Effectiveness of individual versus group programs to treat obesity and reduce cardiovascular disease risk factors in pre-pubertal children: A randomized controlled trial

Journal:	*Clinical Obesity*
Manuscript ID	Draft
Wiley - Manuscript type:	Original Research
Date Submitted by the Author:	n/a
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Keywords:	Obesity, Children, Treatment, Lifestyle, Cardiovascular disease
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	effective in reducing BMI (-0.55 kg/m2; 95% CI -1.16 to 0.06) and BMI-z (-0.08; -0.15 to 0.00) at 6 months, and BMI, BMI-z, WC, NTGMD, total and abdominal fat at 12 months. Discussion: 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.

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

Running title: Effective Programs for Childhood Obesity Treatment

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Registration: Clinical trials NCT01506245, https://www.clinicaltrials.gov/

Source of funding: Swiss National Science Foundation (#3200B0-120437), Bern, and the Geneva University Hospitals Research and Development Fund.

Conflict of interest: None declared

Word count: 5080

Keywords: Obesity, Treatment, Lifestyle, Cardiovascular Diseases, Child, Randomized Controlled Trial

What is already known about this subject?

- Multi-component programs 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 BMI and BMI z-score, compared to standard care, as well as vascular reactivity mediated by smooth muscle cells and carotid arterial stiffness.

ABSTRACT

Introduction: Childhood obesity results in premature atherosclerosis and requires early intervention.

Objectives: 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.

Methods: 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 (3h. pediatrician + 4h. dietician) or group treatment (35h. with a multidisciplinary team). Children participated also to a weekly physical activity program. 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 (NTGMD) of the brachial artery; fasting plasma glucose, insulin, lipids; high-sensitivity C-reactive protein (hs-CRP).

Results: 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% CI -1.16 to 0.06) and BMI-z (-0.08; -0.15 to 0.00) at 6 months, and BMI, BMI-z, WC, NTGMD, total and abdominal fat at 12 months.

Discussion: 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.

Abstract word count: 236

ABBREVIATIONS

BMI	Body Mass Index
BP	Blood Pressure
CDC	Center for Disease Control and Prevention
CIMT	Carotid Intima-Media Thickness
CVD	Cardiovascular Disease
Einc	Incremental Elastic Modulus
FFM	Fat-free mass
FMD	Flow-Mediated Dilation
HDL-C	High-density Lipoprotein Cholesterol
Hs-CRP	High-sensitive C-reactive protein
HOMA-IR	Homeostasis model assessment
LDL-C	Low-density Lipoprotein Cholesterol
NCDs	Non-communicable Diseases
NTGMD	Nitroglycerin-Mediated Dilation
RCT	Randomized controlled trial
TC	Total Cholesterol
TG	Triglycerides
VO_2peak	Maximal Cardiorespiratory Fitness
WHO	World Health Organization

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 programs are considered the gold standard treatment for children with obesity.(3) Family-based behavioral interventions were initially developed to modify the shared family environment, provide role models and support child behavior changes.(4) Treatment in groups without individual attention has been shown to be both effective and cost-effective.(5) Medium (26 to 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 improvements in weight status.(6)

In 2007 we developed, in cooperation with the Swiss Federal Office of Public Health, a large-scale national program 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 program due to travelling time, parents 'work and intensity of intervention.(7) This type of treatment is also quite resource intensive, with multiple health care 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.

MATERIALS AND METHODS

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 center), 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 (TIDieR) checklist.

Subjects were excluded from the study if they: 1) had a Tanner stage assessed by clinical examination (size of the breasts or testicular volume, and development of pubic hair) >1; 2) were involved in any weight control, physical activity, behavioral intervention or bariatric surgery; 3) had a family history of dyslipidemia or essential hypertension; 4) took any medications or hormones that could affect cardiovascular function, body composition, lipid or glucose metabolism; 5) had an orthopedic condition that limited physical activity; 6) had a genetic disorder or another chronic disease; 6) 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.

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 2/3 of intervention and 1/3 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 pediatric consultations (45 min.) at nine and twelve months.

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, 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 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 behaviors (television, computer, electronic games). Self-awareness, problem-solving, goal setting, stimulus control, coping skills training, empowerment, parental guidance and relapse prevention behavior 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 behavioral 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 pediatrician (at 0, 3, 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 h.) 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 behavioral therapy (at least 4 sessions) or a pediatrician experienced in therapeutic patient education. The child sessions consisted of 60 minutes with the same therapists. Each group included 10-12 children and their parents.

Controls (group C) received standard care for twelve months, which included four 45-minute pediatric consultations (every three 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 program including two sessions of 60 minutes per week (total 44 hours between Sep.-Oct. and Mar.-April), in addition to school physical education (135 minutes/week). Children who were already enrolled in a sports club (at least 60 min./week six 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 min 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.

Adverse Events

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

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 h.). The protocol was repeated at 6 and 12 months. The personnel of the Pediatric Research Platform and of the Pediatric Cardiology Unit were blind to group allocation, whereas subjects and intervention delivery staff could not be blinded.

Primary outcome measures

Body weight (Seca™ 701, Germany) and standing height were measured; BMI (weight/height squared, $kg \cdot m^{-2}$) 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)

Secondary outcome measures

Total body fat, abdominal fat and fat-free mass (FFM, kg), were assessed using dual-energy x-ray absorptiometry (DXA – GE Lunar Prodigy™, Lunar Corp., USA). Resting blood pressure (office BP) was measured three times at a 2-minute interval (Philips SureSigns

VS3®, Philips Medical System, Andover, USA), 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, USA) during a multi-stage treadmill test (Marquette 2000™, GE, USA).

Physical activity level was assessed using a uniaxial accelerometer (Actigraph™ GMT1, MTI, Florida, USA), worn on the right waist during a 7-day period (30-second cycle, school week, 24 h./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 venipuncture following a 10-hour overnight fast. Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG)

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}] x 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)

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 $p<0.05$ 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 (IQR 25-75), or means and standard deviation (SD) when indicated. Means of each continuous variable were compared by one-way analysis of variance (ANOVA) with Bonferoni post-hoc tests. The shapes of distributions were compared using Kruskal-Wallis tests. Nonparametric 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 program). They have been included in the ITT analysis and outcomes did not change after removing them from the analysis. The statistical software program Stata release 14 (College Station, Tx) was used and differences were considered significant when the p-value was <0·05.

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 min. + 30 min. 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, 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 three months, so the costs were 444.60 CHF (467 USD) at 6 months and 741 CHF (778 USD) at 12 months.

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.

RESULTS

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, 41% were from the European region (Portugal, Spain, Italy, France, Serbia, Kosovo) in group A, B and C, respectively.

Sixty two percent of mothers were overweight (58, 71, 52% in A, B and C, respectively) and 28% of them had obesity (37, 29, 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.

Effects of treatment A and B

Sixty-six out of 74 children (89%) 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 behavioral 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 proportion of subjects who completed 75% of behavioral sessions, was 95% in group A and 45% in group B.(17)

In group A, 10 of 21 children (48%) 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 of 31 children (52%) 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 program in Group B.

Body weight and composition parameters treatment effects at 6 and 12 month 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.

Treatment A versus Controls

Significant treatment effects at 6 months for abdominal fat (table 2 and 3) and hs-CRP (not shown in table 2, mean difference -2.6 $mmol \cdot l^{-1}$, 95% CI -5.5 to 0.2, p=0.002) were found, whereas physical activity level was not improved (mean difference -300.7 cpm, 95% CI -568.0 to -33.5, p=0.02) in treatment A (individual treatment) versus 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=0.02), fasting glucose (-0.1 $mmol \cdot l^{-1}$, -0.3 to 0.0, p=0.049), insulin (-1.7 $mU \cdot l^{-1}$, -3.5 to 0.2, p=0.04), HOMA-IR (-0.4, -0.7 to 0.0, p=0.02), 24h diastolic BP z-score (-0.3, -0.2 to 1.2, p=0.04), and increases in body weight (3.8 kg, 2.7 to 4.8, p<0.0001), BMI (0.6 $kg \cdot m^{-2}$, 0.1 to 1.0, p=0.001), waist circumference (1.8 cm, 0.6 to 3.1, p=0.004), FFM (1.9 kg, 1.5 to 2.2, p<0.0001), VO_2 peak (180.8 $l.min^{-1}$, 12.3 to 349.3, p=0.02) and FMD (1.3 %, -0.3 to 2.9, p=0.05).

Treatment B versus 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 $mmol \cdot l^{-1}$, 95% CI -4.0 to 1.5,

p=0.004), in treatment B (group treatment) versus 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=0.01) 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=0.006), BMI_{WHO} z-score (-0.15, -0.24 to -0.05, p=0.001) and LDL-cholesterol level (-0.2 $mmol \cdot l^{-1}$, -0.4 to 0.0, p=0.02), whereas body weight (3.1 kg, 2.1 to 4.1, p<0.0001), FFM (1.4 kg, 1.0 to 1.8, p<0.0001), VO_2 peak (205.8 $l.min^{-1}$, 81.7 to 329.8, p=0.002) and Einc (546.5 $mmHg.10^2$, 25.0 to 1068.0, p=0.02) increased .

Comparison between treatment A and B (non-randomized)

At 6 months, no significant difference was shown between groups A and B (table 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=0.03) and Einc (-335.3 $mmHg \cdot 10^2$, -1144.4 to 473.9, p=0.02) in treatment B versus A.

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).

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.

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 to 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)

Effects on body composition and cardiometabolic health

Body mass index is not a direct measure of body composition, thus changes in fat mass may be confounded with changes in fat-free mass.(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

295 could be demonstrated when compared to controls, probably due to small sample size, the
296 statistical power being calculated based on the primary outcome BMI z-score change.
297 Visceral obesity and associated insulin resistance increase CVD risk by classical factors
298 (dyslipidaemia, glucose dysregulation, hypertension, vascular dysfunction), as well as risk
299 factors secreted by adipocytes and macrophages infiltrating adipose tissue (adipokines,
300 proinflammatory cytokines and hypofibrinolytic factors) that, together, might lead to
301 increased oxidative stress, arterial dysfunction, and promoting atherosclerosis.(24) Persistent
302 low-grade inflammation plays a major role in the development of atherosclerosis and several
303 large-scale prospective studies have demonstrated continuous relations between hs-CRP, the
304 risk of CVD and vascular mortality.(25) In children with obesity, a pro-inflammatory state has
305 also been demonstrated even without established co-morbidities,(26) and hs-CRP was
306 associated with pre-clinical signs of atherosclerosis.(27) In addition, a recent study has shown
307 that pre-pubertal insulin-glucose metabolism is associated with adult CVD risk and markers
308 of atherosclerosis.(28) Reduced hs-CRP inflammation markers have also been reported in
309 previous lifestyle interventions in children with obesity.(29, 30)

310 **Effects on arterial parameters**

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

318 Endothelial cell dysfunction is considered the first stage of atherosclerosis, and low flow-
319 mediated dilation (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 remodeling 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 pediatric 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 program 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 versus 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.

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 behavior modification tool aimed at encouraging slower eating and better recognition of satiety.

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 centers 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 h.), 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 apnea, 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 analyzed.

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 co-morbid 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 health care 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.

ACKNOWLEDGEMENTS

NFL 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. XM designed and supervised the physical activity intervention and testing, and managed the data. SBDT designed and supervised the nutritional components of the interventions. LVH participated to the psychological/ behavioral components of interventions. LJE contributed to the interpretation and presentation of results. FRH performed the statistical analysis. YA 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.

We thank the subjects for volunteering for the study, Maurice Beghetti, Albane Maggio, Emmanuelle Golay, Aitziber Lopez de la Calle, Giulio Conicella, Jérôme Martin, Maude Bessat-Macchi, Francine Blanchard, Pauline Brindel and the staff of the Paediatric Research

418 Plateform of the Department of Child and Adolescent. This project was supported financially
419 by the Swiss National Science Foundation (#3200B0-120437) and the Geneva University
420 Hospitals Research and Development Fund.

421 **CONFLICT OF INTEREST**

422 There is no conflict of interest for any authors.

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)		0.18
Age (years) #	21	9.5	1.2	31	9.7	1.1	22	9.7	1.0	0.77
Physical Characteristics										
Height (cm)	21	138	9.0	31	140.0	9.0	22	140.0	13.0	0.82
Body weight (kg)	21	46.1	16	31	50.2	10.3	22	47.9	17.1	0.66
BMI ($kg.cm^2$)	21	23.7	4.7	31	25.8	2.9	22	24.8	6.0	0.67
BMI z-score CDC	21	2.1	0.5	31	2.1	0.3	22	2.0	0.5	0.88
BMI z-score WHO	21	2.8	0.7	31	2.8	0.6	22	2.7	0.8	0.91
Waist circumference (cm)	21	79	13	31	80.0	12.5	22	80.0	12.0	0.89
Waist-to-height ratio	21	0.6	0.1	31	0.6	1	22	0.6	0.1	0.88
Total body fat (%)	20	41.4	9.2	31	44.1	4.1	21	44.0	5.2	0.34
Abdominal fat (%)	20	49.7	8.7	31	52.5	5.6	21	52.3	7.2	0.4
FFM (kg)	20	26.7	5.3	31	27.4	5.1	21	26.5	7.4	0.97
VO_{2peak} ($l.min^{-1}$) #	21	1.8	0.4	29	1.7	0.6	19	1.7	0.9	0.97
$VO2_{peak}$/FFM ($ml.kg^{-1}\cdot min^{-1}$)	20	68.1	11.1	29	64.1	14.1	18	67.5	19.4	0.97
Physical activity (cpm)	16	422.4	189.4	22	363.6	229.2	15	399.8	173.3	0.26
Blood metabolism										
Fasting glucose ($mmol\cdot l^{-1}$)	21	4.7	0.4	31	4.7	0.6	21	4.6	0.5	0.62
Fasting insulin ($mU\cdot l^{-1}$, % high)	19	12.7 (37)	8.0	31	9.3 (22)	6.8	21	9.5 (5)	4.3	0.38
HOMA-IR	19	2.8	1.7	31	1.8	1.3	21	2.1	0.8	0.36
TC ($mmol\cdot l^{-1}$, % high)#	21	4.5 (24)	0.9	31	4.3 (19)	1.1	21	4.4 (19)	0.8	0.97
LDL-C ($mmol\cdot l^{-1}$, % high)	21	2.9 (29)	1.2	31	2.7 (19)	0.7	21	2.9 (14)	1.0	0.96
HDL-C ($mmol\cdot l^{-1}$, % low)	21	1.2 (29)	0.3	31	1.2 (32)	0.5	21	1.2 (19)	0.4	0.92
TG ($mmol\cdot l^{-1}$, % high)	21	0.7 (29)	0.7	31	0.8 (16)	0.7	21	0.7 (5)	0.3	0.67
hs-CRP ($mmol\cdot l^{-1}$)	18	3.6	3.0	26	2.9	2.7	18	2.3	2.8	0.09
Arterial Function										
Office systolic BP (mmHg)	20	111.4	7.4	28	110	12.0	21	111.3	8.7	0.88
Office diastolic BP (mmHg)#	20	69.4	11.2	28	67.7	7.7	21	68.0	9.4	0.82
Office systolic BP z-score#	20	0.8	0.7	28	0.7	0.7	21	0.8	1.0	0.83
Office diastolic BP z-score#	20	0.7	1.0	28	0.6	0.6	21	0.6	0.8	0.78
Office HTN (n syst/ diast, %)	20	2/4	20	28	2/1	7.1	21	3/3	14.3	0.69
24h systolic BP (mmHg)	16	113.5	7.0	28	114	12.0	11	116.0	19.0	0.82
24h diastolic BP (mmHg)	16	67.5	9.0	28	66	7.0	11	65.0	12.0	0.24
24h systolic BP z-score#	16	0.8	1.1	28	0.6	1.2	11	0.7	1.2	0.89
24h diastolic BP z-score#	16	0.8	1.5	28	0.1	1.1	11	0.2	1.4	0.23
24-h HTN (n syst/diast, %)	16	13/11	81%	28	21/14	75%	11	8/5	73%	0.85
CIMT (mm)	20	0.53	0.05	30	0.53	0.06	18	0.52	0.13	0.87
Einc ($mmHg.10^2$)	20	892.1	474.1	30	900.6	768.4	18	895.1	780.5	0.84
FMD (%)	20	4.2	3.4	30	4.0	3.6	18	7.7	4.3	0.35
NTGMD (%)	20	22.9	9.7	30	23.2	11.1	18	22.8	16.4	0.81

Legend TABLE 1.

Results are shown as median and interquartile range (IQR 25-75), or mean and standard deviation (SD) when indicated#. Abbreviations: BMI, Body Mass Index; CDC, Center for Disease Control and Prevention; WHO, World Health Organization; TC, Total cholesterol; LDL- C, LDL-Cholesterol; HOMA-IR, Homeostasis Assessment Model of Insulin resistance; VO2peak, Maximal Cardiorespiratory Fitness; FFM, Fat-Free Mass; TC, Total Cholesterol; LDL-C, Low-density Protein Cholesterol; HDL-C, High-density Protein Cholesterol; HDL-C, HDL-Cholesterol; TG, Triglycerides; hs-CRP, high-sensitive C-reactive Protein; BP, Blood pressure; HTN, Hypertension; CIMT, Intima-media thickness of the left common carotid artery; Einc, incremental elastic modulus; FMD, Flow-mediated dilation; NTGMD, Nitroglycerin-mediated dilation.

The percentage of abnormal glucose, insulin and lipids levels is presented in brackets.

The P values indicate differences between groups (one-way analysis of variance).

There is no significant difference.

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

Non-normalized Variables	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	
	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‡	-3.31 to 1.51
BMI (kg.cm2)	-0.21	-0.89 to 0.46	-0.55*	-1.16 to 0.06	0.31	-0.89 to 1.50	-0.77*‡	-1.86 to 0.32
BMI z-score CDC	-0.06	-0·13 to 0.03	-0.08*	-0.15 to 0.00	-0.02	-0.15 to 0.11	-0.10*‡	-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‡	-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*‡	-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*	-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*	-3.75 to -0.46
Abdominal fat (%)	-2.90*	-5.35 to -0.45	-2.23*	-4.39 to -0.06	-1.18	-4.19 to 1.82	-3.11*	-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

Legend TABLE 2.

Results are shown as means and 95% confidence intervals.

Abbreviations: BMI, Body Mass Index; CDC, Center for Disease Control and Prevention; WHO, World Health Organization; WC, waist circumference.

* 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), $p<0.05$.

‡ 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), $p<0.05$.

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)	$2 \cdot 10^{-3}$	0.56	0.00	0.91	$-0.8 \cdot 10^{-3}$	0.47	$0.3 \cdot 10^{-3}$	0.89	$1 \cdot 10^{-3}$	0.18	$1.6 \cdot 10^{-3}$	0.13 ‡
1/√ BMI (kg.cm2)	$2 \cdot 10^{-3}$	0.54	$1 \cdot 10^{-3}$	0.40	$0.2 \cdot 10^{-3}$	0.90	$2 \cdot 10^{-3}$	0.61	$3 \cdot 10^{-3}$	0.04*	$3 \cdot 10^{-3}$	0.02*‡
BMI z-score CDC[2]	-0.14	0.70	-0.19	0.27	-0.12	0.52	0.19	0.54	-0.32	0.04*	-0.44	0.01*‡
Log BMI z-score WHO	-0.04	0.59	-0.03	0.37	$2 \cdot 10^{-3}$	0.94	0.03	0.6	-0.05	0.1	-0.06	0.06 ‡
Waist circumference[-2] (cm)	$-2 \cdot 10^{-6}$	0.8	$2 \cdot 10^{-6}$	0.75	$3 \cdot 10^{-6}$	0.64	$-8.3 \cdot 10^{-6}$	0.29	$8 \cdot 10^{-6}$	0.13	$12 \cdot 10^{-6}$	0.02*‡
√ Waist-to-height ratio	$-9 \cdot 10^{-5}$	0.99	$-0.5 \cdot 10^{-3}$	0.94	$-4 \cdot 10^{-3}$	0.64	$9 \cdot 10^{-3}$	0.32	$-6 \cdot 10^{-3}$	0.32	0.01	0.045*
Total body fat[2] (%)	-0.01	0.27	-0.01	0.13	-0.01	0.31	$-2 \cdot 10^{-3}$	0.87	-0.01	0.08	-0.01	0.045*
Abdominal fat[3] (%)	-0.01	0.40	-0.02	0.01*	-0.02	0.10	$0.5 \cdot 10^{-3}$	0.96	-0.02	0.03*	-0.02	0.03*
√ FFM[-1] (kg)	$-3 \cdot 10^{-5}$	0.74	$-3 \cdot 10^{-5}$	0.51	$1 \cdot 10^{-5}$	0.82	$2.3 \cdot 10^{-5}$	0.8	$3 \cdot 10^{-5}$	0.39	$9 \cdot 10^{-6}$	0.83
√ VO_2peak (ml·min^{-1})	0.34	0.77	-0.33	0.80	-1.02	0.48	0.23	0.84	0.35	0.76	0.71	0.60
Log Physical activity (cpm)	0.07	0.52	-0.49	0.02*	-0.38	0.06	-0.11	0.30	-0.26	0.08	0.03	0.86 ‡
Fasting glucose[3] (mmol·l^{-1})	3.69	0.59	-4.8	0.51	12.66	0.13	7.38	0.24	-0.70	0.91	12.15	0.12
√ Fasting insulin (mU·l^{-1})	0.29	0.27	-0.39	0.12	-0.18	0.53	0.09	0.73	-0.12	0.59	-0.03	0.92
√ HOMA-IR	0.14	0.25	-0.19	0.12	-0.05	0.71	0.05	0.64	-0.05	0.63	0.02	0.84
Total cholesterol (mmol·l^{-1})	0.07	0.77	-0.09	0.64	-0.03	0.89	0.014	0.95	-0.24	0.20	-0.07	0.73
√ LDL- Cholesterol (mmol·l^{-1})	0.02	0.70	-0.02	0.61	-0.03	0.56	$-9 \cdot 10^{-3}$	0.86	-0.08	0.07	-0.02	0.66
Log HDL-Cholesterol (mmol·l^{-1})	-0.02	0.28	-0.03	0.59	$-0.1 \cdot 10^{-3}$	0.99	$-6 \cdot 10^{-3}$	0.93	0.04	0.42	$4 \cdot 10^{-3}$	0.94
Log Triglycerides (mmol·l^{-1})	0.02	0.91	0.11	0.44	0.17	0.28	-0.03	0.86	-0.04	0.77	0.09	0.56
Log hs-CRP (mmol·l^{-1})	0.29	0.21	-0.73	0.002*	-0.29	0.29	0.16	0.43	-0.64	0.004*	-0.43	0.10
Log Systolic BP (mm Hg)	0.01	0.58	-0.02	0.39	0.02	0.60	-0.01	0.59	$2 \cdot 10^{-3}$	0.92	$0.4 \cdot 10^{-3}$	0.97
Diastolic BP (mm Hg)	1.95	0.49	-1.34	0.71	-3.20	0.42	-1.06	0.68	2.55	0.44	-0.2	0.96
Systolic BP z-score	0.07	0.80	-0.10	0.72	0.28	0.39	-0.18	0.46	0.12	0.64	0.14	0.63
Diastolic BP z-score	0.16	0.51	-0.08	0.79	-0.26	0.46	-0.1	0.66	0.25	0.40	-0.01	0.99
Log CIMT (mm)	-0.01	0.84	0.04	0.33	-0.13	0.87	0.02	0.56	$4 \cdot 10^{-3}$	0.92	-0.1	0.13
Log Einc (mmHg.10^{-2})	0.01	0.94	-0.06	0.78	0.58	0.15	0.04	0.75	0.17	0.40	-0.28	0.38 ‡
FMD[-1] (%)	0.03	0.18	-0.03	0.41	-0.06	0.41	0.05	0.049*	0.03	0.40	-0.06	0.34
√ NTGMD (%)	-0.03	0.92	-0.04	0.92	0.56	0.44	-0.11	0.64	-0.21	0.58	1.5	0.011*

Legend TABLE 3.

When indicated, variables were transformed and successfully normalized. Results are shown as coefficient and P-value. Abbreviations: BMI, Body Mass Index, HOMA-IR, Homeostasis Assessment Model of Insulin resistance; VO_2peak, Maximal Cardiorespiratory Fitness; FFM, Fat-Free Mass; TC, Total Cholesterol; LDL-C, Low-density Protein Cholesterol; HDL-C, High-density Protein Cholesterol ; TG, Triglycerides; hs-CRP, high-sensitive C-reactive Protein; BP, Blood pressure; HTN, Hypertension; CIMT, Intima-media thickness of the left common carotid artery; Einc, incremental elastic modulus; FMD, Flow-mediated dilation; NTGMD, Nitroglycerin-mediated dilation.

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.

Treatment effects:

The p values indicate significant effects between experimental groups A (individual delivery) or B (group delivery) versus C (control group): * $p<0.05$;

The treatment effects between experimental groups A and B have been compared and are indicated: ‡ significantly lower than experimental group A ($p<0.05$).

REFERENCES

1. Global status report on noncommunicable diseases. World Health Organization; 2014. Contract No.: ISBN: 978 92 4 156485

2. Llewellyn A, Simmonds M, Owen CG, Woolacott N. Childhood obesity as a predictor of morbidity in adulthood: a systematic review and meta-analysis. Obes Rev. 2016;17(1):56-67.

3. Ells LJ, Rees K, Brown T, Mead E, Al-Khudairy L, Azevedo L, et al. Interventions for treating children and adolescents with overweight and obesity: an overview of Cochrane reviews. Int J Obes (Lond). 2018;42(11):1823-33.

4. Epstein LH, Wing RR, Steranchak L, Dickson B, Michelson J. Comparison of family-based behavior modification and nutrition education for childhood obesity. J Pediatr Psychol. 1980;5(1):25-36.

5. Goldfield GS, Epstein LH, Kilanowski CK, Paluch RA, Kogut-Bossler B. Cost-effectiveness of group and mixed family-based treatment for childhood obesity. Int J Obes Relat Metab Disord. 2001;25(12):1843-9.

6. Whitlock EP, O'Connor EA, Williams SB, Beil TL, Lutz KW. Effectiveness of weight management interventions in children: a targeted systematic review for the USPSTF. Pediatrics. 2010;125(2):e396-418.

7. L'allemand D KE, Bolten M, Zumbrunn A, Martin XE, Sempach R. Evaluation of therapy for overweight children and adolescents in Switzerland: Therapy in multiprofessional group programs - Part 2 of KIDSSTEP - Final report. Swiss Federal Office of Public Health; 2014.

8. Mead E, Brown T, Rees K, Azevedo LB, Whittaker V, Jones D, et al. Diet, physical activity and behavioural interventions for the treatment of overweight or obese children from the age of 6 to 11 years. Cochrane Database Syst Rev. 2017;6:CD012651.

9. WHO Child Growth Standards. Geneva: World Health Organization; 2006.

10. Aggoun Y, Farpour-Lambert NJ, Marchand LM, Golay E, Maggio AB, Beghetti M. Impaired endothelial and smooth muscle functions and arterial stiffness appear before puberty in obese children and are associated with elevated ambulatory blood pressure. Eur Heart J. 2008;29(6):792-9.

11. Farpour-Lambert NJ, Aggoun Y, Marchand LM, Martin XE, Herrmann FR, Beghetti M. Physical activity reduces systemic blood pressure and improves early markers of atherosclerosis in pre-pubertal obese children. J Am Coll Cardiol. 2009;54(25):2396-406.

12. Kuczmarski RJ, Ogden CL, Guo SS, Grummer-Strawn LM, Flegal KM, Mei Z, et al. 2000 CDC Growth Charts for the United States: methods and development. Vital Health Stat 11. 2002(246):1-190.

13. National High Blood Pressure Education Program Working Group on High Blood Pressure in C, Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics. 2004;114(2 Suppl 4th Report):555-76.

14. Wuhl E, Witte K, Soergel M, Mehls O, Schaefer F, German Working Group on Pediatric H. Distribution of 24-h ambulatory blood pressure in children: normalized reference values and role of body dimensions. J Hypertens. 2002;20(10):1995-2007.

15. Le J, Zhang D, Menees S, Chen J, Raghuveer G. "Vascular age" is advanced in children with atherosclerosis-promoting risk factors. Circ Cardiovasc Imaging. 2010;3(1):8-14.

16. Maggio ABR, Farpour-Lambert NJ, Aggoun Y, Galan K, Montecucco F, Mach F, et al. Serum cardiovascular risk biomarkers in pre-pubertal obese children. Eur J Clin Invest. 2018;48(9):e12995.

17. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachme

nt_data/file/771536/KPI_CandF_Weight_management_services.pdf. London: Public Health England; 2018 [

18. Baker JL, Olsen LW, Sorensen TI. Childhood body-mass index and the risk of coronary heart disease in adulthood. N Engl J Med. 2007;357(23):2329-37.

19. Garipagaoglu M, Sahip Y, Darendeliler F, Akdikmen O, Kopuz S, Sut N. Family-based group treatment versus individual treatment in the management of childhood obesity: randomized, prospective clinical trial. Eur J Pediatr. 2009;168(9):1091-9.

20. Saelens BE, Sallis JF, Wilfley DE, Patrick K, Cella JA, Buchta R. Behavioral weight control for overweight adolescents initiated in primary care. Obes Res. 2002;10(1):22-32.

21. Nowicka P, Pietrobelli A, Flodmark CE. Low-intensity family therapy intervention is useful in a clinical setting to treat obese and extremely obese children. Int J Pediatr Obes. 2007;2(4):211-7.

22. Neovius MG, Linne YM, Barkeling BS, Rossner SO. Sensitivity and specificity of classification systems for fatness in adolescents. Am J Clin Nutr. 2004;80(3):597-603.

23. Zhang C, Rexrode KM, van Dam RM, Li TY, Hu FB. Abdominal obesity and the risk of all-cause, cardiovascular, and cancer mortality: sixteen years of follow-up in US women. Circulation. 2008;117(13):1658-67.

24. Van Gaal LF, Mertens IL, De Block CE. Mechanisms linking obesity with cardiovascular disease. Nature. 2006;444(7121):875-80.

25. Emerging Risk Factors C, Kaptoge S, Di Angelantonio E, Lowe G, Pepys MB, Thompson SG, et al. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet. 2010;375(9709):132-40.

26. Mauras N, Delgiorno C, Kollman C, Bird K, Morgan M, Sweeten S, et al. Obesity without established comorbidities of the metabolic syndrome is associated with a

proinflammatory and prothrombotic state, even before the onset of puberty in children. J Clin Endocrinol Metab. 2010;95(3):1060-8.

27. Giannini C, de Giorgis T, Scarinci A, Ciampani M, Marcovecchio ML, Chiarelli F, et al. Obese related effects of inflammatory markers and insulin resistance on increased carotid intima media thickness in pre-pubertal children. Atherosclerosis. 2008;197(1):448-56.

28. Yajnik CS, Katre PA, Joshi SM, Kumaran K, Bhat DS, Lubree HG, et al. Higher glucose, insulin and insulin resistance (HOMA-IR) in childhood predict adverse cardiovascular risk in early adulthood: the Pune Children's Study. Diabetologia. 2015;58(7):1626-36.

29. Roth CL, Kratz M, Ralston MM, Reinehr T. Changes in adipose-derived inflammatory cytokines and chemokines after successful lifestyle intervention in obese children. Metabolism. 2011;60(4):445-52.

30. Bocca G, Corpeleijn E, Stolk RP, Wolffenbuttel BH, Sauer PJ. Effect of obesity intervention programs on adipokines, insulin resistance, lipid profile, and low-grade inflammation in 3- to 5-y-old children. Pediatr Res. 2014;75(2):352-7.

31. Wirix AJ, Kaspers PJ, Nauta J, Chinapaw MJ, Kist-van Holthe JE. Pathophysiology of hypertension in obese children: a systematic review. Obes Rev. 2015;16(10):831-42.

32. Celermajer DS, Sorensen KE, Gooch VM, Spiegelhalter DJ, Miller OI, Sullivan ID, et al. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. Lancet. 1992;340(8828):1111-5.

33. Tounian P, Aggoun Y, Dubern B, Varille V, Guy-Grand B, Sidi D, et al. Presence of increased stiffness of the common carotid artery and endothelial dysfunction in severely obese children: a prospective study. Lancet. 2001;358(9291):1400-4.

34. Inaba Y, Chen JA, Bergmann SR. Prediction of future cardiovascular outcomes by flow-mediated vasodilatation of brachial artery: a meta-analysis. Int J Cardiovasc Imaging. 2010;26(6):631-40.

35. Woo KS, Chook P, Yu CW, Sung RY, Qiao M, Leung SS, et al. Effects of diet and exercise on obesity-related vascular dysfunction in children. Circulation. 2004;109(16):1981-6.

36. Iantorno M, Campia U, Di Daniele N, Nistico S, Forleo GB, Cardillo C, et al. Obesity, inflammation and endothelial dysfunction. J Biol Regul Homeost Agents. 2014;28(2):169-76.

37. Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2010;56(25):e50-103.

38. Gately PJ, Cooke CB, Barth JH, Bewick BM, Radley D, Hill AJ. Children's residential weight-loss programs can work: a prospective cohort study of short-term outcomes for overweight and obese children. Pediatrics. 2005;116(1):73-7.

39. Wake M, Baur LA, Gerner B, Gibbons K, Gold L, Gunn J, et al. Outcomes and costs of primary care surveillance and intervention for overweight or obese children: the LEAP 2 randomised controlled trial. BMJ. 2009;339:b3308.

40. Farpour-Lambert NJ, Baker JL, Hassapidou M, Holm JC, Nowicka P, O'Malley G, et al. Childhood Obesity Is a Chronic Disease Demanding Specific Health Care--a Position Statement from the Childhood Obesity Task Force (COTF) of the European Association for the Study of Obesity (EASO). Obes Facts. 2015;8(5):342-9.

Figure 1. Flowchart for Enrolment, Randomization, Intervention and Follow-Up of Study Participants

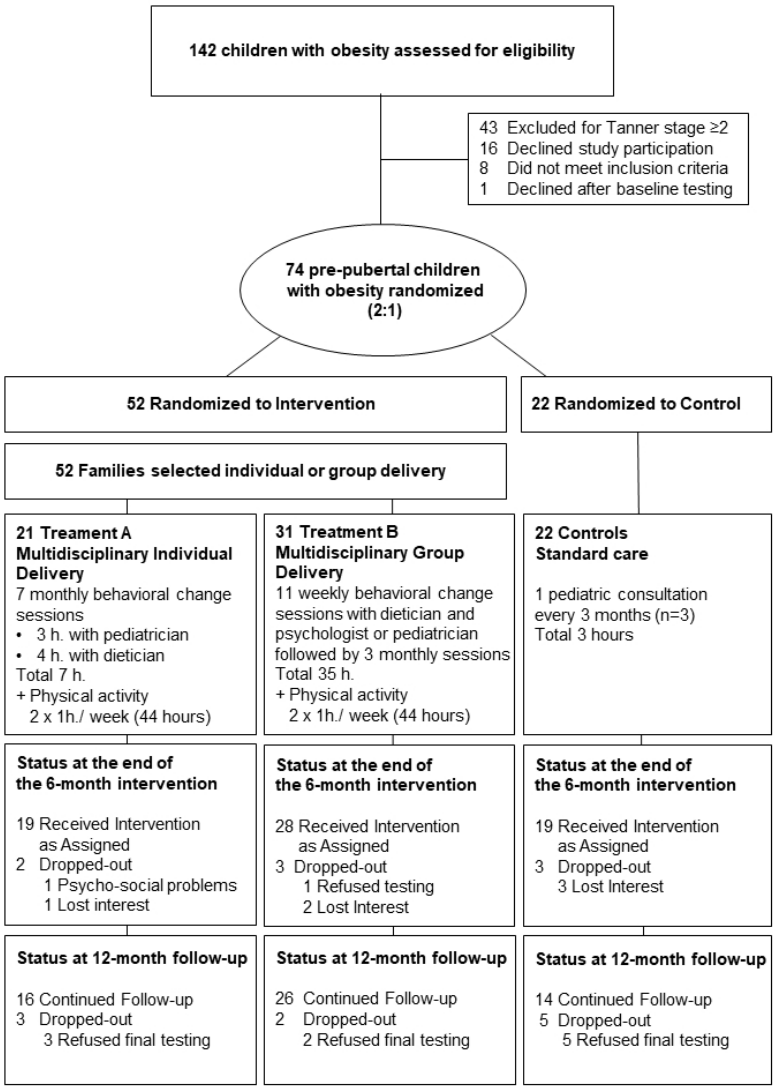

Figure 1. Flowchart for enrolment, randomization, intervention and follow-up of study participants

190x275mm (96 x 96 DPI)

Manuscript: Effectiveness of individual versus group programs to treat obesity and reduce cardiovascular disease risk factors in pre-pubertal children: A randomized Controlled trial

Farpour-Lambert NJ et al.

Transfer from Pediatric Obesity to Clinical Obesity (IJPO-2018-0317)

Response to reviewers

We would like to thank both reviewers for their helpful comments. Please find below our answers and proposed changes (highlighted in yellow in the revised manuscript).

Reviewer 1:

1. **The authors need to include upfront the rationale for choice for the two interventions. No scientific reason is presented.**

   The current state of knowledge is already presented. We have added an additional evidence review in the references.

2. **What is the criteria used to classify the intervention as medium-intensity or high-intensity? A reference (or rationale) is needed.**

   The description and one reference has been added in the introduction.

3. **The experimental groups are different in the "intensity" and mode "individual vs group", so it is not clear if the differences are related to intensity or mode.**

   It is not possible to answer this question with the current study design. This is why we have already indicated "Further research is now needed to determine the optimum intensity and composition of interventions in this age group …" in the conclusion.

4. **Please provide more information related to sample selection.**

   The sample selection is already described in details in the "METHODS" (Study design, setting and participants, and "Randomization and concealment"), and figure 1 and the trial registry.

5. **Please provide more information related to Tanner Stage assessments.**

   We have added some clinical information in the exclusion criteria.

6. **Please clarify if the children signed the assent form. It's not clear in the manuscript.**

   This information is already provided in the last paragraph of the "Study design, setting and participants"

7. **The characteristics of the interventions are essential to the readers, it should be presented in the main document and not as a supplement. The description of the intervention are not easy to flow. There are a wide range of activities performed by the individuals. In my opinion the study lacks details on how the he activities are controlled; what was the plan for the RCT. Give details.**

   The full description of the interventions has been imported in the main document and the supplement has been deleted. The report of this trial conforms to CONSORT 2010

guidelines and the Template for intervention description and replication (TIDieR) checklist.

8. **Reference 7 is not accurate as it does not establish the cut-off for childhood obesity, it is an Editorial.**

   Thank you for your comment. Reference 7 has been corrected.

9. **Sample size was based on z-BMI changes. Is the sample size large enough for the CVD outcomes?** The sample size was based on BMI z-score (see "Sample size and statistical analysis"). We have also added a sentence in the "Strength and limitations to acknowledge this potential limitation".

10. **It seems that this trial has been published before, if yes, the authors should declare what is the differences between the data previous published and the current one.**

    Serum cardiovascular risk biomarkers (serum level of cytokine [CCL2], adiponectin, and neutrophil product [MMP-8]) were measured in a sub-sample of 48 children and results are published elsewhere. (Maggio AB et al. Eur J Clin Invest. 2018 Sep;48). This publication was not accepted at the time of submission to Pediatric Obesity.

11. **How some variables has been transformed and normalized?**

    The transformation and normalization procedures are indicated in the "Sample size and statistical analysis" section and in table 3.

12. **Why individuals who did not meet the inclusion criteria were included in the sample?**

    They were included by mistake and we decided not to exclude them post-randomization. We have modified the sentence in the "Sample size and statistical analysis" section to improve clarity.

13. **Why the authors chose for conducting the comparisons between groups separated (A x C; B X C; A x B)? For me, it is more appropriate to perform all comparisons in the same model (AXBXC).** Because the 3 groups were not randomized separately (see "Study design"), so group A and B were compared to group C (standard care).

14. **Only 10% of the participants adhered to the intervention in group B (Line 159)? is that correct? How was ITT performed in this case? Did the authors impute any data? It is a very low adherence ratio, I am very confused and have major concerns for using this group in the analysis.**

    We initially defined the adherence "as the proportion of subjects who completed all behavioral sessions" which is unrealistic in children due to common infectious diseases. We have modified the definition as followed: "the proportion of subjects who completed 75% of behavioral sessions". This definition aligns with that defined by public health England (2018): https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/771536/KPI_CandF_Weight_management_services.pdf.

The adherence is now 95%% in group A (individually delivered intervention by appointment) and 45% in group B (group intervention on fixed days during 11 weeks).

15. **The results are hard to flow, the tables are difficult to understand. The results section should be rewritten in a more clear way.**

    The RESULTS section has been improved for clarity.

16. **My main concern about the discussion and data interpretation is regarding the adherence to intervention B. Despite the differences for some outcomes between groups, the adherence should be considered for the conclusions. The other issue to be considered in the interpretation is the wide range of activities that are not controlled in both groups.**

    See point 14.

Reviewer: 2

1. **The article title is misleading. The title states that the study is a RCT, which is true. But the title implies that the randomization is between individual vs. group lifestyle programs, which is not true.**

   The title has been modified as followed: “Effectiveness of individual and group programs to treat obesity and reduce cardiovascular disease risk factors in pre-pubertal children”

2. **The last sentence of the Introduction states, "The aim of this study was to compare the effectiveness of a medium-intensity individually delivered intervention with a high-intensity group delivered intervention..." This is not an accurate statement, as the study was not designed to test this hypothesis. The study was designed to test the effectiveness of a 6 month lifestyle intervention (with choice of either individual vs. group therapy) vs. a control group. No randomization occurred to determine whether the participant would be placed in the individual intervention arm vs. the group intervention arm, this decision was made purely on the participants choice.**

   The last sentence of the “INTRODUCTION” has been corrected as requested.

3. **Please provide more description in the Methods section on the nutrition component of the intervention. The current statement is: "The nutrition education component used a healthy eating approach." "Healthy eating" can mean a lot of different things to a lot of different people.**

   The full description of the interventions, including the nutrition component, has been imported into the main document and the supplement has been deleted.

4. **The sentence on Page 10 in the Statistical Analysis section that starts, "Within-group differences..." needs to be rephrased for clarity.**

   The sentence has been corrected.

5. **It is troublesome to presents the results as Treatment A vs Control and Treatment B vs Control. The results should be presented at Intervention vs. Control. When participants choose Treatment A vs B, potential bias is**

introduced. Were those who chose Treatment B more motivated than those who chose Treatment A? And if so, is this increased motivation the explanation for the difference in findings? The control group was not divided into any such treatment groups, therefore it is unfair to compare one sub-group within the Intervention to the Control group as if they were both randomized from the same sample. This should be described as a hypothesis generating sub-analysis.

As the components and intensities of the interventions A and B are very different, it is not useful to combine the 2 groups for the analysis. We admit however that there a selection bias as participants could choose between the two interventions (see limitations"). We have indicated "non-randomized" in the section "Comparison between treatment A and B", and acknowledged this as a limitation within the discussion.

6. **The first paragraph of the Discussion section states: "However, treatment B was more successful than treatment A for reducing BMI, BMI z-score and 218 abdominal fat at 6 months." This conclusion cannot be stated this strongly. As stated above, the study was not designed to test treatment A vs treatment B, as there was not randomization between these two groups. These two participants groups came from two different populations, therefore any number of explanations (motivation level comes quickly to mind) could be present to explain the differences in outcomes between these two nonrandomized groups.**

   The corrections have been made through the manuscript (abstract, results, discussion, conclusion).

7. **As above, please temper all instances of language that implies causality (e.g. Treatment x was more successful than Treatment y) in differences between treatment arms that were not randomized, as is currently found in the Abstract conclusion, Results, and Discussion.**

   The corrections have been made through the manuscript (abstract, results, discussion, conclusion).

8. **Line 305-307 in the Discussion section: I would not conclude that the difference in compliance rates between A and B means that there was not a difference in motivation. The higher compliance rate in A may have simply been due to less amount of hours required.**

   The corrections have been made in the "Strength and limitation" section.

9. **In the Limitation section of the Discussion, please explore potential bias that may be introduced by not randomizing between Treatment A and Treatment B. Conversely, I encourage you to also explore the presence of two treatment options as a strength in terms of facilitating the implementation of this research into clinical practice.**

   The corrections have been made in the "Strength and limitation" section.