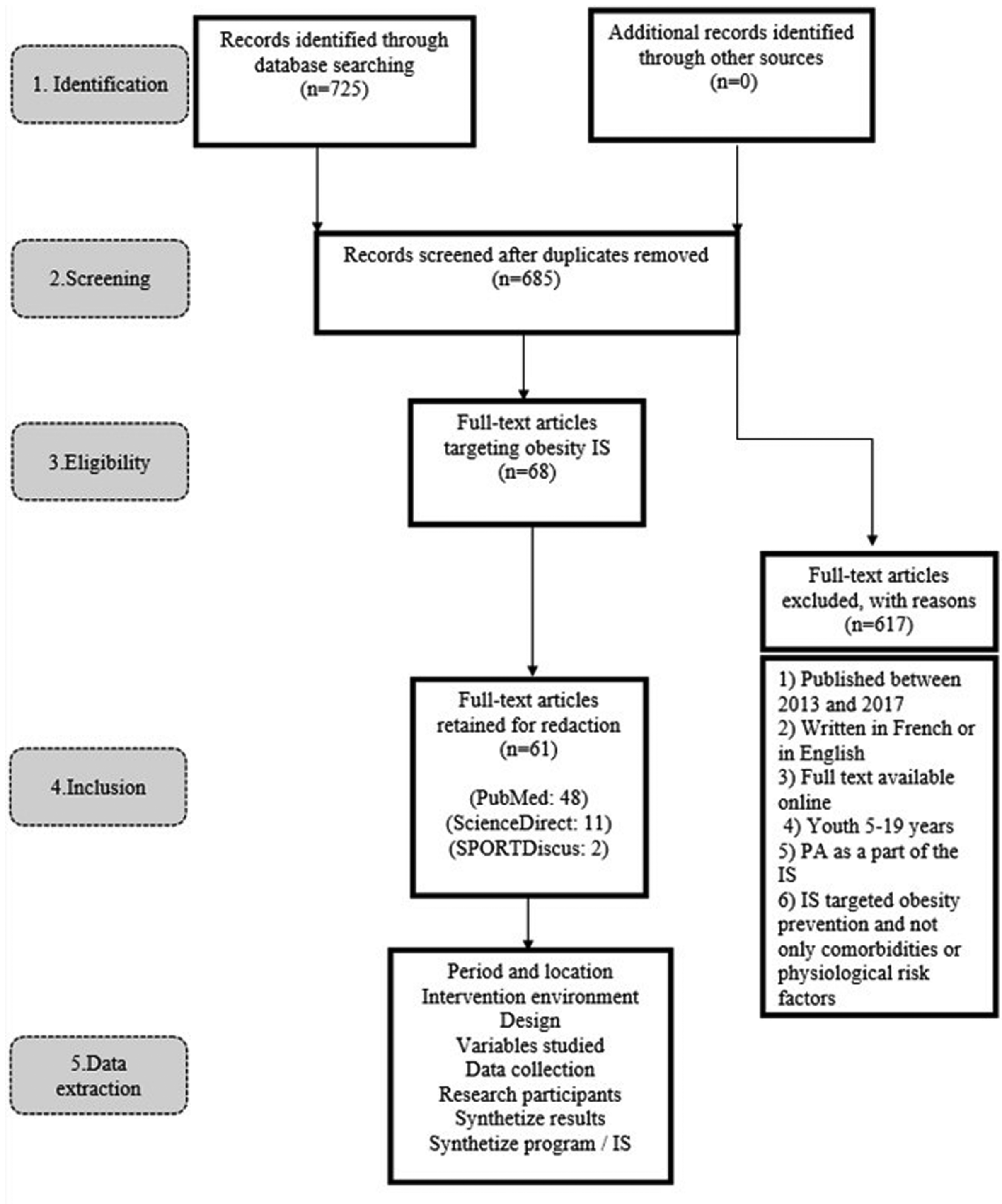

FIGURE 1
PRISMA flow chart.

2.3. Phase 3: Eligibility

The selection of the abstract was done on the basis of inclusion criteria. To dispel any doubts on this process, the third author was consulted. Six inclusion criteria were applied for article eligibility: (1) articles published between 2013 and 2017, (2) those written in French or in English, (3) full text available online, (4) youths 5–19 years' old targeted by studies, (5) PA as a part of ISs, (6) ISs that targeted obesity prevention and not only comorbidities or physiological risk factors (e.g., diabetes). In total, 68 full articles were reserved for data extraction and synthesis and

617 were excluded because they did not meet the eligibility criteria.

2.4. Phase 4: Inclusion

The fourth phase of the literature search involved obtaining copies of the articles previously identified in phase 3. After collecting the articles, the overall sample was reassessed. A complete reading was made in order to eliminate non-relevant articles (according to inclusion criteria). Finally, 61 articles were retained for data extraction by meeting all inclusion criteria and focusing on the topic of this study.

2.5. Phase 5: Data extraction

A data sheet was used to extract information concerning the date of the study; intervention sector (school/community or clinical); design (collaborative ISs or not); variables studied; data collection (equipment, hardware); participants (non-obese, overweight, obese, age); synthesized results; synthesized ISs. The first and the second author performed data extraction. To dispel any doubts on this process, data synthesis tables were discussed until agreement was reached on the presentation form and what should be extracted. The completion of phase 5 marked the start of the content analysis of the 61 articles.

2.6. Phase 6: Data analysis

To identify the differences, the results will be presented in five different categories (i.e., intervention team, prevention objective, duration, material, and efficiency). As previously mentioned, the intervention sectors (clinical and school/community) are different from each other but show interesting results (10–12). Therefore, it is interesting to see who conducted the intervention, its purpose, the means available, how long the ISs lasted, and the results.

The first author carried out the initial selection in the literature search on the basis of the abstract and title ($n = 725$). He also performed the initial analysis of the data and wrote the first draft of the manuscript. The second and third authors helped with data analysis and result presentation. They also revised the entire manuscript.

3. Results

3.1. School and community ISs

3.1.1. Intervention team

Of the 36 school/community-based studies (**Table 1**), 11 used one type of stakeholder. Of these 11, 6 studies involved only teachers (23, 31–35). For example, Grao-Cruces et al. (32) mentioned "weekly follow-up and control by PE teachers" and Sacchetti et al. (23) "taught by the ordinary classroom teacher." The use of the teacher as the only intervener increases from 54.5% (6/11) to 75% (6/8) (36–38) if we exclude studies occurring only in the community. Twenty-five studies used at least two types of stakeholders (18, 24, 25, 39–60), and eight involved health professionals (e.g., doctors, nurses, psychiatrists) (18, 25, 39, 42, 45, 48, 59, 60). Among these eight, two relied solely on school nurses (42, 48). Globally, six studies involved non-school-based stakeholders with experience in healthcare.

3.1.2. Prevention objective

Of all the studies aimed at preventing childhood obesity through school/community ISs, nine dealt with secondary or tertiary obesity prevention, since they were only interested in young people who were already overweight or obese (18, 25, 37, 38, 47, 48, 51, 59, 60). For example, Larsen et al. (48) selected "One hundred fifteen 11–13 year-old children with overweight and obesity" and Wright et al. (25) mentioned, "Students ($n = 251$) were English or Spanish speaking, had a BMI > the 85th percentile". The majority of the studies (23, 24, 27, 31–36, 39–46, 49, 50, 52–58, 61, 62) directed their attention toward a relatively primary prevention of obesity and did not necessarily target an overweight or obese population but rather an entire population. For example, Lau et al. (49) mentioned, "the average BMI was 17, which was within a healthy range." These studies tended to include children "at risk" as their participants because of the absence of selection criteria. For example, Smith et al.'s (57) intervention group included 2 underweight children, 110 normal weight, 39 overweight, and 30 obese.

3.1.3. Duration

The duration of 19 of the studies was a year or more (23, 24, 31, 33, 36, 39, 41–43, 45, 51, 52, 54–56, 58, 59, 61, 62). For example, Erfle and Gamble (42) reported "30 min of daily PE throughout 1 academic year" and Santos et al. (24) mentioned, "performed during the 2009–2010 school year." Of the 17 remaining with a shorter duration, 14 of them lasted 6 months or less (18, 25, 32, 34, 37, 38, 40, 44, 46–49, 53, 60). Larsen et al. (48) used "the six-week intervention" and Parra-Medina et al. (53) "a 12-week family focused healthy lifestyle program."

3.1.4. Material

Studies from the school/community sector did not automatically consider BMI with age and sex in their anthropometric measurement (e.g., BMI *z*-score, BMI percentile). Two studies did not consider anthropometric measurement in their outcomes (40, 46) and two others considered only BMI (not for age and sex) (49, 59). Of the 34 studies with anthropometric measurements, 23 were based on a measurement related to BMI or abdominal circumferences (e.g., BMI score, waist circumference). Other studies (indicating anthropometric measurements) systematically considered at least a second objective measure such as dual energy x-ray absorptiometry (DXA) (one study), skinfold thickness (three studies), or impedance (seven studies). Ning et al. (37) mentioned that "body composition was assessed by bioelectrical impedance analysis

TABLE 1 Illustrations of studies for school/community ISs.

Authors, year	Participants, prevention type	Material and variables	Program/ISs summary	Results summary	City (country)
Safdie et al. (2013)	RCT, youth aged 9–11 years old (*n*: 886) Primary/secondary prevention (impact on obesity risk factors) Collaboration between the physical education general direction, The National Institute of Public Health, The Federal Administration of Educational Services	Food and beverage availability, food intake PA levels and quality of PE lessons BMI-SD	The basic program focused on nutrition, physical activity, communication, and education. The Plus program focused on nutrition, physical education, communication, and education but with workshops and not only booklets	- The availability of recommended foods increased significantly ($p < 0.05$) - ($p = 0.06$) children in basic schools and (=0.03) in Plus schools maintained a status of reaching cut-off for steps in school relative to students in the control group - The intervention had no significant effect on the prevalence of overweight and obesity or children's BMI	Mexico City (Mexico)
Wright et al. (2013).	RCT, youth aged 8–12 years (*n*: 251) Secondary prevention (BMI > 85th percentile) Community collaboration and University partnership with school	BMI BMI z-score Health behaviors knowledge	Phase 1 (KNF© intervention): Focused on youth PA (practice) and nutrition (group sessions with parents) Parental involvement (sessions on obesity consequences and healthy lifestyle) Phase 2 ("Environmental" activities): Healthcare offered to participating children Establishment of a school health advisory council (establishment of health policy, providing newsletter to parents, offering seminars to school staff and parents on health promotion)	- Significant decrease in BMI z-for girls ($p < 0.005$) stays at 4 and 12 months. - Boys and girls fit with the recommendations of 60 min of daily PA ($p = 0.002$ and $p = 0.005$) at 12 months. - Boys and girls increased their attendance in PE classes ($p = 0.003$ and $p = 0.002$) - Boys and girls decreased their TV use at 4 months but maintained only by boys at 12 months ($p = 0.03$)	Los Angeles (USA)
Staiano et al. (2013)	RCT, youth aged 15–19 years (*n*: 54) Secondary/tertiary prevention (BMI percentile >75th)	Anthropometric BMI z-score Psychosocial variables (e.g., Rosenberg self-esteem scale)	Competitive exergaming 30–60 min of exergaming per school day during 7 months—1 coordinator → encourage daily exergaming + ensure the maintenance of the social environment of the classes Goal = Earn more points than opponents Cooperative exergaming: 30–60 min of exergaming per school day during 7 months - 1 coordinator → encourage daily exergaming + ensure the maintenance of the social environment of the classes Goal = Earn the most points with partner Control: Usual activities	- Cooperative group lost significantly more weight than the control group ($p = 0.021$) - Competitive group did not experience significant weight variation, compared with others	Georgetown (USA)

ISs, intervention strategies; PA, physical activity RCT, randomized controlled trial ; PE, physical education.

(…) body composition was also estimated at baseline and 6 months using dual x-ray absorptiometry" and Johnston et al. (47) mentioned that "body composition was assessed using triceps skinfold thickness." For studies that assessed PA measurement (32/36), 20 used one objective measurement (not a self-reported). Among these, the most common instruments were accelerometer (9 studies), pedometer (5 studies), and various fitness tests (13 studies) (e.g., Fitnessgram). For example, Larsen et al. (48) used a "progressive bicycle ergometer protocol (…) Actigraph GT3X + for ten consecutive days" and Grao-Cruces et al. (32) reported that "a pedometer was used for evaluation and follow-up purposes." Finally, regarding nutrition, 19 studies collected data. Most of them were carried out through three types of instruments: survey (15 studies), recall/diary (6 studies), and interview (1 study). For example, Ning et al. (37) mentioned that it was "assessed by a 48-hr diet recall."

3.1.5. Efficacy

In the school/community sector, the major objective tended to be the prevention of obesity, and interestingly, "lose weight" was not the first goal.

However, 26 studies still presented significant positive results regarding the anthropometric measurements of the participants (e.g., BMI, waist circumferences) (18, 23–25, 31–35, 37–39, 41, 42, 45, 47, 48, 50–52, 55, 56, 59–62). Nevertheless, some studies showed effects only on a part of the population (25, 33) or "mixed effects" (23, 41, 56). Of the 10 remaining studies, which did not clearly show an effect on BMI, 9 had, at least, a significant influence on health factors (36, 40, 43, 44, 46, 49, 54, 57, 58) (e.g., physical, psychological, or nutritional). To illustrate, Smith et al. (57) showed that "significant intervention effects were found for screen time (mean SE: -30 ± 10.08 min/day; $p = 0.03$), sugar-sweetened beverage consumption (mean: -0.6 ± 0.26

glass/day; $p = 0.01$).” Only the article by Parra-Medina et al. (53) showed no significantly interesting effect on children because “child participants that completed the program ($n = 72$) showed no improvements.”

3.2. Clinical ISs

3.2.1. Intervention team

Of the 19 studies we identified (**Table 2**) in the literature and that were carried out in a clinical setting, 3 (19, 63, 64) used a single type of contributor. It was systematically a doctor who delivered recommendations on psychological, nutritional, or PA. For Brennan et al. (63), “the clinician discussed topics such as physical activity, nutrition, helpful thoughts and emotions,” and for Davis et al. (64), “the clinician covered several topics such as self-esteem, energy balance, portion size, screen time and sedentary.” The 16 remaining studies included a multidisciplinary team composed of at least two specialists (65–80). For example, for Nemet et al. (73), “the intervention team was composed of 3 specialists: dietitian, coach and physician” and Endevelt et al. (68) used a “multidisciplinary team including a pediatrician, a dietician, a physical activity expert, and a social worker.”

3.2.2. Prevention objective

None of the studies targeted the primary prevention of obesity and 18 of them worked on secondary or tertiary prevention of obesity, because they only targeted participants with a BMI >85th percentile. For example, Staiano et al. (79) selected only participants with a BMI percentile >85th, according to the Center of Disease Control (CDC) growth chart; and Serra-Paya et al. (76) selected children overweight or obese, according to the International Obesity Task Force (IOTF) criteria. Only one study (19) used a BMI between the 75th and the 95th percentiles as an inclusion criterion. Nevertheless, participants were judged at risk of weight gain due to their BMI, based on their last medical consultation.

3.2.3. Duration

For the duration of the ISs, 16 studies covered at least 1 year (63–69, 71–79). Luca et al. (70) mentioned a “2-year interdisciplinary obesity management program.” Moreover, 10/19 studies had an effective duration of less than or equal to 6 months (64, 65, 69, 72–75, 77–79). Martín-García et al. (72) implemented a 3-month vigorous physical activity plan and Staiano et al. (78) a 12-week group exergaming intervention. It should also be noted that all studies covering one or more years consisted of only a few meetings throughout the year. To illustrate, for Stettler et al. (19), the ISs consisted of 12 meetings of 15–25 min over 12 months, and for Luca et al. (70), it was 6 meetings of 2 h per week, then 1.5 h every 2 weeks the first year, and 1.5 h monthly until the 18th month.

3.2.4. Material

Anthropometric measurement at the clinical level consistently considered BMI by age and sex (BMI score). Nevertheless, in 10 studies, BMI was coupled with a second measure related to body composition and something more (19, 63, 65, 69, 71, 72, 76–79) [DXA (4 studies), skinfold thickness (2 studies), Waist to Height Ratio (WHtR) (2 studies), and impedance (1 study)]. For example, Staiano et al. (78) used DXA to assess body composition and quantify body fat, and Gerards et al. (69) measured skinfold thickness to evaluate the percentage of body fat. With regard to PA, 12 studies used one or more objective measurements (63, 65, 66, 69–74, 76, 78, 79). Of these 12, the pedometer was used in 2 studies; PA was tested in 5 studies, and accelerometers in 7 studies. Brennan et al. (63) used a cycle ergometer test to assess cardiovascular fitness and participants had to get an accelerometer fixed on them to have their physical activity assessed. With regard to nutrition, measurements were made in 14 studies (19, 63–70, 72–76) and three tools were frequently used: survey (3 studies), interview (4 studies), and dietary recall (5 studies). Nemet et al. (74) mentioned the “use of a 48-h dietary recall”; Davis et al. (64) spoke about the “use of a 24-h dietary recall,” and Brennan et al. (63) referred to the “use of a dietary checklist and of the Fat, Fruit and Vegetables Diet Questionnaire (FFVDQ).” It should be noted that some studies did not clearly mention their measurement instruments.

3.2.5. Efficacy

In the context of secondary or tertiary prevention of obesity, one of the main objectives remained BMI decrease and fat loss in favor of lean mass. Out of 19, 14 (73.68%) studies showed significant effects on BMI or participant body fat (19, 63–65, 68, 71–75, 77–80). For example, Marild et al. (71) “reported a significant reduction in BMI and BMI-SD in the Nurse-Dietician-Physiotherapist managed treatment compared to the control group with obesity ($p = 0.0007$ and $p = 0.0005$ respectively).” Nevertheless, some studies showed significant effects only on some of their participants. For example, Martín-García et al. (72) “found that, in the intervention group, boys decreased their whole-body fat mass ($p < 0.04$) and reduced their percentage of body fat ($p < 0.001$); moreover, boys’ body lean mass increased significantly ($p = 0.003$).” Of the five other studies that did not have a direct effect on BMI, four had at least a significant influence on physical, psychological, or nutritional health factors (66, 69, 70, 76). Furthermore, in these studies, the intervention group was compared with a control group performing a “less advanced” intervention. Serra-Paya et al. (76) mentioned that “the intervention group received organized physical activity sessions, theoretical and practical sessions for parents, behavior counselling for children and parents, 3 weekend activities organized outside the family for children; unlike the counselling group that received only the behavior counselling sessions.” Only one article showed no effects (67).

3.3. Mixed ISs

3.3.1. Intervention team

Of the six studies we identified (**Table 3**) and that were carried out in a “mixed” setting (school/community and clinical), all of them used at least two types of contributors, with one (or more)

TABLE 2 Illustrations of studies for clinical ISs.

Authors, year	Participants, prevention type	Material and variables	Program/ISs summary	Results summary	City (country)
Martín-García et al. (2017)	Youth aged 7–16 years old (*n*: 61) Secondary/ tertiary prevention (BMI > 85th percentile)	Anthropometric (height, weight, BMI *z*-score) Body composition (DXA) Eating behaviors PA intensity and enjoyment Health-related quality of life	Focused on recreational PA games (mainly aerobic games, at least 10 min per game) at a high intensity; 75.5% of child's maximal HR (mean 151 ± 13 bpm)	- Significant decrease in whole-body fat mass and % body fat mass for boys ($p < 0.05$ and $p < 0.001$, respectively) - Significant increase in ($p = 0.003$) lean mass (whole body) - VPA reduce overeating behaviors especially linked to negative mood state (reduction of emotional eating traits)	Madrid (Spain)
Serra-Paya et al. (2015)	Youth (B/G) 6–12 years old (*n*: 113) Secondary/ tertiary prevention (BMI > 85th percentile)	Anthropometric (height, weight, BMI *z*-score) Dietary habits PA and sedentary time	Supervised PA for the child (3 × 1 h/ week) Practical and theoretical Sessions for parents (1 × 1 h/week) Weekends of activities offered outside the family (3×) Session on good behaviors to adopt	Decrease BMI: - If attendance ratio = 0.547 ($p < 0.001$) - Improve LPA and MVPA ($p < 0.001$) - Improve MVPA by 2.5 h/day - Increase MVPA in all analysis subgroups (puberty vs. not; boys vs. girls) - Increase fruit consumption (3/ day and decrease in sugar-sweetened juices/soft drinks)	Leida (Spain)
Staiano et al. (2017)	Young girls, 14–18 years old (*n*: 41) Secondary/ tertiary prevention (BMI > 85th percentile)	Anthropometric (height, weight, BMI *z*-score) Body composition (DXA) Cardiovascular risk factors (blood sample, blood pressure, resting electrocardiogram)	Supervised ("gaming coaches") dance exergaming sessions with a self-selected intensity, dance partner, game. (60 min, 3×x per week for 12 weeks)	- Per protocol analysis (attendance >75%): significant improvement in BMD for trunk and spine ($p = 0.03$ and $p = 0.008$, respectively) - Per protocol analysis (steps per session >2,600): significant decrease in leg fat % ($p = 0.049$), subcutaneous adipose tissue ($p = 0.02$) and total adipose tissue ($p = 0.03$)	Baton-Rouge (USA)
Marild et al. (2013)	Youths 9–13 years old (*n*: 64) Tertiary prevention (BMI-SD > IOTF-30)	Anthropometric (height, weight, BMI *z*-score, WHtR) Cardiovascular risk factors (blood sample) Pubertal stage (Tanner stages)	NDT: 8 × 1 h nurse visits for 1 year (monitor weight development, reinforce diet messages and try to reduce inactivity) 4 × 1 h dietician visits for 1 year (dietary habits) NDPT: 4 × 1 h nurse visits for 1 year (monitor weight development and reinforce diet messages) 4 × 1 h dietician visits for 1 year (dietary habits) 4 × 1 h physiotherapist visits for1 year (reduce inactivity, change transportation, use pedometer for motivation and diary to register steps, reduce inactivity, stimulate child to participate in PE lessons at school, and talk about PA recommendations)	- No significant differences were observed between NDPT and NDT interventions. - Significant decrease in BMI for NDPT and NDT ($p = 0.0007$ and $p = 0.002$ respectively) compared with the non-intervention group - Significant decrease in BMI-SD for NDPT and NDT ($p = 0.0005$ and $p = 0.002$ respectively) compared with the non-intervention group	Alingsås, Göteborg, Trollhättan, and Skövde (Sweden)

ISs, intervention strategies; PA, physical activity; DXA, dual energy x-ray absorptiometry; BMD, bone mass density; NDT, Nurse-Dietician management treatment; NDPT, Nurse-Dietician-physiotherapist management treatment. HR, heart rate; VPA, vigourous physical activity; LPA, low physical activity; MVPA, moderate to vigourous physical activity.

having health-related skills or knowledge. Rito et al. (81) reported that "four individual counselling sessions performed by trained nutritionists (…) healthy cooking workshops performed by a certified renowned 'chef' in a school kitchen." All of these studies used a multidisciplinary team having in common a dietician. Maatoug et al. (82) mentioned that the ISs "included a multidisciplinary team with a pediatrician, dietician, physical activity teacher and psychologist."

TABLE 3 Illustrations of studies for mixed ISs.

Authors, year	Participants, prevention type	Material and variables	Program/ISs summary	Results summary	City (country)
Morano et al. (2016)	Youth (B/G) 11.3 ± 0.4 years (n = 18) Secondary/tertiary prevention (BMI ≥ 85th percentile; CDC)	BMI-SD/percentile Anthropometric Physical fitness (Eurofit, Fitnessgram) Dietary habits PA enjoyment and perceived PA abilities; HRQoL	Exercise training and fun-type PA 2 × 2 h/week PA diary review 1 × 30 min/week in groups Nutrition counseling sessions 3 times during the 6-month intervention + 1 time at the beginning to give recommendations. Parents monitor their child on the completion of the PA diary	- Significant decrease in BMI variables (e.g., BMI z-score $p = 0.001$; BMI percentile $p = 0.001$) and % body fat ($p < 0.001$) - Skinfold thickness reduction (e.g., biceps, $p < 0.001$; Subscapular $p = 0.008$) except for triceps skinfold ($p = 0.363$) - Physical performance significantly improved (e.g., 10 m sprint, $p < 0.001$) as Perceived PA ($p = 0.026$) and Enjoyment of PA ($p = 0.035$) - Psychosocial health improved significantly ($p = 0.048$) but there was no significant effect on physical health. - Better dietary habits showed [e.g., reduction in caloric intake (kcal/day) $p < 0.001$]	Parisi-De-Sanctis, Foggia (Italy)
Maatoug et al. (2015)	Youth (B/G) 13.1 ± 0.96 years (n: 317) Secondary/tertiary prevention (BMI-SD >1; WHO) Transfer of a clinical strategy to a school-based intervention	BMI-SD Anthropometric PA expenditure Dietary intake	2 arms: collective intervention: PA group sessions on - healthy eating - self-esteem - snacking PA sessions proposed by teachers Individual intervention: Only obese meeting on - self-esteem and depression screening - dietician consultation - causes of obesity - educate and motivate participants on healthy eating and PA habits	- BMI-SD decrease pre-post ($p < 0.001$) and after follow-up 4 months ($p < 0.001$) - BMI-SD decrease pre-post ($p < 0.001$) and after follow-up 4 months ($p = 0.230$) in the control group - Decrease in caloric intake ($p < 0.001$) pre-post in CG and IG - No PA drop in IG ($p = 0.690$) contrary to CG ($p = 0.001$)	Sousse (Tunisia)
Rito et al. (2013)	Youth (B/G) 6–10 years (n: 266) Secondary/tertiary prevention (BMI ≥ 85th percentile; CDC)	BMI percentile Anthropometric PA and sedentary Dietary intake Nutritional and physical activity knowledge, attitudes and behavior	Health center (individual) 4 × 1 h nutrition counseling sessions Family "healthy cooking" workshop 1 × 3 h cooking practice for skills development and knowledge (e.g., food preservation and storage) + POZ recipe book School intervention Child: 6 h of intervention focusing on healthy eating and PA Parents: 3 h of intervention focusing on healthy eating and PA (improve knowledge + support their child) + Brochures Teachers "Nutrition and physical activity sheets" given to facilitate additional initiatives in classrooms	- Significant decrease in BMI variables (e.g., BMI percentile, CI 95% −2.2; −1.3; $p < 0.001$) - No significant effect on dietary variables, except for fiber consumption ($p = 0.005$) - VPA improvement (CI 95% 0.1; 0.5; $p = 0.008$) Nutrition knowledge and attitude improvement (Knowledge, CI 95% 4.6; 7.1; $p < 0.001$ and attitude CI 95% 0.9; 1.6; $p < 0.001$)	Melgaço, Cascais, Mealhada, Beja, and Silves (Portugal)

ISs, intervention strategies; CDC, Center of Disease Control; PA, physical activity; WHO, World Health Organization. CG, control group; IG, intervention group; B/G, blood glucose; HRQoL, health-related quality of life; POZ, POZ scale https://www.pozqol.org/about-pozqol/; VPA, vigorous physical activity

3.3.2. Prevention objective

All these studies were part of a secondary or a tertiary prevention of obesity, because they were interested only in children who were already overweight or obese. Four of them were based on data on overweight and obesity for age and sex of CDC (BMI > 85th percentile). For example, Morano et al. (83) selected participants "with a BMI ≥ 85th percentile for age and sex according to the CDC growth reference" and Sanders et al.

(84) selected "overweight or obese based on the CDC growth chart." The two remaining studies were based on different data from the WHO: in Maatoug et al. (82), "Z-score were derived using the world health organization references" or from English references; in Kokkvoll et al. (85), "≥98th percentile according to the UK references." None of these studies were directly concerned with the primary prevention of the pathology.

3.3.3. Duration

With regard to these mixed studies, two had a duration above or equal to 1 year (82, 85). Kokkvol et al.'s (85) ISs lasted 2 years, and Maatoug et al.'s (82) ISs (50%) lasted 1 year and the remaining (50%) lasted 6 months or less (81, 83, 84). Sanders et al. (84) formulated a 4-week IS. Only Rieder et al.'s (86) strategies had an "intermediate" duration equal to 9 months. It should be noted that, unlike the clinical studies previously seen, the frequency of proposed activities or meetings with professionals was higher in mixed programs lasting 1 year or more. For example, Kokkvoll et al. (85) used "weekly group-based physical activity" and Maatoug et al. (82) used "twice-a-week physical activity sessions in school."

3.3.4. Material

Anthropometric measurements, in these mixed studies, systematically considered BMI for age and sex (e.g., BMI *z*-score, BMI percentile). Nevertheless, it was not the only measurement, because in three studies, this was combined with at least one other measurement of body composition [WC (three studies), skinfold thickness (two studies), impedance (one study)]. For example, Kokkvoll et al. (85) used "bioelectrical impedance," in Morano et al. (83), "Skinfold thickness was determined (…) with a skinfold caliper," and in Rito et al. (81), "waist circumference was obtained for every child." With regard to PA, three studies clearly used an objective measurement coupled with a second self-reported one. This helped avoid over/underestimating the results. Sanders et al. (84) mentioned that "pre- and post-intervention fitness tests were administered to participants (…) program participants and their parents completed a physical activity and nutrition behavior questionnaire." The other studies were based only on self-reported data [Maatoug et al. (82) mentioned that participants "responded to a 24 h food and physical activity recall questionnaire"] or no PA measurement was done in them (85). Three tools were mainly used to measure nutrition: questionnaire (two studies), 24 h recall (two studies), and a 7-day dietary diary (one study). For example, Morano et al. (83) reported, "dietary habits were assessed with a 7-day food diary." Only in one study, nutritional measurement (85) was not performed.

3.3.5. Efficacy

As mentioned previously, all mixed studies focused on secondary or tertiary prevention of obesity. One of the major objectives was therefore to influence downward BMI and weight in order to reduce the fat mass of the participants. Of the six programs, five had direct effects on BMI (81–85). One article did not show significant BMI reduction, even though it indicated a tendency to slow its growth. Rieder et al. (86) mentioned that percentile BMI measurements taken before and after the intervention indicated a general upward trend ($p = 0.0003$). Nevertheless, during the intervention period, the slope of the BMI percentile showed a downward trend ($p = -0.0001$). Moreover, a comparison of the results of the preintervention phase and the intervention phase showed significant variations ($p = 0.003$). "For intervals T12 to T0 vs. T0 to T9, there were significant decreases in rates of gain in BMI (0.13 vs. 0.04, $p < 0.01$, BMI percentile [0.0002 vs. −0.0001, $p < 0.01$]."

Each of these studies also presented at least one positive variation on one of the various health, physical, psychological, or nutritional factors. For example, Maatoug et al. (82) showed positive effects on PA, *p*-value (pre-post) = 0.001, and reduction of caloric intake; *p*-value (pre-post) < 0.001; Rito et al. (81) mentioned "vigorous physical activity (day/week), CI 95% 0.1–0.5, *p*-value = 0.008" and Morano et al. (83) showed that "Actual ($p < 0.001$) and perceived ($p < 0.03$) physical abilities, physical activity enjoyment ($p = 0.03$), and psychosocial HRQoL ($p < 0.05$) also improved from pre- to post-intervention."

4. Discussion

4.1. Summary of the findings

This study identified a number of differences between the studies of the various IS settings (**Table 4**); these differences could be grouped into five elements (intervention team, prevention objective, duration, material, and results).

Intervention team: The intervention team in the school/community was mostly composed of a single stakeholder that was often the teacher (54.5% of cases). In the clinical and mixed sectors, the ISs largely depended on a multidisciplinary team with various members specialized in health. In both sectors, stakeholders contributed to the success of the ISs as key actors.

Prevention objective: The school/community ISs mainly targeted primary prevention because there was no selection of participants, while participants in the other sector were chosen by targeted criteria such as overweight or obese (according to their BMI for age and sex), and the same was the case for mixed studies.

TABLE 4 Results summary.

	School/ Community	Clinical	Mixed
Intervention team	Rarely multidisciplinary	Widely multidisciplinary	Totally multidisciplinary
Prevention goal	Primary/secondary (preventive)	Secondary/tertiary (curative)	Secondary/tertiary (curative)
Duration	Variable (53% more than a year; 39% less than 6 months)	Short (84% less than a year)	Relatively short (66% less than a year)
Material	Reliable	Reliable ++	Reliable +
Efficacy	Anthropometric measurements (72%) and health factors (90%)	Anthropometric measurements (74%) and health factors (83%)	Anthropometric measurements (83%) and health factors (100%)

Duration: One interesting point in the school/community setting was that it allowed for a relatively long intervention duration, and ISs aimed at preventing obesity needed time to embed and develop before being evaluated (60). On the other hand, clinical and mixed ISs tended to last for a shorter period of time. More than three-fourths of the studies done in the clinical setting and two-third in the mixed setting lasted less than a year.

4.2. Findings: What can be understood and learned?

4.2.1. Material

Clinical and mixed ISs tended to use more objective instruments, requiring more skills and knowledge. This allowed them to associate and combine certain measurements to achieve more accurate results and not over/underestimate their results.

4.2.2. Efficacy

Many authors agreed (23–25) that school was a privileged place for prevention. Our results seem to confirm this tendency, because school/community ISs showed significant and promising results both on anthropometric measurements relative to obesity (72%) and on health-related factors (90%). The clinical setting was also a beneficial location for the treatment of obesity (secondary/tertiary preventions). This setting was seen as a source of quality and reliable information (17) and it provided important results on both obesity (74% of the studies) and health-related factors (83% of the studies) (87).

4.3. Prospects

In light of these findings, it is necessary that mixed studies should be prioritized, with a combination of school/community-based and clinical-based strengths. Indeed, our study found that mixed ISs provided the most promising results; 83% of the studies showed a positive influence on obesity and 100% on health-related factors. Nevertheless, those we considered sought to apply a relatively clinical model to the school/community setting (82) but did not participate in an exchange relationship, and therefore, the strengths of school/community-based ISs were "left behind." To enhance global obesity prevention and in line with health recommendations to prevent childhood obesity, **Table 5**) proposes recommendations for future studies to be more effective.

Clinical:

TABLE 5 Recommendations for future ISs.

	Recommendations	Ideas for optimization	
		Clinical	School/Community
Intervention team	Multidisciplinary/specialized - Each contributor is specialized in their field or has the skills/knowledge to intervene (e.g., training) - ISs must be multidisciplinary and intervene on essential fields (i.e., PA, Nutrition, Psychology)	- Doctor - PA specialist - Psychologist - Dietician	- PE teacher - Other teachers - School nurses
Prevention goal	Primary/secondary/tertiary (global prevention) - ISs should focus on the entire youth population with the opportunity to identify young people at risk (material and skills/knowledge) in order to intervene and/or guide as well as possible - Possibility of further control examination not requiring the personal initiative of youth (examination by medical staff with more objective measuring equipment, to confirm or deny the presence of overweight or obesity)	Individual ISs Secondary prevention: - Additional individual consultation with a dietician every 3 months Tertiary prevention: - Start a clinical weight loss management program (after an "ability to change" assessment)	Collective ISs Primary prevention: - Control consultation with the school nurse every year - Availability of free water - Availability of fruits and vegetables - Posters - Flyers Secondary prevention: - Courses on obesity - Workshops on "how to eat healthy" with a dietician - Additional PA classes (new activities or tailored PA)
Duration	- Various - "Daily" integrated primary prevention - "Extended" primary/secondary prevention (1 year) renewable - "Shorter" tertiary prevention (<6 months) after needs assessment and with a follow-up. In addition to the two other axes mentioned above	Shorter interventions duration focusing on: - Life habits (enjoyable PA, gradual increase in difficulty, reduced sedentary time) - Nutrition (tailored diet to avoid the feeling of frustration, deprivation) - Psychology (climate free from judgment; behavioral therapy) At least a 3-month follow-up (Canadian recommendations)	Extensive duration focusing on: - Information - Environment
Material	- "Classic" measurement, estimated Measures in first report + possibility of further control if deemed necessary, with objective measurement	Impedance DXA Blood samples Interview Monitored stress test	BMI BMI for age and sex WtHR WC Questionnaires and field tests

ISs, intervention strategies; PA, physical activity PE, physical education; WC, waist circumference.

- Multidisciplinary team with specialists;
- Objective measurements;
- Relative efficiency to treat.

School/Community:

- Pleasure/enjoyment;
- Various activities;
- Relative efficiency to prevent;
- Time (place where children spend most of their time).

For the purposes of synthesis (**Figure 2**), we recommend the implementation of a transparent local council involving the entire local community (e.g., school children, representatives, clinical specialists, stakeholders, parents, associative representatives) (25) responsible for the development, improvement, and implementation of prevention programs at the local level. The most important point here is that each intervention sector should have its own prerogatives. Nevertheless, to achieve effective obesity prevention, the different settings need to function in a more transparent manner without ignoring the three different aspects of prevention (primary secondary = school/community; secondary tertiary = clinical). Another interesting aspect is the use of new technologies in prevention. On this point, further studies are needed to evaluate the potential added value of technological tools in obesity prevention.

4.4. Limitations

Many studies use BMI as a measurement variable or other variables related to it. However, although it is easy to use, BMI alone is not a representative indicator of the benefits of a program. Morano et al. (83) showed that the use of multiple body composition measurements provide better indications of changes in body fat, which is more representative of expected changes. Furthermore, weight-related measurements can skew the results (72). In PA-oriented programs, which lead to positive body composition change (e.g., lean mass gain and body fat loss), the participant weight can increase (lean mass is heavier), which can induce an increase in BMI measurements. This lack of precision relative to these measurements can also distort the results of the studies that use only BMI as the measurement variable or variables relative to the weight of the participants (22).

A second limitation could be the lack of information about programs in some studies to assess the quality of the study. This sometimes makes it difficult to identify the equipment used, the staff involved, and their skills/knowledge. The duration of the program is another limitation. Indeed, all the identified studies do not last the same amount of time (e.g., more than 1 year; less than 6 months; a few weeks). Furthermore, they do not use the same evaluation time (e.g., pre-post; pre-post + follow-up). It is, therefore, difficult to evaluate the effectiveness of one IS in relation to another over a short period of time. Moreover, to assess the efficacy of ISs, more time is required to embed them (60). The number of participants in each study is also highly variable and therefore can make a generalization or a comparison with other studies impossible. The last limitation pertains to the number of studies selected for each setting. Indeed, the number of studies being relatively low in the mixed setting can lead to an over/underestimation of the results. Nevertheless, this work seems to yield promising results, and future studies must continue to move to mixed setting, to nested ISs.

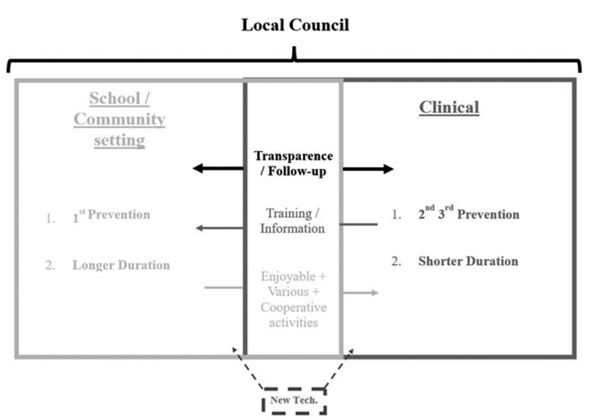

FIGURE 2
Modelling of physical activity ISs.

5. Conclusion

The main objective of this study was to propose a first combination and comparison of obesity prevention intervention programs from the clinical and the school or community sectors. However, our review showed that comparisons are difficult to make since the standards and units used for measurements are different and vary according to the protocols and areas of application. Nevertheless, we believe that this study offers an initial proposal for bridging the gap between the clinical and the school/community sectors, the two most promising sectors in terms of outcomes for obesity prevention in youth in particular.

Future studies should focus on establishing a prevention program in a given geographical area (e.g., town, county), involving all stakeholders with their respective skills/knowledge, in the decision-making process and in the development of ISs (e.g., parent association, professors, doctors, local representatives, sports association), so that it becomes the most efficient and best adapted to its environment. Although this study focused on physical activity interventions, it would be relevant to also look at nutrition interventions, since nutrition is a major theme in obesity prevention. The main objective of this study was to propose a first combination of obesity prevention intervention programs with the clinical and the school or community sectors. Our review showed that comparisons are difficult since the standards and units used to measure are different and vary according to the protocols and areas of application. However, we believe that this study offers an initial proposal for bridging the gap between the clinical and school/community sectors, the two most promising sectors in terms of outcomes for obesity prevention in youth in particular.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

Conceptualization was done by TC and TG; the methodology of the study was prepared by TC and TG; software was provided by PB; validation was done by TC, PB, and TG; formal analysis was done by TC; investigation was performed by TC; resources were provided by TG; data curation was done by PB and TG; writing—original draft preparation—was done by TC; writing—review and editing—was done by PB and TG; supervision was carried out by TG; project administration was looked after by TC. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Appendix A Keywords and meshterms

Theme 1	Theme 2	Theme 3	Theme 4
Program	Obese	"Physical activity"	Child
Protocol	Obesity	Sport	Childhood
Plan	Overweight		Young
"Intervention strategy"	"Obesity Management"		Youth
Method			"Elementary school"
Recommendation			Children
Treatment			Adolescence
Prevention			Adolescent
			"under 18"
			Student
			Pediatric

Appendix B Equations of research

((((program[Title/Abstract] OR "intervention strategy"[Title/Abstract] OR proto-col[Title/Abstract] OR method[Title/Abstract] OR plan[Title/Abstract] OR recommenda-tion[Title/Abstract] OR treatment[Title/Abstract] OR prevention [Title/Abstract])) AND (obese[Title/Abstract] OR obesity[Title/Abstract] OR overweight[Title/Abstract] OR "obesi-ty management"[Title/Abstract])] AND ["physical activity"[Title/Abstract] OR sport[Title/Abstract]]) AND (Child[Title/Abstract] OR childhood[Title/Abstract] OR young[Title/Abstract] OR youth[Title/Abstract] OR "elementary school"[Title/Abstract] OR children[Title/Abstract] OR adolescent[Title/Abstract] OR adolescence[Title/Abstract] OR under 18[Title/Abstract] OR student[Title/Abstract] OR pediatric[Title/Abstract]) AND ([Observational Study[ptyp] OR Multicenter Study[ptyp] OR Clinical Study[ptyp] OR Clinical Trial[ptyp] OR Comparative Study[ptyp] OR Evaluation Studies[ptyp] OR Gov-ernment Publications[ptyp] OR Letter[ptyp] OR Meta-Analysis[ptyp] OR Randomized Controlled Trial[ptyp] OR Validation Studies[ptyp]] AND full text [sb] AND "last 5 years"[PDat] AND Humans[Mesh] AND [English[lang] OR French[lang]] AND [child[MeSH:noexp] OR adolescent[MeSH]])