



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

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Keywords:	Obesity, Children, Treatment, Lifestyle, Cardiovascular disease
Abstract:	<p>Introduction: Childhood obesity results in premature atherosclerosis and requires early intervention.</p> <p>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.</p> <p>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).</p> <p>Results: Compared to controls, at 6 months, abdominal fat and hs-CRP were reduced in both interventions. The group intervention was also</p>

	<p>effective in reducing BMI (-0.55 kg/m<sup>2</sup>; 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.</p> <p>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.</p>

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## **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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**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<sup>2</sup>; 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 <sub>2</sub> peak	Maximal Cardiorespiratory Fitness
WHO	World Health Organization

## 1 INTRODUCTION

2 Non-communicable diseases (NCDs) have overtaken infectious diseases as the world's major  
3 global disease burden. Among NCDs, cardiovascular diseases (CVDs) account for nearly half  
4 the total burden and are the leading cause of death globally.(1) Childhood obesity lays the  
5 foundation for CVDs and has a strong tendency to track into adulthood if left untreated.(2)  
6 Childhood therefore presents a unique opportunity for intervention to prevent lifelong  
7 exposure and premature morbidity, and control associated health costs.  
8 Multidisciplinary programs are considered the gold standard treatment for children with  
9 obesity.(3) Family-based behavioral interventions were initially developed to modify the  
10 shared family environment, provide role models and support child behavior changes.(4)  
11 Treatment in groups without individual attention has been shown to be both effective and  
12 cost-effective.(5) **Medium (26 to 75 hours contact time) to high-intensity (>75 hours contact**  
13 **time) interventions are more effective than lower ones (<25 hours) with a small to moderate**  
14 **improvements in weight status.(6)**  
15 In 2007 we developed, in cooperation with the Swiss Federal Office of Public Health, a large-  
16 scale national program for the management of childhood obesity using a standardized  
17 intensive group treatment covered by health insurances. However, the national evaluation  
18 study showed that only 0.8% of patients could be included in a group program due to  
19 travelling time, parents' work and intensity of intervention.(7) This type of treatment is also  
20 quite resource intensive, with multiple health care workers required to meet different age  
21 groups of children and their parents. A recent Cochrane review of lifestyle interventions for  
22 the treatment of obesity in children aged 6 to 11 years concluded that there is insufficient  
23 evidence to determine the most effective and sustainable type or setting of intervention.(8)



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

## 27 MATERIALS AND METHODS

### 28 Study design, setting and participants

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

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

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

### 44 Randomization and concealment

45 Enrolment, randomization, interventions and follow-up of study participants are summarized  
46 in Figure 1; 74 subjects were randomly assigned (2:1) to a 6-month lifestyle intervention

47 (n=52) or a control group (C, n=22, standard care) arm. Sealed opaque envelopes containing  
48 2/3 of intervention and 1/3 of control were used.

49 **In order to facilitate the implementation of this research into clinical practice,** children and  
50 parents who were selected in the intervention arm could choose to participate in a moderate-  
51 intensity individually delivered intervention (treatment A, n=21) or a high-intensity group  
52 delivered intervention (treatment B, n=31), according to their will and availability. During the  
53 6-month follow-up period, groups A and B were invited to attend two pediatric consultations  
54 (45 min.) at nine and twelve months.

### 55 **Interventions**

56 **During the pilot phase of the study, an adapted mastery approach “Contrepoids©” was**  
57 **developed and evaluated with 10 volunteer families. The manual contained modules on**  
58 **healthy nutrition, physical activity, family habits, parenting and coping with psychosocial**  
59 **problems commonly experienced by children with obesity, such as teasing and body image**  
60 **concerns. The nutrition education component used a healthy eating approach encouraging low**  
61 **saturated fat and nutrient-dense food (vegetables, fruits, whole grain foods) and portion size**  
62 **moderation. Modules included food choices, balanced meals, carbonated and non-carbonated**  
63 **sugar-sweetened beverages, food promotion and labelling, healthy cooking recipes,**  
64 **recognition of hunger and satiety, eating disorders, management of high-risk situations and**  
65 **prevention of relapses. The physical activity component focused on encouraging active**  
66 **transport (walking, biking), use of stairs, leisure-time activities and sport, and reduction of**  
67 **sedentary behaviors (television, computer, electronic games). Self-awareness, problem-**  
68 **solving, goal setting, stimulus control, coping skills training, empowerment, parental guidance**  
69 **and relapse prevention behavior change techniques were used. At the end of each session,**  
70 **individual goals were set and participants received homework to complete before the next**  
71 **one. Therapists communicated at least weekly with the physical education teachers to**

72 reinforce behavioral changes. The moderate-intensity individually delivered intervention  
73 (treatment A) comprised 7 monthly 60-minute sessions with the child and his/her parent/s (at  
74 least the mother), which were conducted by a trained pediatrician (at 0, 3, 6 months) and a  
75 dietician (at 1, 2, 4, and 5 months). Parents could choose a convenient appointment time  
76 which could be changed if unexpected events arose. Similar mastery approach and education  
77 manuals “Contrepoids©” were used in both treatment arms, but topics were chosen according  
78 to family needs in individual care.

79 The high-intensity group delivered intervention (treatment B) comprised 14 sessions (11  
80 weekly then 3 monthly meetings, total 35 h.) over a 6-month period. Ideally both parents, but  
81 at least the mother, were asked to participate. Parental and child sessions were held separately.  
82 The parental group sessions consisted of 90 minutes with a dietician (at all sessions), a  
83 psychologist trained in cognitive behavioral therapy (at least 4 sessions) or a pediatrician  
84 experienced in therapeutic patient education. The child sessions consisted of 60 minutes with  
85 the same therapists. Each group included 10-12 children and their parents.

86 Controls (group C) received standard care for twelve months, which included four 45-minute  
87 pediatric consultations (every three months) and instruction to maintain their current level of  
88 physical activity.

89 Treatment groups A and B could participate in a 6-month after school moderate-to-vigorous  
90 physical activity training program including two sessions of 60 minutes per week (total 44  
91 hours between Sep.-Oct. and Mar.-April), in addition to school physical education (135  
92 minutes/week). Children who were already enrolled in a sports club (at least 60 min./week six  
93 months/year) attended only one physical activity session per week at the Children’s Hospital.  
94 One session per week was organized at the gym hall and the other one at the swimming pool,  
95 under close supervision of two physical education teachers. Training sessions included 40  
96 minutes of aerobic exercise, 10 minutes of resistance training of the legs, arms and trunk, and

97 10 min of stretching. The intensity was progressively increased during the 6-month period, to  
98 reach intermittent vigorous intensities. During each session, physical education teachers  
99 discussed theoretical aspects of exercise such as discomfort, sweating and fatigue in relation  
100 to intensity, progress, self-esteem, benefits on health and well-being, leisure-time physical  
101 activity and active transport. Children and parents received a pedometer to assess and increase  
102 progressively their number of steps per day. The final goal was to do 10'000 steps per day for  
103 adults and 12'000 to 13'000 steps for children.

#### 104 **Adverse Events**

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

#### 106 **Procedures**

107 All measurement techniques have been described in detail, in our previous publications.(10,  
108 11) All subjects underwent an identical testing protocol starting at 8 am at the Pediatric  
109 Research Platform, and a second visit was generally needed due to the long duration of testing  
110 (5 h.). The protocol was repeated at 6 and 12 months. The personnel of the Pediatric Research  
111 Platform and of the Pediatric Cardiology Unit were blind to group allocation, whereas  
112 subjects and intervention delivery staff could not be blinded.

#### 113 **Primary outcome measures**

114 Body weight (Seca™ 701, Germany) and standing height were measured; BMI (weight/height  
115 squared, kg·m<sup>-2</sup>) and BMI z-score (primary outcome) were calculated using the United States  
116 Centre for Disease Control (BMI<sub>CDC</sub>),(12) and the WHO (BMI<sub>WHO</sub>) references.(9)

#### 117 **Secondary outcome measures**

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

121 VS3®, Philips Medical System, Andover, USA), the average BP was calculated and  
122 hypertension was defined as BP >95<sup>th</sup> gender-, age-, and height-specific percentiles.(13)  
123 The 24-hour ambulatory BP was assessed every 30 minutes at the non-dominant arm (Dyasis  
124 Integra II™, Physicor S.A., France). The 24-hour mean BP and z-scores were calculated, and  
125 hypertension was defined as 24-hour BP >95<sup>th</sup> age- and gender-specific percentile.(14)  
126 The common carotid intima media thickness (CIMT) was measured using a real time B-mode  
127 ultrasound imager (Vingmed™ CFM800C system Ltd, Norway and Iôtéc System™, Iôdata  
128 Processing™, France).(10) Advanced vascular age was defined as CIMT > 25<sup>th</sup> percentile  
129 using 45 years old references.(15)  
130 The pulse wave of the radial artery was assessed using an applanation tonometry probe  
131 (SphygmoCor™; Atcor Medical Ltd., Australia) to estimate central aortic pressure non-  
132 invasively and determine arterial stiffness using the incremental elastic modulus (Einc).  
133 After 30 minutes of rest in a recumbent position, the flow-mediated dilation (FMD) and  
134 nitroglycerin-mediated dilation (NTGMD) of the brachial artery were measured.  
135 Cardiorespiratory fitness was assessed as the maximal oxygen consumption (VO<sub>2</sub> peak) by  
136 direct gas analysis (Vmax Spectra™, Vyasis Healthcare, GE, USA) during a multi-stage  
137 treadmill test (Marquette 2000™, GE, USA).  
138 Physical activity level was assessed using a uniaxial accelerometer (Actigraph™ GMT1, MTI,  
139 Florida, USA), worn on the right waist during a 7-day period (30-second cycle, school week,  
140 24 h./day), except during bathing or swimming. Data was expressed as mean activity counts  
141 per minute between 8 am and 9 pm, if the monitor was worn during ≥4 days including one  
142 week-end day. Zero activity periods of 20 minutes or longer were interpreted as being due to  
143 unworn accelerometers and were removed from the total count.  
144 Blood samples were collected at 8 am via venipuncture following a 10-hour overnight fast.  
145 Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG)

146 levels [ $\text{mmol}\cdot\text{l}^{-1}$ ] concentrations were determined by standard automotive techniques. Low-  
147 density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald's formula.  
148 Plasma insulin concentrations were measured by radioimmunoassay and insulin resistance  
149 was assessed by using the homeostasis model assessment (HOMA-IR), according to the  
150 equation:  $\text{HOMA-IR} = \text{fasting insulin } [\mu\text{U}\cdot\text{ml}^{-1}] \times \text{fasting glucose } [\text{mmol}\cdot\text{l}^{-1}] / 22 \cdot 5$ . High-  
151 sensitive C-reactive protein (hs-CRP) level was measured by nephelometry. Results were  
152 considered as abnormal according to the Integrated Guidelines for Cardiovascular Health and  
153 Risk Reduction in Children and Adolescents of the US National Heart, Lung, and Blood  
154 Institute (2012) and International Diabetes Foundation guidelines. Serum cardiovascular risk  
155 biomarkers (serum level of cytokine [CCL2], adiponectin, and neutrophil product [MMP-8])  
156 were also measured in a sub-sample of 48 children and results are published elsewhere. (16)

### 157 **Sample size and statistical analysis**

158 The sample size calculation was based on our previous RCT in the same age group.(11) For  
159 an anticipated effect size of 0.1 for BMI z-score (SD 0.1), a sample size of 16 subjects in  
160 each group was required to detect a statistically significant differences at  $p < 0.05$  with a  
161 statistical power of 80% ( $\beta = 0.80$ ).

162 An intention-to-treat analysis (ITT,  $n=74$ ) was performed. Data were screened for normality  
163 using Francia-Shapiro tests and, when necessary, variables were transformed and  
164 successfully normalized ( $x^2$ ,  $x^3$ ,  $\log x$ ,  $1/x^2$ ,  $\sqrt{x}$ ,  $1/\sqrt{x}$ ; see table 3). Baseline data were  
165 expressed as median and interquartile range (IQR 25-75), or means and standard deviation  
166 (SD) when indicated. Means of each continuous variable were compared by one-way  
167 analysis of variance (ANOVA) with Bonferoni post-hoc tests. The shapes of distributions  
168 were compared using Kruskal-Wallis tests. Nonparametric comparisons were made by chi-  
169 square tests. Within-group (A, B or C) differences were assessed using paired t-tests, then  
170 mixed linear regressions, which take into account the repeated measure design, were used to

171 evaluate outcome changes over time (0, 6 and 12 months) according to the effects of  
172 intervention while adjusting for age and gender. After starting the intervention, we noticed  
173 **an error in the recruitment of** two subjects in Group A, **in that they** did not meet the inclusion  
174 criteria (one girl was only overweight and one boy had a psychiatric disorder and cognitive  
175 retardation which limited his participation in a lifestyle program). They have been included  
176 in the ITT analysis and outcomes did not change after removing them from the analysis. The  
177 statistical software program Stata release 14 (College Station, Tx) was used and differences  
178 were considered significant when the p-value was  $<0.05$ .

### 179 **Costs calculation**

180 **During the 6-month trial, treatment A comprised three medical (600 CHF/630 USD), four**  
181 **dietetic (296.40 CHF/311 USD) and two medical follow-up consultations (330 CHF/347**  
182 **USD) plus 44 sessions of physical activity at the hospital or in a sports club (60 min. + 30**  
183 **min. of preparation per session for six participants per teacher, 660 CHF/693 USD). One hour**  
184 **per child was added for medical coordination (196.10 CHF/206 USD). The direct costs for**  
185 **treatment A were 1786.10 CHF (1876 USD) for 6 months and 2082.50 CHF (2187 USD) for**  
186 **12 months. In treatment B, the fixed rate for behavioural and physical activity sessions, was**  
187 **4200 CHF (4411 USD). In addition, patients had three paediatric consultations at 0, 3, 6**  
188 **months (444.60 CHF/467 USD) and two follow-up consultations (296.40 CHF/311 USD).**  
189 **The direct costs for treatment B were 4644.60 CHF (4877 USD) for 6 months and 4941 CHF**  
190 **(5189 USD) for 12 months. The control group received standard care including one paediatric**  
191 **consultation every three months, so the costs were 444.60 CHF (467 USD) at 6 months and**  
192 **741 CHF (778 USD) at 12 months.**

### 193 **Role of funding sources**

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

## 196 **RESULTS**

### 197 **Comparison of groups at baseline**

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

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

205 Sixty two percent of mothers were overweight (58, 71, 52% in A, B and C, respectively) and  
206 28% of them had obesity (37, 29, 19% in A, B and C, respectively); 19% of children had both  
207 parents with obesity, and 23% had a family history of type 2 diabetes.

### 208 **Effects of treatment A and B**

209 Sixty-six out of 74 children (89%) received the 6-month intervention as assigned. The  
210 retention rate was 90, 90 and 86 % of subjects in group A, B and C, respectively, and the  
211 compliance, which was determined as the proportion of attended behavioral and physical  
212 activity sessions during the 6-month intervention, was 87 and 50% in group A, and 64 and  
213 45% in group B, respectively (excluding children that attended sports club). The adherence,  
214 which was the proportion of subjects who completed 75% of behavioral sessions, was 95% in  
215 group A and 45% in group B.(17)

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



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

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

### 230 *Treatment A versus Controls*

231 Significant treatment effects at 6 months for abdominal fat (table 2 and 3) and hs-CRP (not  
232 shown in table 2, mean difference  $-2.6 \text{ mmol}\cdot\text{l}^{-1}$ , 95% CI -5.5 to 0.2,  $p=0.002$ ) were found,  
233 whereas physical activity level was not improved (mean difference  $-300.7 \text{ cpm}$ , 95% CI -  
234  $568.0$  to  $-33.5$ ,  $p=0.02$ ) in treatment A (individual treatment) versus controls. At 12 months,  
235 there was no significant change for any parameter.

236 **At 6 months, we also observed significant within-group reductions (paired t-tests,** not shown  
237 in tables) in BMI<sub>CDC</sub> z-score (mean difference  $-0.06$ , 95% CI  $-0.11$  to  $0.00$ ,  $p=0.02$ ), fasting  
238 glucose ( $-0.1 \text{ mmol}\cdot\text{l}^{-1}$ ,  $-0.3$  to  $0.0$ ,  $p=0.049$ ), insulin ( $-1.7 \text{ mU}\cdot\text{l}^{-1}$ ,  $-3.5$  to  $0.2$ ,  $p=0.04$ ),  
239 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  
240 increases in body weight ( $3.8 \text{ kg}$ ,  $2.7$  to  $4.8$ ,  $p<0.0001$ ), BMI ( $0.6 \text{ kg}\cdot\text{m}^{-2}$ ,  $0.1$  to  $1.0$ ,  $p=0.001$ ),  
241 waist circumference ( $1.8 \text{ cm}$ ,  $0.6$  to  $3.1$ ,  $p=0.004$ ), FFM ( $1.9 \text{ kg}$ ,  $1.5$  to  $2.2$ ,  $p<0.0001$ ), VO<sub>2</sub>  
242 peak ( $180.8 \text{ l}\cdot\text{min}^{-1}$ ,  $12.3$  to  $349.3$ ,  $p=0.02$ ) and FMD ( $1.3 \%$ ,  $-0.3$  to  $2.9$ ,  $p=0.05$ ).

### 243 *Treatment B versus Controls*

244 Significant treatment effects were found at 6 months for BMI, BMI<sub>CDC</sub> z-score, abdominal fat  
245 (table 3) and hs-CRP level (not shown; mean difference  $-1.3 \text{ mmol}\cdot\text{l}^{-1}$ , 95% CI  $-4.0$  to  $1.5$ ,

246  $p=0.004$ ), in treatment B (group treatment) versus controls. At 12 months, further  
247 improvement in BMI, BMI<sub>CDC</sub> z-score, total and abdominal fat, as well as NTGMD (15.0%, -  
248 0.76 to 30.7,  $p=0.01$ ) were found.

249 **At 6 months, we also observed significant within-group reductions (paired t-tests,** not shown  
250 in tables) in BMI<sub>CDC</sub> z-score (mean difference -0.08, 95% CI -0.13 to -0.02,  $p=0.006$ ),  
251 BMI<sub>WHO</sub> z-score (-0.15, -0.24 to -0.05,  $p=0.001$ ) and LDL-cholesterol level (-0.2 mmol·l<sup>-1</sup>, -  
252 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  
253 1.8,  $p<0.0001$ ), VO<sub>2</sub> peak (205.8 l·min<sup>-1</sup>, 81.7 to 329.8,  $p=0.002$ ) and Einc (546.5 mmHg·10<sup>2</sup>,  
254 25.0 to 1068.0,  $p=0.02$ ) increased .

### 255 ***Comparison between treatment A and B (non-randomized)***

256 **At 6 months, no significant difference was shown between groups A and B (table 2 and 3). At**  
257 **12 months, changes** were significantly greater for body weight, BMI, BMI<sub>CDC</sub> and BMI<sub>WHO</sub> z-  
258 scores, waist circumference, physical activity (result not shown; mean difference 131.1 cpm,  
259 95% CI -232.6 to 494.7,  $p=0.03$ ) and Einc (-335.3 mmHg·10<sup>2</sup>, -1144.4 to 473.9,  $p=0.02$ ) in  
260 treatment B versus A.

### 261 **Costs calculation**

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

### 266 **DISCUSSION**

267 The evidence to determine the most effective and sustainable type or setting of intervention is  
268 lacking for pre-pubertal children. Our study showed that both medium-intensity individually  
269 delivered intervention (treatment A) and high-intensity group intervention (treatment B)

270 resulted in significant reductions at 6 months in abdominal fat and low grade inflammation  
271 (hs-CRP) in pre-pubertal children with obesity, compared to standard care. Treatment B was  
272 also effective for reducing BMI and BMI z-score at 6 and 12 months, when compared to  
273 controls, as well as waist circumference, total and abdominal fat, and vascular reactivity  
274 mediated by smooth muscle cells (NTGMD) at 12 months. Carotid arterial stiffness was also  
275 reduced at 12 months in treatment B compared to A.

### 276 **Effects on BMI**

277 A decrease in BMI z-score during growth is of particular importance because it is inversely  
278 associated with the risk of coronary heart disease in adulthood.(18) In a recent systematic  
279 review including 70 studies in 6 to 11 years old children, a mean BMI z-score change of -0.06  
280 (95%CI: -0.10 to -0.02) was reported after intervention, the majority of studies using CDC  
281 references (only one using WHO references).(9) However, only half of studies included a  
282 post-intervention follow up (range 1 to 30 months). The effect observed in treatment B was of  
283 similar magnitude (BMI<sub>CDC</sub> z-score -0.08) compared to controls, and further changes were  
284 observed at 12 months (-0.10).

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

### 289 **Effects on body composition and cardiometabolic health**

290 Body mass index is not a direct measure of body composition, thus changes in fat mass may  
291 be confounded with changes in fat-free mass.(22) The significant decreases in abdominal fat  
292 and hs-CRP observed in treatment A and B have important implications for the  
293 cardiometabolic health of this at risk population.(23) Within-group changes at 6 months in  
294 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

320 association with increased arterial stiffness and systemic hypertension,(10) whereas signs of  
321 arterial wall remodeling are detectable later during adolescence.(33) In our study, a within-  
322 group A increase of FMD (+1.3 %) was observed, suggesting improved endothelial cell  
323 function. As a meta-analysis of 5547 adults associated a 1% increase in FMD with a 13%  
324 decrease in cardiovascular events,(34) an improvement in FMD of 1.3% in this at-risk  
325 pediatric population would be expected to ameliorate their cardiovascular risk profile.  
326 However, the treatment effect was not significant compared to controls, probably due to the  
327 procurement of standard care in controls, a small sample size and missing longitudinal data.  
328 In children aged 9 to 12 years (pre-pubertal and pubertal), a significant increase in FMD  
329 (+1.2% at 6 weeks, +1.7% at 12 months) was previously reported after a high-intensity  
330 exercise training program was combined with a group lifestyle intervention comprising of a  
331 balanced hypocaloric diet.(35) Diet and exercise together, and maintenance of exercise at 12  
332 months, were associated with a significantly greater improvements in endothelial function.  
333 We also observed improvement of vascular reactivity mediated by smooth muscle cells  
334 (NTGMD) at 12 months in treatment B versus controls. In adults with metabolic syndrome, a  
335 reduction of the inflammatory state improves both endothelium-dependent and endothelium-  
336 independent vasodilator reactivity.(36)

337 Arterial stiffness is a consequence of arteriosclerosis, the process of arterial wall thickening,  
338 and loss of elasticity that occurs with the onset of vascular disease. In this study, vascular age  
339 was advanced in a large proportion of children and a reduction of Einc was found at 12  
340 months in group B, compared to group A (non-randomized). We showed previously that  
341 moderate-to-vigorous exercise at least twice a week during 6 months resulted in reduced  
342 arterial stiffness and stabilization of CIMT.(11) Adult studies have shown that arterial  
343 stiffness may predict CVD and mortality.(37) We may therefore hypothesize that high-

344 intensity group intervention may have a long-term clinical impact on cardiovascular health,  
345 however results remain to be verified in a RCT.

### 346 **Costs**

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

### 354 **Strength and limitations**

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

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

## 380 **Conclusions**

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

386 Both 6-month lifestyle interventions resulted in significant reductions in abdominal fat and  
387 low grade inflammation (hs-CRP) in pre-pubertal children with obesity, compared to standard  
388 care. To our knowledge, this is the first study showing such changes after an individually  
389 delivered intervention in this population. We also showed that the high-intensity group  
390 intervention was effective in reducing BMI and BMI z-score, as well as vascular reactivity  
391 mediated by smooth muscle cells and carotid arterial stiffness. These findings are important  
392 given the global increases in childhood obesity and in the promotion of cardio-metabolic  
393 health and prevention of NCDs later in life. Individually delivered intervention is less costly

394 than group intervention, facilitating its dissemination at large scale as it could be easily  
395 transferred to a primary care setting, in collaboration with sports clubs and physical education  
396 teachers.

397 However, to improve the management of obesity in children, both in individual and group  
398 setting, healthcare systems need to be adapted; the nutritional, psychological and physical  
399 therapy should be covered by health insurance, and health care workers should be trained to  
400 treat obesity similarly to other chronic diseases of childhood.(40) Primary care providers  
401 could then play a major role in the early treatment of childhood obesity and prevent the  
402 burden of CVD later in life. Further research is now needed to determine the optimum  
403 intensity and composition of interventions in this age group, and long-term efficacy at 5 or 10  
404 years. Treatment effects using different BMI z-score references should also be evaluated.

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406 NFL conceptualized the study design and wrote the research protocol, recruited the subjects,  
407 supervised the implementation and completion of the study, and drafted the initial manuscript.  
408 XM designed and supervised the physical activity intervention and testing, and managed the  
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410 participated to the psychological/ behavioral components of interventions. LJE contributed to  
411 the interpretation and presentation of results. FRH performed the statistical analysis. YA  
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421 **CONFLICT OF INTEREST**

422 There is no conflict of interest for any authors.

For Review Only

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

Variables	Group A Individual delivery			Group B Group delivery			Group C Control			P-value
	N	Mean/ Median	SD/ IQR	N	Mean/ Median	SD/ IQR	N	Mean/ Median	SD/ IQR	
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
<b>Physical Characteristics</b>										
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 <sup>2</sup> )	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 <sub>2peak</sub> (l.min <sup>-1</sup> ) #	21	1.8	0.4	29	1.7	0.6	19	1.7	0.9	0.97
VO <sub>2peak</sub> /FFM (ml.kg <sup>-1</sup> .min <sup>-1</sup> )	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
<b>Blood metabolism</b>										
Fasting glucose (mmol.l <sup>-1</sup> )	21	4.7	0.4	31	4.7	0.6	21	4.6	0.5	0.62
Fasting insulin (mU.l <sup>-1</sup> , % 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.l <sup>-1</sup> , % high)#	21	4.5 (24)	0.9	31	4.3 (19)	1.1	21	4.4 (19)	0.8	0.97
LDL-C (mmol.l <sup>-1</sup> , % high)	21	2.9 (29)	1.2	31	2.7 (19)	0.7	21	2.9 (14)	1.0	0.96
HDL-C (mmol.l <sup>-1</sup> , % low)	21	1.2 (29)	0.3	31	1.2 (32)	0.5	21	1.2 (19)	0.4	0.92
TG (mmol.l <sup>-1</sup> , % high)	21	0.7 (29)	0.7	31	0.8 (16)	0.7	21	0.7 (5)	0.3	0.67
hs-CRP (mmol.l <sup>-1</sup> )	18	3.6	3.0	26	2.9	2.7	18	2.3	2.8	0.09
<b>Arterial Function</b>										
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 <sup>2</sup> )	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; VO<sub>2</sub>peak, 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		Group B		Group A		Group B	
	Individual delivery		Group delivery		Individual delivery		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**

Variables	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	
	$\beta$	P-value	$\beta$	P-value	$\beta$	P-value	$\beta$	P-value	$\beta$	P-value	$\beta$	P-value
1/ $\sqrt$ Body weight (kg)	2·10 <sup>-3</sup>	0.56	0.00	0.91	-0.8·10 <sup>-3</sup>	0.47	0.3·10 <sup>-3</sup>	0.89	1·10 <sup>-3</sup>	0.18	1.6·10 <sup>-3</sup>	0.13 ‡
1/ $\sqrt$ BMI (kg.cm <sup>2</sup> )	2·10 <sup>-3</sup>	0.54	1·10 <sup>-3</sup>	0.40	0.2·10 <sup>-3</sup>	0.90	2·10 <sup>-3</sup>	0.61	3·10 <sup>-3</sup>	0.04*	3·10 <sup>-3</sup>	0.02*‡
BMI z-score CDC <sup>2</sup>	-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	2·10 <sup>-3</sup>	0.94	0.03	0.6	-0.05	0.1	-0.06	0.06 ‡
Waist circumference <sup>2</sup> (cm)	-2·10 <sup>-6</sup>	0.8	2·10 <sup>-6</sup>	0.75	3·10 <sup>-6</sup>	0.64	-8.3·10 <sup>-6</sup>	0.29	8·10 <sup>-6</sup>	0.13	12·10 <sup>-6</sup>	0.02*‡
$\sqrt$ Waist-to-height ratio	-9·10 <sup>-5</sup>	0.99	-0.5·10 <sup>-3</sup>	0.94	-4·10 <sup>-3</sup>	0.64	9·10 <sup>-3</sup>	0.32	-6·10 <sup>-3</sup>	0.32	0.01	0.045*
Total body fat <sup>2</sup> (%)	-0.01	0.27	-0.01	0.13	-0.01	0.31	-2·10 <sup>-3</sup>	0.87	-0.01	0.08	-0.01	0.045*
Abdominal fat <sup>3</sup> (%)	-0.01	0.40	-0.02	0.01*	-0.02	0.10	0.5·10 <sup>-3</sup>	0.96	-0.02	0.03*	-0.02	0.03*
$\sqrt$ FFM <sup>1</sup> (kg)	-3·10 <sup>-5</sup>	0.74	-3·10 <sup>-5</sup>	0.51	1·10 <sup>-5</sup>	0.82	2.3·10 <sup>-5</sup>	0.8	3·10 <sup>-5</sup>	0.39	9·10 <sup>-6</sup>	0.83
$\sqrt$ VO <sub>2</sub> peak (ml·min <sup>-1</sup> )	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 <sup>3</sup> (mmol·l <sup>-1</sup> )	3.69	0.59	-4.8	0.51	12.66	0.13	7.38	0.24	-0.70	0.91	12.15	0.12
$\sqrt$ Fasting insulin (mU·l <sup>-1</sup> )	0.29	0.27	-0.39	0.12	-0.18	0.53	0.09	0.73	-0.12	0.59	-0.03	0.92
$\sqrt$ 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 <sup>-1</sup> )	0.07	0.77	-0.09	0.64	-0.03	0.89	0.014	0.95	-0.24	0.20	-0.07	0.73
$\sqrt$ LDL- Cholesterol (mmol·l <sup>-1</sup> )	0.02	0.70	-0.02	0.61	-0.03	0.56	-9·10 <sup>-3</sup>	0.86	-0.08	0.07	-0.02	0.66
Log HDL-Cholesterol (mmol·l <sup>-1</sup> )	-0.02	0.28	-0.03	0.59	-0.1·10 <sup>-3</sup>	0.99	-6·10 <sup>-3</sup>	0.93	0.04	0.42	4·10 <sup>-3</sup>	0.94
Log Triglycerides (mmol·l <sup>-1</sup> )	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 <sup>-1</sup> )	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	2·10 <sup>-3</sup>	0.92	0.4·10 <sup>-3</sup>	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	4·10 <sup>-3</sup>	0.92	-0.1	0.13
Log Einc (mmHg.10 <sup>-2</sup> )	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 <sup>-1</sup> (%)	0.03	0.18	-0.03	0.41	-0.06	0.41	0.05	0.049*	0.03	0.40	-0.06	0.34
$\sqrt$ 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;  $VO_2$ peak, 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 ( $p < 0.05$ ).

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

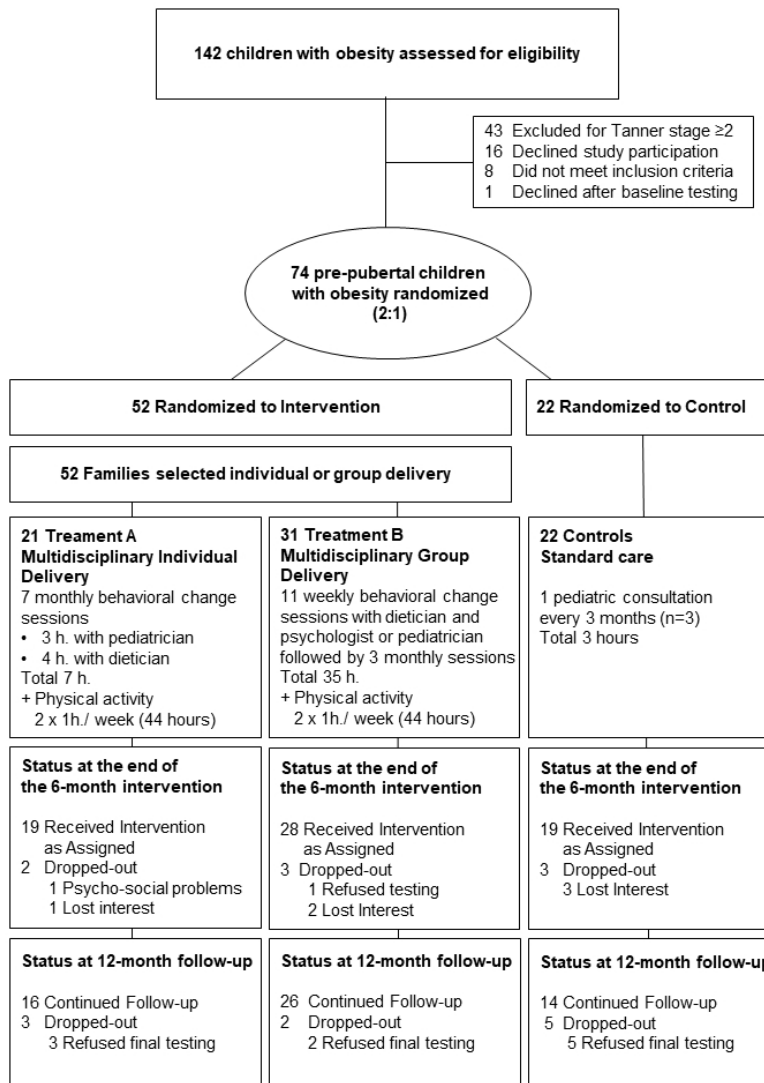


Figure 1. Flowchart for enrolment, randomization, intervention and follow-up of study participants

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](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.