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Effectiveness of individual and group programmes to treat obesity and reduce cardiovascular disease risk factors in pre-pubertal children

Nathalie J. Farpour-Lambert[1,2] | Xavier E. Martin[3] | Sophie Bucher Della Torre[1,4] | Lydia von Haller[3] | Louisa J. Ells[5] | François R. Herrmann[6] | Yacine Aggoun[7]

[1]Obesity Prevention and Care Program "Contrepoids," Service of Therapeutic Education for Chronic Diseases, Department of Primary Care, University Hospitals of Geneva and University of Geneva, Geneva, Switzerland

[2]Paediatric Sports Medicine Consultation, Service of General Paediatrics, Department of Women, Child and Adolescent, University Hospitals of Geneva and University of Geneva, Geneva, Switzerland

[3]Health and Movement Consultation, Paediatric Cardiology Unit, Service of Paediatric Specialties, Department of Women, Child and Adolescent, University Hospitals of Geneva and University of Geneva, Geneva, Switzerland

[4]Department of Nutrition and Dietetics, School of Health Sciences, Geneva, HES-SO University of Applied Sciences and Arts Western, Geneva, Switzerland

[5]School of Health and Social Care, Teesside University, Middlesbrough, UK

[6]Division of Geriatrics, Department of Internal Medicine, Rehabilitation and Geriatrics, University Hospitals of Geneva and University of Geneva, Geneva, Switzerland

[7]Paediatric Cardiology Unit, Service of Paediatric Specialties, Department of Women, Child and Adolescent, University Hospitals of Geneva and University of Geneva, Geneva, Switzerland

Correspondence
Nathalie Farpour-Lambert, Obesity Prevention and Care Program "Contrepoids," Service of Therapeutic Education for Chronic Diseases, Department of Primary Care, University Hospitals of Geneva, Rue Gabrielle Perret-Gentil 4/CH-1211 Geneva 14, Switzerland.
Email: nathalie.farpourlambert@hcuge.ch

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Summary

Childhood obesity results in premature atherosclerosis and requires early intervention. Compare the effectiveness of 6-month lifestyle interventions (with choice of either individual or group therapy) with standard care on body mass index (BMI) *z*-score and cardiovascular disease (CVD) risks factors in children with obesity. This 6-month randomized controlled trial with a 6-month follow-up included 74 pre-pubertal children with obesity (7.5-11.9 years) assigned randomly (2:1) to intervention or control. Families in the intervention arm choose between an individually delivered treatment (3 hours paediatrician + 4 hours dietician) or group treatment (35 hours with a multidisciplinary team). Children participated also to a weekly physical activity programme. We measured BMI, BMI *z*-score; waist circumference (WC); total and abdominal fat; blood pressure; common carotid artery intima-media thickness and incremental elastic modulus (Einc); endothelium-dependent and independent dilation (nitroglycerin-mediated dilation [NTGMD]) of the brachial artery; fasting plasma glucose, insulin, lipids; and high-sensitivity C-reactive protein (hs-CRP). Compared to controls, at 6 months, abdominal fat and hs-CRP were reduced in both interventions. The group intervention was also effective in reducing BMI (−0.55 kg/m^2; 95% confidence interval −1.16 to 0.06) and BMI z-score (−0.08; −0.15 to 0.00) at 6 months and BMI, BMI *z*-score, WC, NTGMD, total and abdominal fat at 12 months. Abdominal fat and low-grade inflammation were significantly decreased in both

interventions. High-intensity group treatment improved early signs of atherosclerosis in children with obesity. These findings are important for the promotion of cardiometabolic health in this population.

KEYWORDS
cardiovascular diseases, child, lifestyle, obesity, randomized controlled trial, treatment

1 | INTRODUCTION

Non-communicable diseases (NCDs) have overtaken infectious diseases as the world's major global disease burden. Among NCDs, cardiovascular diseases (CVDs) account for nearly half the total burden and are the leading cause of death globally.[1] Childhood obesity lays the foundation for CVDs and has a strong tendency to track into adulthood if left untreated.[2] Childhood therefore presents a unique opportunity for intervention to prevent lifelong exposure and premature morbidity, and control associated health costs.

Multidisciplinary programmes are considered the gold standard treatment for children with obesity.[3] Family-based behavioural interventions were initially developed to modify the shared family environment, provide role models and support child behaviour changes.[4] Treatment in groups without individual attention has been shown to be both effective and cost-effective.[5] Medium (26-75 hours contact time) to high-intensity (>75 hours contact time) interventions are more effective than lower ones (<25 hours) with a small to moderate improvement in weight status.[6]

In 2007 we developed, in cooperation with the Swiss Federal Office of Public Health, a large-scale national programme for the management of childhood obesity using a standardized intensive group treatment covered by health insurances. However, the national evaluation study showed that only 0.8% of patients could be included in a group programme due to travelling time, parents "work and intensity of intervention."[7] This type of treatment is also quite resource intensive, with multiple healthcare workers required to meet different age groups of children and their parents. A recent Cochrane review of lifestyle interventions for the treatment of obesity in children aged 6 to 11 years concluded that there is insufficient evidence to determine the most effective and sustainable type or setting of intervention.[8]

The aim of this study was to compare the effectiveness of 6-month lifestyle interventions (with choice of either individual or group therapy) with standard care on body mass index (BMI) *z*-score and CVD risk factors.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Multi-component programmes are considered the gold standard treatment for children with obesity.
- There is insufficient evidence to determine the most effective and sustainable type or setting of lifestyle intervention.

WHAT THIS STUDY ADDS

- Individually delivered or group lifestyle interventions during 6 months resulted in significant reductions in abdominal fat and low-grade inflammation in pre-pubertal children with obesity, compared to standard care.
- To our knowledge, this is the first study showing such changes after an individually delivered intervention in this population.
- High-intensity group intervention was also effective in reducing body mass index (BMI) and BMI *z*-score, compared to standard care, as well as vascular reactivity mediated by smooth muscle cells and carotid arterial stiffness.

2 | MATERIALS AND METHODS

2.1 | Study design, setting and participants

This randomized controlled trial (RCT) included 74 pre-pubertal new patients with obesity aged 7.5 to 11.9 years who were recruited over a 4-year period at the Obesity Clinic of the Children's Hospital of Geneva (tertiary centre), if their BMI was >97th age- and gender-specific percentile according to the World Health Organization (WHO) references.[9] The report of this trial conforms to CONSORT 2010 guidelines and the Template for intervention description and replication checklist.

Subjects were excluded from the study if they: (a) had a Tanner stage assessed by clinical examination (size of the breasts or testicular volume, and development of pubic hair) >1; (b) were involved in any weight control, physical activity, behavioural intervention or bariatric surgery; (c) had a family history of dyslipidaemia or essential hypertension; (d) took any medications or hormones that could affect cardiovascular function, body composition, lipid or glucose metabolism; (e) had an orthopaedic condition that limited physical activity; (f) had a genetic disorder or another chronic disease; and (g) received therapy for psychiatric problems.

The Ethics Committee of the University Hospitals of Geneva approved this study and informed written consent was obtained from all participating parents and children.

2.2 | Randomization and concealment

Enrolment, randomization, interventions and follow-up of study participants are summarized in Figure 1; 74 subjects were randomly assigned (2:1) to a 6-month lifestyle intervention (n = 52) or a control group (C, n = 22, standard care) arm. Sealed opaque envelopes containing two-thirds of intervention and one-third of control were used.

In order to facilitate the implementation of this research into clinical practice, children and parents who were selected in the intervention arm could choose to participate in a moderate-intensity individually delivered intervention (treatment A, n = 21) or a high-intensity group delivered intervention (treatment B, n = 31), according to their will and availability. During the 6-month follow-up period, groups A and B were invited to attend two paediatric consultations (45 minutes.) at 9 and 12 months.

2.3 | Interventions

During the pilot phase of the study, an adapted mastery approach "Contrepoids" was developed and evaluated with 10 volunteer families. The manual contained modules on healthy nutrition, physical activity, family habits, parenting and coping with psychosocial problems commonly experienced by children with obesity, such as teasing and body image concerns. The nutrition education component used a healthy eating approach encouraging low saturated fat and nutrient-dense food (vegetables, fruits and whole grain foods) and portion size moderation. Modules included food choices, balanced meals, carbonated and non-carbonated sugar-sweetened beverages, food promotion and labelling, healthy cooking recipes, recognition of hunger and satiety, eating disorders, management of high-risk situations and

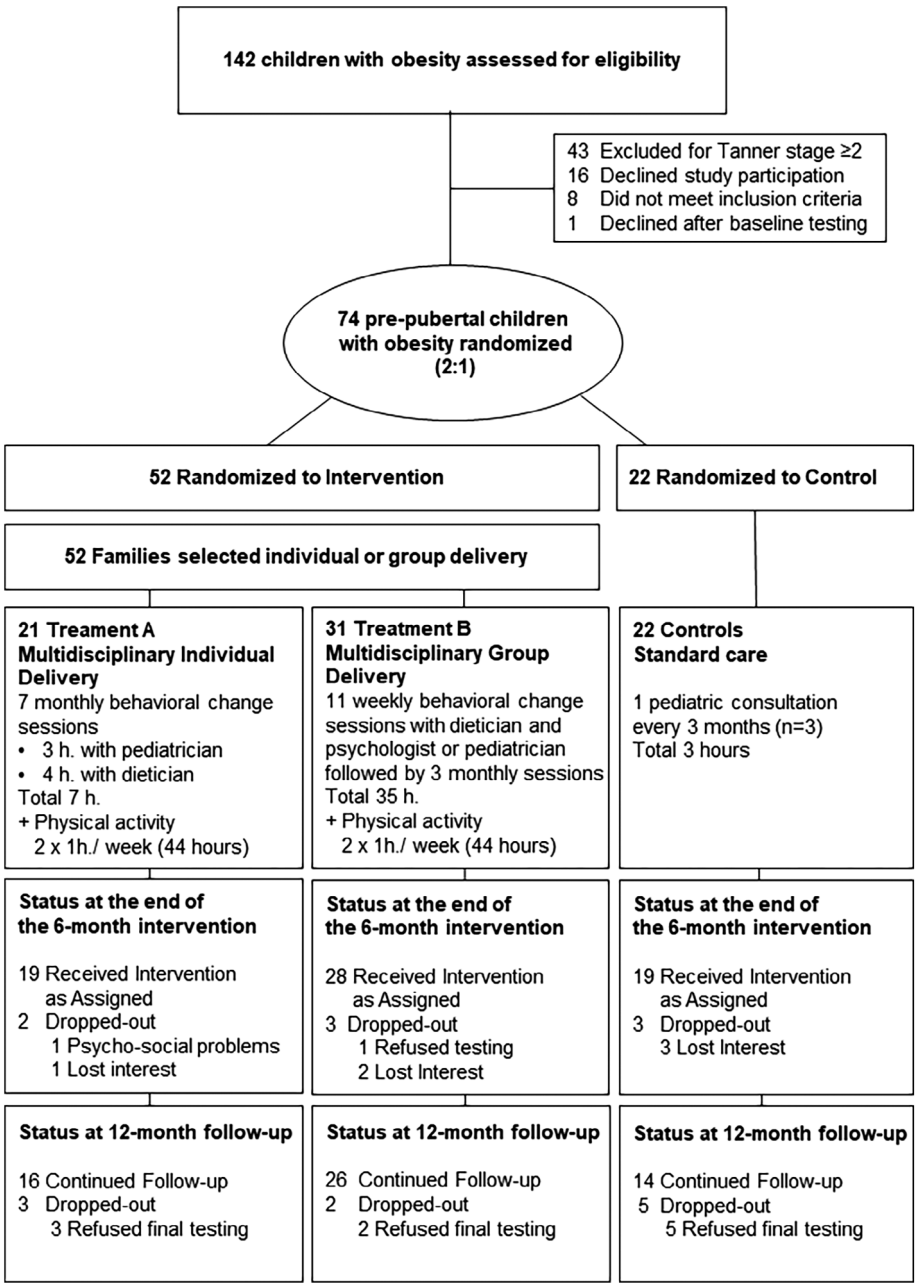

FIGURE 1 Flowchart for enrolment, randomization, intervention and follow-up of study participants

prevention of relapses. The physical activity component focused on encouraging active transport (walking, biking), use of stairs, leisure-time activities and sport and reduction of sedentary behaviours (television, computer and electronic games). Self-awareness, problem-solving, goal setting, stimulus control, coping skills training, empowerment, parental guidance and relapse prevention behaviour change techniques were used. At the end of each session, individual goals were set and participants received homework to complete before the next one. Therapists communicated at least weekly with the physical education teachers to reinforce behavioural changes. The moderate-intensity individually delivered intervention (treatment A) comprised 7 monthly 60-minute sessions with the child and his/her parent/s (at least the mother), which were conducted by a trained paediatrician (at 0, 3 and 6 months) and a dietician (at 1, 2, 4 and 5 months). Parents could choose a convenient appointment time which could be changed if unexpected events arose. Similar mastery approach and education manuals "Contrepoids" were used in both treatment arms, but topics were chosen according to family needs in individual care.

The high-intensity group delivered intervention (treatment B) comprised 14 sessions (11 weekly then 3 monthly meetings, total 35 hours) over a 6-month period. Ideally both parents, but at least the mother, were asked to participate. Parental and child sessions were held separately. The parental group sessions consisted of 90 minutes with a dietician (at all sessions), a psychologist trained in cognitive behavioural therapy (at least four sessions) or a paediatrician experienced in therapeutic patient education. The child sessions consisted of 60 minutesutes with the same therapists. Each group included 10 to 12 children and their parents.

Controls (group C) received standard care for 12 months, which included four 45-minute paediatric consultations (every 3 months) and instruction to maintain their current level of physical activity.

Treatment groups A and B could participate in a 6-month after school moderate-to-vigorous physical activity training programme including two sessions of 60 minutes per week (total 44 hours between September-October and March-April), in addition to school physical education (135 minutes/week). Children who were already enrolled in a sports club (at least 60 minute/week 6 months/year) attended only one physical activity session per week at the Children's Hospital.

One session per week was organized at the gym hall and the other one at the swimming pool, under close supervision of two physical education teachers. Training sessions included 40 minutes of aerobic exercise, 10 minutes of resistance training of the legs, arms and trunk and 10-minute of stretching. The intensity was progressively increased during the 6-month period, to reach intermittent vigorous intensities. During each session, physical education teachers discussed theoretical aspects of exercise such as discomfort, sweating and fatigue in relation to intensity, progress, self-esteem, benefits on health and well-being, leisure-time physical activity and active transport. Children and parents received a pedometer to assess and increase progressively their number of steps per day. The final goal was to do 10 000 steps per day for adults and 12 000 to 13 000 steps for children.

2.4 | Adverse events

Adverse events were recorded in both groups during the 6-month active intervention period.

2.5 | Procedures

All measurement techniques have been described in detail, in our previous publications.[10,11] All subjects underwent an identical testing protocol starting at 8 AM at the Pediatric Research Platform, and a second visit was generally needed due to the long duration of testing (5 hours). The protocol was repeated at 6 and 12 months. The personnel of the Pediatric Research Platform and of the Paediatric Cardiology Unit were blind to group allocation, whereas subjects and intervention delivery staff could not be blinded.

2.6 | Primary outcome measures

Body weight (Seca 701, Germany) and standing height were measured; BMI (weight/height squared, $kg \times m^{-2}$) and BMI *z*-score (primary outcome) were calculated using the United States Centre for Disease Control (BMI_{CDC}),[12] and the WHO (BMI_{WHO}) references.[9]

2.7 | Secondary outcome measures

Total body fat, abdominal fat and fat-free mass (FFM [kg]), were assessed using dual-energy X-ray absorptiometry (GE Lunar Prodigy, Lunar Corp.). Resting blood pressure (office BP) was measured three times at a 2-minute interval (Philips SureSigns VS3, Philips Medical System, Andover), the average BP was calculated and hypertension was defined as BP >95th gender-, age- and height-specific percentiles.[13]

The 24-hour ambulatory BP was assessed every 30 minutes at the non-dominant arm (Dyasis Integra II, Physicor S.A., France). The 24-hour mean BP and *z*-scores were calculated, and hypertension was defined as 24-hour BP >95th age- and gender-specific percentile.[14]

The common carotid intima-media thickness (CIMT) was measured using a real-time B-mode ultrasound imager (Vingmed CFM800C System Ltd, Norway and Iôtec System, Iôdata Processing, France).[10] Advanced vascular age was defined as CIMT >25th percentile using 45-years-old references.[15]

The pulse wave of the radial artery was assessed using an applanation tonometry probe (SphygmoCor; Atcor Medical Ltd., Australia) to estimate central aortic pressure non-invasively and determine arterial stiffness using the incremental elastic modulus (Einc).

After 30 minutes of rest in a recumbent position, the flow-mediated dilation (FMD) and nitroglycerin-mediated dilation (NTGMD) of the brachial artery were measured.

Cardiorespiratory fitness was assessed as the maximal oxygen consumption (VO_2 peak) by direct gas analysis (Vmax Spectra, Vyasis Healthcare, GE) during a multi-stage treadmill test (Marquette 2000, GE).

Physical activity level was assessed using a uniaxial accelerometer (Actigraph GMT1, MTI, Florida), worn on the right waist during a

7-day period (30-second cycle, school week, 24 hours/day), except during bathing or swimming. Data was expressed as mean activity counts per minute between 8 AM and 9 PM, if the monitor was worn during ≥4 days including one week-end day. Zero activity periods of 20 minutes or longer were interpreted as being due to unworn accelerometers and were removed from the total count.

Blood samples were collected at 8 AM via venepuncture following a 10-hour overnight fast. Total cholesterol, high-density lipoprotein cholesterol, triglycerides (TGs) levels (mmol × L^{-1}) concentrations were determined by standard automotive techniques. Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald's formula. Plasma insulin concentrations were measured by radioimmunoassay and insulin resistance was assessed by using the homeostasis model assessment (HOMA-IR), according to the equation: HOMA-IR = fasting insulin (μU × mL^{-1}) × fasting glucose (mmol × L^{-1})/22.5. High-sensitive C-reactive protein (hs-CRP) level was measured by nephelometry. Results were considered as abnormal according to the Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents of the US National Heart, Lung, and Blood Institute (2012) and International Diabetes Foundation guidelines. Serum cardiovascular risk biomarkers (serum level of cytokine [CCL2], adiponectin and neutrophil product [MMP-8]) were also measured in a sub-sample of 48 children and results are published elsewhere.[16]

2.8 | Sample size and statistical analysis

The sample size calculation was based on our previous RCT in the same age group.[11] For an anticipated effect size of 0.1 for BMI *z*-score (SD 0.1), a sample size of 16 subjects in each group was required to detect a statistically significant differences at $P < .05$ with a statistical power of 80% ($\beta = 0.80$).

An intention-to-treat analysis (ITT, n = 74) was performed. Data were screened for normality using Francia-Shapiro tests and, when necessary, variables were transformed and successfully normalized (x^2, x^3, log x, $1/x^2$, $\sqrt{x}$, $1/\sqrt{x}$; see Table 3). Baseline data were expressed as median and interquartile range (25-75), or means and SD when indicated. Means of each continuous variable were compared by one-way analysis of variance with Bonferoni post-hoc tests. The shapes of distributions were compared using Kruskal-Wallis tests. Non-parametric comparisons were made by chi-square tests. Within-group (A, B or C) differences were assessed using paired *t* tests, then mixed linear regressions, which take into account the repeated measure design, were used to evaluate outcome changes over time (0, 6 and 12 months) according to the effects of intervention while adjusting for age and gender. After starting the intervention, we noticed an error in the recruitment of two subjects in group A, in that they did not meet the inclusion criteria (one girl was only overweight and one boy had a psychiatric disorder and cognitive retardation which limited his participation in a lifestyle programme). They have been included in the ITT analysis and outcomes did not change after removing them from the analysis. The statistical software programme Stata release 14 (College Station, Texas) was used and differences were considered significant when the *P*-value was <.05.

2.9 | Costs calculation

During the 6-month trial, treatment A comprised three medical (600 CHF/630 USD), four dietetic (296.40 CHF/311 USD) and two medical follow-up consultations (330 CHF/347 USD) plus 44 sessions of physical activity at the hospital or in a sports club (60 minutes + 30 minutes of preparation per session for six participants per teacher, 660 CHF/693 USD). One hour per child was added for medical coordination (196.10 CHF/206 USD). The direct costs for treatment A were 1786.10 CHF (1876 USD) for 6 months and 2082.50 CHF (2187 USD) for 12 months. In treatment B, the fixed rate for behavioural and physical activity sessions, was 4200 CHF (4411 USD). In addition, patients had three paediatric consultations at 0, 3 and 6 months (444.60 CHF/467 USD) and two follow-up consultations (296.40 CHF/311 USD). The direct costs for treatment B were 4644.60 CHF (4877 USD) for 6 months and 4941 CHF (5189 USD) for 12 months. The control group received standard care including one paediatric consultation every 3 months, so the costs were 444.60 CHF (467 USD) at 6 months and 741 CHF (778 USD) at 12 months.

2.10 | Role of funding sources

The funders were not involved in the study design, data collection, analysis, interpretation or in the manuscript preparation and decision to publish.

3 | RESULTS

3.1 | Comparison of groups at baseline

There were no statistically significant differences between groups for baseline physical characteristics, blood metabolism and arterial function (Table 1). The vascular age was advanced in 74% of children.

Eighty seven percent of subjects were Caucasian and the remaining 4% were African, 4% Asian and 5% Hispanic; 57%, 42% and 55% of subjects had a Swiss citizenship and 24%, 42% and 41% were from the European region (Portugal, Spain, Italy, France, Serbia and Kosovo) in group A, B and C, respectively.

Sixty two percent of mothers were overweight (58%, 71% and 52% in A, B and C, respectively) and 28% of them had obesity (37%, 29% and 19% in A, B and C, respectively); 19% of children had both parents with obesity, and 23% had a family history of type 2 diabetes.

3.2 | Effects of treatment A and B

Sixty-six (89%) out of 74 children received the 6-month intervention as assigned. The retention rate was 90%, 90% and 86% of subjects in group A, B and C, respectively, and the compliance, which was determined as the proportion of attended behavioural and physical activity sessions during the 6-month intervention, was 87% and 50% in group A, and 64% and 45% in group B, respectively (excluding children that attended sports club). The adherence, which was the

TABLE 1 Baseline physical characteristics, metabolism and arterial function in pre-pubertal children with obesity (n = 74)

	Group A: Individual delivery			Group B: Group delivery			Group C: Control			
Variables	**N**	**Mean/Median**	**SD/IQR**	**N**	**Mean/Median**	**SD/IQR**	**N**	**Mean/Median**	**SD/IQR**	***P*-value***
Gender (M, %)	21	13 (62)		31	12 (39)		22	13 (59)		.18
Age (years)#	21	9.5	1.2	31	9.7	1.1	22	9.7	1.0	.77
Physical characteristics										
Height (cm)	21	138.0	9.0	31	140.0	9.0	22	140.0	13.0	.82
Body weight (kg)	21	46.1	16.0	31	50.2	10.3	22	47.9	17.1	.66
BMI ($kg \times cm^2$)	21	23.7	4.7	31	25.8	2.9	22	24.8	6.0	.67
BMI *z*-score CDC	21	2.1	0.5	31	2.1	0.3	22	2.0	0.5	.88
BMI *z*-score WHO	21	2.8	0.7	31	2.8	0.6	22	2.7	0.8	.91
Waist circumference (cm)	21	79.0	13.0	31	80.0	12.5	22	80.0	12.0	.89
Waist-to-height ratio	21	0.6	0.1	31	0.6	1.0	22	0.6	0.1	.88
Total body fat (%)	20	41.4	9.2	31	44.1	4.1	21	44.0	5.2	.34
Abdominal fat (%)	20	49.7	8.7	31	52.5	5.6	21	52.3	7.2	.4
FFM (kg)	20	26.7	5.3	31	27.4	5.1	21	26.5	7.4	.97
VO_2 peak ($L \times min^{-1}$) #	21	1.8	0.4	29	1.7	0.6	19	1.7	0.9	.97
VO_2 peak/FFM ($mL \times kg^{-1} \times min^{-1}$)	20	68.1	11.1	29	64.1	14.1	18	67.5	19.4	.97
Physical activity (cpm)	16	422.4	189.4	22	363.6	229.2	15	399.8	173.3	.26
Blood metabolism										
Fasting glucose ($mmol \times L^{-1}$)	21	4.7	0.4	31	4.7	0.6	21	4.6	0.5	.62
Fasting insulin ($mU \times L^{-1}$, % high)	19	12.7 (37)	8.0	31	9.3 (22)	6.8	21	9.5 (5)	4.3	.38
HOMA-IR	19	2.8	1.7	31	1.8	1.3	21	2.1	0.8	.36
TC ($mmol \times L^{-1}$, % high)#	21	4.5 (24)	0.9	31	4.3 (19)	1.1	21	4.4 (19)	0.8	.97
LDL-C ($mmol \times L^{-1}$, % high)	21	2.9 (29)	1.2	31	2.7 (19)	0.7	21	2.9 (14)	1.0	.96
HDL-C ($mmol \times L^{-1}$, % low)	21	1.2 (29)	0.3	31	1.2 (32)	0.5	21	1.2 (19)	0.4	.92
TG ($mmol \times L^{-1}$, % high)	21	0.7 (29)	0.7	31	0.8 (16)	0.7	21	0.7 (5)	0.3	.67
hs-CRP ($mmol \times L^{-1}$)	18	3.6	3.0	26	2.9	2.7	18	2.3	2.8	.09
Arterial function										
Office systolic BP (mm Hg)	20	111.4	7.4	28	110.0	12.0	21	111.3	8.7	.88
Office diastolic BP (mm Hg)#	20	69.4	11.2	28	67.7	7.7	21	68.0	9.4	.82
Office systolic BP *z*-score#	20	0.8	0.7	28	0.7	0.7	21	0.8	1.0	.83
Office diastolic BP *z*-score#	20	0.7	1.0	28	0.6	0.6	21	0.6	0.8	.78
Office HTN (n systolic/diastolic, %)	20	2/4	20%	28	2/1	7.1%	21	3/3	14.3	.69
24-h systolic BP (mm Hg)	16	113.5	7.0	28	114	12.0	11	116.0	19.0	.82
24-h diastolic BP (mm Hg)	16	67.5	9.0	28	66.0	7.0	11	65.0	12.0	.24
24-h systolic BP *z*-score#	16	0.8	1.1	28	0.6	1.2	11	0.7	1.2	.89
24-h diastolic BP *z*-score#	16	0.8	1.5	28	0.1	1.1	11	0.2	1.4	.23
24-h HTN (n syst/diast, %)	16	13/11	81%	28	21/14	75%	11	8/5	73%	.85
CIMT (mm)	20	0.53	0.05	30	0.53	0.06	18	0.52	0.13	.87
Einc ($mm\ Hg \times 10^2$)	20	892.1	474.1	30	900.6	768.4	18	895.1	780.5	.84
FMD (%)	20	4.2	3.4	30	4.0	3.6	18	7.7	4.3	.35
NTGMD (%)	20	22.9	9.7	30	23.2	11.1	18	22.8	16.4	.81

Notes: Results are shown as median and interquartile range (IQR 25–75), or mean and SD when indicated #. The percentage of abnormal glucose, insulin and lipids levels is presented in brackets.

Abbreviations: BMI, body mass index; BP, blood pressure; CDC, Centers for Disease Control and Prevention; CIMT, intima-media thickness of the left common carotid artery; Einc, incremental elastic modulus; FFM, fat-free mass; FMD, flow-mediated dilation; HDL-C, high-density protein cholesterol; HOMA-IR, homeostasis assessment model of insulin resistance; hs-CRP, high-sensitive C-reactive protein; HTN, hypertension; LDL-C, low-density protein cholesterol; NTGMD, nitroglycerin-mediated dilation; TC, total cholesterol; TG, triglycerides; VO_2 peak, maximal cardiorespiratory fitness; WHO, World Health Organization.

*The *P*-values indicate differences between groups (one-way analysis of variance). There is no significant difference.

proportion of subjects who completed 75% of behavioural sessions, was 95% in group A and 45% in group B.[17]

In group A, 10 (48%) of 21 children participated on a weekly basis in sports club: swimming (n = 3), soccer (n = 2), horse riding (n = 1), badminton (n = 1), basketball (n = 1), biking (n = 1) and judo (n = 1). In group B, 16 (52%) of 31 children were involved in sports club: swimming (n = 6), soccer (n = 3), dance (n = 1), gymnastics (n = 2), boxing (n = 1), basketball (n = 1) and judo (n = 2). The compliance could unfortunately not be evaluated for the sports club participation.

The main reasons for incomplete testing was the time needed (absence from school) and discomfort of ambulatory BP and arterial function measures. Only one adverse event was reported during the intervention: a mild ankle sprain during the physical activity programme in Group B.

Body weight and composition parameters treatment effects at 6 and 12 months are presented in Table 2. Mixed effects regression models with repeated measures predicting changes in physical, metabolic and arterial function parameters, with intervention × time interaction, while adjusting for age and gender are shown in Table 3. As only few ambulatory BP data (n = 6) were available at 12 months, analysis were only performed from baseline to 6 months.

3.2.1 | Treatment A vs controls

Significant treatment effects at 6 months for abdominal fat (Tables 2 and 3) and hs-CRP (not shown in Table 2, mean difference − 2.6 mmol·l^{-1}, 95% confidence interval [CI] −5.5 to 0.2, P = .002) were found, whereas physical activity level was not improved (mean difference −300.7 cpm, 95% CI −568.0 to −33.5, P = .02) in treatment A (individual treatment) vs controls. At 12 months, there was no significant change for any parameter.

At 6 months, we also observed significant within-group reductions (paired t tests, not shown in tables) in BMI_{CDC} z-score (mean difference −0.06, 95% CI −0.11 to 0.00, P = .02), fasting glucose (−0.1 mmol × L^{-1}, −0.3 to 0.0, P = .049), insulin (−1.7 mU × L^{-1}, −3.5 to 0.2, P = .04), HOMA-IR (−0.4, −0.7 to 0.0, P = .02), 24 hours diastolic BP z-score (−0.3, −0.2 to 1.2, P = .04), and increases in body weight (3.8 kg, 2.7 to 4.8, P < .0001), BMI (0.6 kg × m^{-2}, 0.1 to 1.0, P = .001), waist circumference (1.8 cm, 0.6 to 3.1, P = .004), FFM (1.9 kg, 1.5 to 2.2, P < .0001), VO_2 peak (180.8 L × min^{-1}, 12.3 to 349.3, P = .02) and FMD (1.3%, −0.3 to 2.9, P = .05).

3.2.2 | Treatment B vs controls

Significant treatment effects were found at 6 months for BMI, BMI_{CDC} z-score, abdominal fat (Table 3) and hs-CRP level (not shown; mean difference −1.3 mmol × L^{-1}, 95% CI −4.0 to 1.5, P = .004), in treatment B (group treatment) vs controls. At 12 months, further improvement in BMI, BMI_{CDC} z-score, total and abdominal fat, as well as NTGMD (15.0%, −0.76 to 30.7, P = .01) were found.

At 6 months, we also observed significant within-group reductions (paired t tests, not shown in tables) in BMI_{CDC} z-score (mean difference −0.08, 95% CI −0.13 to −0.02, P = .006), BMI_{WHO} z-score (−0.15, −0.24 to −0.05, P = .001) and LDL-cholesterol level (−0.2 mmol × L^{-1}, −0.4 to 0.0, P = .02), whereas body weight (3.1 kg, 2.1 to 4.1, P < .0001), FFM (1.4 kg, 1.0 to 1.8, P < .0001), VO_2 peak (205.8 L × min^{-1}, 81.7 to 329.8, P = .002) and Einc (546.5 mm Hg × 10^2, 25.0 to 1068.0, P = .02) increased.

TABLE 2 Body weight and composition parameters treatment effects at 6 and 12 months in experimental groups A and B compared with control group

	Treatment effect at 6 months				Treatment effect at 12 months			
	Group A: Individual delivery		Group B: Group delivery		Group A: Individual delivery		Group B: Group delivery	
Non-normalized variables	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
Body weight (kg)	0.13	−1.28 to 1.55	−0.57	−1.86 to 0.73	1.47	−1.18 to 4.13	−0.90[b]	−3.31 to 1.51
BMI (kg × cm^2)	−0.21	−0.89 to 0.46	−0.55[a]	−1.16 to 0.06	0.31	−0.89 to 1.50	−0.77[a,b]	−1.86 to 0.32
BMI z-score CDC	−0.06	−0·13 to 0.03	−0.08[a]	−0.15 to 0.00	−0.02	−0.15 to 0.11	−0.10[a,b]	−0.22 to 0.01
BMI z-score WHO	−0.03	−0.17 to 0.11	−0.10	−0.23 to 0.03	0.06	−0.16 to 0.29	−0.09[b]	−0.29 to 0.11
WC (cm)	0.63	−2.86 to 4.12	−0.84	−4.02 to 2.34	−1.09	−2.99 to 5.17	−1.77[a,b]	−5.59 to 2.05
Waist-to-height ratio	0.001	−0.02 to 0.03	−0.008	−0.03 to 0.01	0.03	−0.03 to 0.03	−0.02[a]	−0.04 to 0.01
Total body fat (%)	−1.18	−2.62 to 0.27	−1.20	−2.48 to 0.07	−0.33	2.58 to 1.92	−1.65[a]	−3.75 to −0.46
Abdominal fat (%)	−2.90[a]	−5.35 to −0.45	−2.23[a]	−4.39 to −0.06	−1.18	−4.19 to 1.82	−3.11[a]	−5.91 to −0.30
Fat-free mass (kg)	0.23	0.51 to 0.97	−0.21	−0.85 to 0.45	0.86	−0.32 to 2.04	0.46	−0.65 to 1.56

Notes: Results are shown as means and 95% CI.

Abbreviations: BMI, body mass index; CDC, Centers for Disease Control and Prevention; CI, confidence interval; WHO, World Health Organization; WC, waist circumference.

[a]Significant treatment effects in experimental groups A (individual delivery) or B (group delivery) compared with control group C using mixed effects regression model with intervention × time interaction while adjusting for age and gender (intention-to-treat analysis), P < .05.

[b]Significant treatment effects in experimental groups A (individual delivery) compared with group B (group delivery) using mixed effects regression model with intervention × time interaction while adjusting for age and gender (intention-to-treat analysis), P < .05.

TABLE 3 Mixed effects regression model with repeated measures predicting changes in physical, metabolic and arterial function parameters (group A vs control, group B vs control), time (not shown), with intervention × time interaction, while adjusting for age and gender

	Group A: Individual delivery						Group B: Group delivery					
	Group A		Group A × 6 m		Group A × 12 m		Group B		Group B × 6 m		Group B × 12 m	
Variables	β	*P*-value	β	*P*-value	β	*P*-value	β	*P*-value	β	*P*-value	β	*P*-value
1/√Body weight (kg)	2×10^{-3}	.56	0.00	.91	-0.8×10^{-3}	.47	0.3×10^{-3}	.89	1×10^{-3}	.18	1.6×10^{-3}	.13[b]
1/√BMI (kg.cm^2)	2×10^{-3}	.54	1×10^{-3}	.40	0.2×10^{-3}	.90	2×10^{-3}	.61	3×10^{-3}	.04[a]	3×10^{-3}	.02[a,b]
BMI *z*-score CDC[2]	−0.14	.70	−0.19	.27	−0.12	.52	0.19	.54	−0.32	.04[a]	−0.44	.01[a,b]
Log BMI *z*-score WHO	−0.04	.59	−0.03	.37	2×10^{-3}	.94	0.03	.6	−0.05	.1	−0.06	.06[b]
Waist circumference^{-2} (cm)	-2×10^{-6}	.80	2×10^{-6}	.75	3×10^{-6}	.64	-8.3×10^{-6}	.29	8×10^{-6}	.13	12×10^{-6}	.02[a,b]
√Waist-to-height ratio	-9×10^{-5}	.99	-0.5×10^{-3}	.94	-4×10^{-3}	.64	9×10^{-3}	.32	-6×10^{-3}	.32	0.01	.045[a]
Total body fat[2] (%)	−0.01	.27	−0.01	.13	−0.01	.31	-2×10^{-3}	.87	−0.01	.08	−0.01	.045[a]
Abdominal fat[3] (%)	−0.01	.40	−0.02	.01[a]	−0.02	.10	0.5×10^{-3}	.96	−0.02	.03[a]	−0.02	.03[a]
√FFM^{-1} (kg)	-3×10^{-5}	.74	-3×10^{-5}	.51	1×10^{-5}	.82	2.3×10^{-5}	.8	3×10^{-5}	.39	9×10^{-6}	.83
√VO_2 peak (mL × min^{-1})	0.34	.77	−0.33	.80	−1.02	.48	0.23	.84	0.35	.76	0.71	.60
Log physical activity (cpm)	0.07	.52	−0.49	.02[a]	−0.38	.06	−0.11	.30	−0.26	.08	0.03	.86[b]
Fasting glucose[3] (mmol × L^{-1})	3.69	.59	−4.8	.51	12.66	.13	7.38	.24	−0.70	.91	12.15	.12
√Fasting insulin (mU × L^{-1})	0.29	.27	−0.39	.12	−0.18	.53	0.09	.73	−0.12	.59	−0.03	.92
√HOMA-IR	0.14	.25	−0.19	.12	−0.05	.71	0.05	.64	−0.05	.63	0.02	.84
Total cholesterol (mmol × L^{-1})	0.07	.77	−0.09	.64	−0.03	.89	0.014	.95	−0.24	.20	−0.07	.73
√LDL-cholesterol (mmol × L^{-1})	0.02	.70	−0.02	.61	−0.03	.56	-9×10^{-3}	.86	−0.08	.07	−0.02	.66
Log HDL-cholesterol (mmol × L^{-1})	−0.02	.28	−0.03	.59	-0.1×10^{-3}	.99	-6×10^{-3}	.93	0.04	.42	4×10^{-3}	.94
Log triglycerides (mmol × L^{-1})	0.02	.91	0.11	.44	0.17	.28	−0.03	.86	−0.04	.77	0.09	.56
Log hs-CRP (mmol × L^{-1})	0.29	.21	−0.73	.002[a]	−0.29	.29	0.16	.43	−0.64	.004[a]	−0.43	.10
Log systolic BP (mm Hg)	0.01	.58	−0.02	.39	0.02	.60	−0.01	.59	2×10^{-3}	.92	0.4×10^{-3}	.97
Diastolic BP (mm Hg)	1.95	.49	−1.34	.71	−3.20	.42	−1.06	.68	2.55	.44	−0.2	.96
Systolic BP *z*-score	0.07	.80	−0.10	.72	0.28	.39	−0.18	.46	0.12	.64	0.14	.63
Diastolic BP *z*-score	0.16	.51	−0.08	.79	−0.26	.46	−0.1	.66	0.25	.40	−0.01	.99
Log CIMT (mm)	−0.01	.84	0.04	.33	−0.13	.87	0.02	.56	4×10^{-3}	.92	−0.1	.13
Log Einc (mm Hg × 10^2)	0.01	.94	−0.06	.78	0.58	.15	0.04	.75	0.17	.40	−0.28	.38[b]
FMD^{-1} (%)	0.03	.18	−0.03	.41	−0.06	.41	0.05	.049[a]	0.03	.40	−0.06	.34
√ NTGMD (%)	−0.03	.92	−0.04	.92	0.56	.44	−0.11	.64	−0.21	.58	1.5	.011[a]

Notes: When indicated, variables were transformed and successfully normalized. Results are shown as coefficient and *P*-value. Missing data: Blood values are available in 19, 26, 17 subjects at 6 months and in 15, 21 and 11 subjects at 12 months, in group A, B and C, respectively. Physical activity count data are available in 4, 17, 10 subjects at 6 months and in 5, 9 and 7 subjects at 12 months, in group A, B and C, respectively. Arterial parameters (using high-resolution ultrasound) data are available in 14, 14, 11 subjects at 6 months and in 2, 5 and 3 subjects at 12 months, in group A, B and C, respectively.
Abbreviations: BMI, body mass index; BP, blood pressure; CIMT, intima-media thickness of the left common carotid artery; Einc, incremental elastic modulus; FFM, fat-free mass; FMD, flow-mediated dilation; HDL-C, high-density protein cholesterol; HOMA-IR, homeostasis assessment model of insulin resistance; hs-CRP, high-sensitive C-reactive protein; HTN, hypertension; LDL-C, low-density protein cholesterol; NTGMD, nitroglycerin-mediated dilation; TC, total cholesterol; TG, triglycerides; VO_2 peak, maximal cardiorespiratory fitness.
[a]Treatment effects: The *P*-values indicate significant effects between experimental groups A (individual delivery) or B (group delivery) versus C (control group): $P < .05$.
[b]The treatment effects between experimental groups A and B have been compared and are indicated: significantly lower than experimental group A ($P < .05$).

3.2.3 | Comparison between treatment A and B (non-randomized)

At 6 months, no significant difference was shown between groups A and B (Tables 2 and 3). At 12 months, changes were significantly greater for body weight, BMI, BMI_{CDC} and BMI_{WHO} *z*-scores, waist circumference, physical activity (result not shown; mean difference 131.1 cpm, 95% CI −232.6 to 494.7, $P = .03$) and Einc (−335.3 mm Hg × 10^2, −1144.4 to 473.9, $P = .02$) in treatment B vs A.

3.3 | Costs calculation

The direct costs were 1786 CHF (1876 USD) at 6 months and 2083 CHF (2188 USD) at 12 months for treatment A, and 4645 CHF (4878 USD) at 6 months and 4941 CHF (5189 USD) at 12 months for treatment B. The later was 2.4-fold more costly than treatment A, and 6.7 more costly than standard care (controls).

4 | DISCUSSION

The evidence to determine the most effective and sustainable type or setting of intervention is lacking for pre-pubertal children. Our study showed that both medium-intensity individually delivered intervention (treatment A) and high-intensity group intervention (treatment B) resulted in significant reductions at 6 months in abdominal fat and low-grade inflammation (hs-CRP) in pre-pubertal children with obesity, compared to standard care. Treatment B was also effective for reducing BMI and BMI *z*-score at 6 and 12 months, when compared to controls, as well as waist circumference, total and abdominal fat and vascular reactivity mediated by smooth muscle cells (NTGMD) at 12 months. Carotid arterial stiffness was also reduced at 12 months in treatment B compared to A.

4.1 | Effects on BMI

A decrease in BMI *z*-score during growth is of particular importance because it is inversely associated with the risk of coronary heart disease in adulthood.[18] In a recent systematic review including 70 studies in 6 to 11 years old children, a mean BMI *z*-score change of −0.06 (95% CI −0.10 to −0.02) was reported after intervention, the majority of studies using CDC references (only one using WHO references).[9] However, only half of studies included a post-intervention follow-up (range 1-30 months). The effect observed in treatment B was of similar magnitude (BMI_{CDC} *z*-score −0.08) compared to controls, and further changes were observed at 12 months (−0.10).

Treatment A did not lead to significant reduction of BMI *z*-score at 6 or 12 months, likewise a previous study evaluating the effects of a similar individually delivered intervention in 6 to 14-year-old children and adolescents.[19] Only a few studies have examined the effectiveness and generalizability of such intervention in teenagers.[20,21]

4.2 | Effects on body composition and cardiometabolic health

BMI is not a direct measure of body composition, thus changes in fat mass may be confounded with changes in FFM.[22] The significant decreases in abdominal fat and hs-CRP observed in treatment A and B have important implications for the cardiometabolic health of this at risk population.[23] Within-group changes at 6 months in treatment A were also significant for glucose, insulin and HOMA-IR, but no treatment effect could be demonstrated when compared to controls, probably due to small sample size, the statistical power being calculated based on the primary outcome BMI *z*-score change.

Visceral obesity and associated insulin resistance increase CVD risk by classical factors (dyslipidaemia, glucose dysregulation, hypertension and vascular dysfunction), as well as risk factors secreted by adipocytes and macrophages infiltrating adipose tissue (adipokines, pro-inflammatory cytokines and hypofibrinolytic factors) that, together, might lead to increased oxidative stress, arterial dysfunction and promoting atherosclerosis.[24] Persistent low-grade inflammation plays a major role in the development of atherosclerosis and several large-scale prospective studies have demonstrated continuous relations between hs-CRP, the risk of CVD and vascular mortality.[25] In children with obesity, a pro-inflammatory state has also been demonstrated even without established comorbidities,[26] and hs-CRP was associated with pre-clinical signs of atherosclerosis.[27] In addition, a recent study has shown that pre-pubertal insulin-glucose metabolism is associated with adult CVD risk and markers of atherosclerosis.[28] Reduced hs-CRP inflammation markers have also been reported in previous lifestyle interventions in children with obesity.[29,30]

4.3 | Effects on arterial parameters

In children and adolescents, BMI is strongly related to high BP.[31] At baseline, moderate hypertension ranged from 20% at rest to 81% by ambulatory monitoring, but no effect of treatment A or B could be seen compared to controls. The attendance rate at exercise sessions was low in both groups and physical activity levels decreased in group A compared to B. We previously reported significant improvement of BP after a 3-month moderate-to-vigorous exercise training programme including three sessions per week. A dose-effect relationship may explain differences between studies.[11]

Endothelial cell dysfunction is considered the first stage of atherosclerosis, and low FMD has been reported previously in children with obesity,[32] in association with increased arterial stiffness and systemic hypertension,[10] whereas signs of arterial wall remodelling are detectable later during adolescence.[33] In our study, a within-group A increase of FMD (+1.3%) was observed, suggesting improved endothelial cell function. As a meta-analysis of 5547 adults associated a 1% increase in FMD with a 13% decrease in cardiovascular events,[34] an improvement in FMD of 1.3% in this at-risk paediatric population would be expected to ameliorate their cardiovascular risk profile. However, the treatment effect was not significant compared to controls, probably due to the procurement of standard care in controls, a

small sample size and missing longitudinal data. In children aged 9 to 12 years (pre-pubertal and pubertal), a significant increase in FMD (+1.2% at 6 weeks, +1.7% at 12 months) was previously reported after a high-intensity exercise training programme was combined with a group lifestyle intervention comprising of a balanced hypocaloric diet.[35] Diet and exercise together, and maintenance of exercise at 12 months, were associated with a significantly greater improvements in endothelial function.

We also observed improvement of vascular reactivity mediated by smooth muscle cells (NTGMD) at 12 months in treatment B vs controls. In adults with metabolic syndrome, a reduction of the inflammatory state improves both endothelium-dependent and endothelium-independent vasodilator reactivity.[36]

Arterial stiffness is a consequence of arteriosclerosis, the process of arterial wall thickening and loss of elasticity that occurs with the onset of vascular disease. In this study, vascular age was advanced in a large proportion of children and a reduction of Einc was found at 12 months in group B, compared to group A (non-randomized). We showed previously that moderate-to-vigorous exercise at least twice a week during 6 months resulted in reduced arterial stiffness and stabilization of CIMT.[11] Adult studies have shown that arterial stiffness may predict CVD and mortality.[37] We may therefore hypothesize that high-intensity group intervention may have a long-term clinical impact on cardiovascular health; however, results remain to be verified in a RCT.

4.4 | Costs

The costs of treatment B were twice as much as treatment A. Few studies have investigated the cost estimates of childhood obesity management and showed a wide range of costs and evidence.[5,38,39] We found only one with a full economic evaluation.[36] Authors concluded that simple multi-component obesity interventions (hospital-based or nurse-led in primary care) can be provided at relatively low cost per 0.1 BMI improvement compared to an intensive and costly behaviour modification tool aimed at encouraging slower eating and better recognition of satiety.

4.5 | Strength and limitations

The strengths of this RCT were the evaluation of both benefits and harms, and the assessment of long-term efficacy. The possibility to choose between two treatment options facilitated the implementation of this research into clinical practice. A high retention rate in treatment arms A and B was also a strength compared to most obesity management centres reports.[8] The calculation of direct costs of treatment may be of special interest for policy makers and health insurance providers. Ideally, children should have been randomized in three groups to avoid selection bias, however it was difficult to impose a high-intensity group intervention to parents who could not attend sessions on a fixed day, time and location. The high compliance rate in the individually delivered intervention (treatment A) may be due to a smaller amount of visits and hours required. The choice and quality of the measures performed allowed us to evaluate the effects of the trial not only on BMI *z*-score, but also on markers of cardiometabolic health. However, the sample size calculation was based on the primary outcome: BMI *z*-score and not on these secondary outcome markers, which may have influenced the results.

The main limitation of this study was the time needed for testing (5 hours), which led to absences from school, and the discomfort of arterial parameters measures resulting in incomplete follow-up data. The higher drop-out rate in the control group compared to intervention groups was also a limitation for the interpretation of follow-up analysis. In patients with obesity, hypertension may be due to altered autonomous system activity and sleep apnoea, although these were not measured in our study. The control group received standard care, even if considered minimal, and this may have attenuated the treatment effects between groups. The attendance rate of children participating in sports club could not be evaluated, and this may also explain differences between groups. Finally, it would have been useful to know whether children changed their diet during intervention; data were collected using 3-day food records but were too poor to be analysed.

5 | CONCLUSIONS

The increasing prevalence of childhood obesity globally is likely to lead to a tsunami of NCDs in the coming decades unless urgent action is taken. It must be considered as a chronic disease to increase societal awareness, improve care and prevent the significant comorbid clinical and psychosocial problems.[40] However few children with obesity receive adequate treatment, and cost-effective interventions are urgently needed before puberty.

Both 6-month lifestyle interventions resulted in significant reductions in abdominal fat and low-grade inflammation (hs-CRP) in pre-pubertal children with obesity, compared to standard care. To our knowledge, this is the first study showing such changes after an individually delivered intervention in this population. We also showed that the high-intensity group intervention was effective in reducing BMI and BMI *z*-score, as well as vascular reactivity mediated by smooth muscle cells and carotid arterial stiffness. These findings are important given the global increases in childhood obesity and in the promotion of cardio-metabolic health and prevention of NCDs later in life. Individually delivered intervention is less costly than group intervention, facilitating its dissemination at large scale as it could be easily transferred to a primary care setting, in collaboration with sports clubs and physical education teachers.

However, to improve the management of obesity in children, both in individual and group setting, healthcare systems need to be adapted; the nutritional, psychological and physical therapy should be covered by health insurance, and healthcare workers should be trained to treat obesity similarly to other chronic diseases of childhood.[40] Primary care providers could then play a major role in the early treatment of childhood obesity and prevent the burden of CVD later in life. Further research is now needed to determine the optimum

intensity and composition of interventions in this age group, and long-term efficacy at 5 or 10 years. Treatment effects using different BMI *z*-score references should also be evaluated.

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CONFLICT OF INTEREST

No conflict of interest was declared.

AUTHOR CONTRIBUTIONS

N.J.F.-L. conceptualized the study design and wrote the research protocol, recruited the subjects, supervised the implementation and completion of the study and drafted the initial manuscript. X.E.M. designed and supervised the physical activity intervention and testing, and managed the data. S.B.D.T. designed and supervised the nutritional components of the interventions. L.H. participated to the psychological/behavioural components of interventions. L.J.E. contributed to the interpretation and presentation of results. F.R.H. performed the statistical analysis. Y.A. designed and supervised the acquisition and interpretation of arterial parameters data. All authors were involved in writing the paper and had final approval of the submitted and published versions.

ORCID

Nathalie J. Farpour-Lambert https://orcid.org/0000-0001-6478-7269
Louisa J. Ells https://orcid.org/0000-0003-0559-4832

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