

# Aerobic interval training reduces cardiovascular risk factors more than a multitreatment approach in overweight adolescents

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## A B S T R A C T

The aim of the present study was to compare the effects of a multidisciplinary approach (MTG) and aerobic interval training (AIT) on cardiovascular risk factors in overweight adolescents. A total of 62 overweight and obese adolescents from Trøndelag County in Norway, referred to medical treatment at St Olav's Hospital, Trondheim, Norway, were invited to participate. Of these, 54 adolescents (age,  $14.0 \pm 0.3$  years) were randomized to either AIT ( $4 \times 4$  min intervals at 90% of maximal heart rate, each interval separated by 3 min at 70%, twice a week for 3 months) or to MTG (exercise, dietary and psychological advice, twice a month for 12 months). Follow-up testing occurred at 3 and 12 months.  $\dot{V}O_{2\max}$  (maximal oxygen uptake) increased more after AIT compared with MTG, both at 3 months (11 compared with 0%;  $P < 0.01$ ) and 12 months (12 compared with  $-1$ %;  $P < 0.01$ ). AIT enhanced endothelial function compared with MTG at both 3 months (absolute change, 5.1 compared with 3.9%;  $P < 0.01$ ) and 12 months (absolute change, 6.3 compared with 1.0%;  $P < 0.01$ ). AIT was favourable compared with MTG in reducing BMI (body mass index), percentage of fat, MAP (mean arterial blood pressure) and increasing peak oxygen pulse. In addition, AIT induced a more favourable regulation of blood glucose and insulin compared with MTG. In conclusion, the novel findings of the present proof-of-concept study was that 3 months of twice weekly high-intensity exercise sessions reduced several known cardiovascular risk factors in obese adolescents more than that observed after a multitreatment strategy, which was initiated as hospital treatment. Follow-up at 12 months confirmed that AIT improved or maintained these risk factors to a better degree than MTG.

## INTRODUCTION

Worldwide there is a growing epidemic of both childhood and adult obesity, mainly due to an unhealthy diet and

lack of physical activity [1]. Childhood obesity has tripled between 1960 and 1990, approximately twice the increase observed in adults [2,3]. Obesity in children is independently associated with arterial endothelial dysfunction,

**Key words:** adolescent, aerobic interval training, blood pressure, cardiovascular risk factor, endothelial function, obesity.

**Abbreviations:** AIT, aerobic interval training; BMI, body mass index; BP, blood pressure; DBP, diastolic BP; FMD, flow-mediated dilation; HDL, high-density lipoprotein;  $Hf_{\max}$ , maximal heart frequency; HOMA, homoeostasis model assessment;  $Lm_b$ , lean body mass; MAP, mean arterial BP; MTG, multidisciplinary approach; oxLDL, oxidized low-density lipoprotein; SBP, systolic BP;  $\dot{V}O_2$ , oxygen uptake;  $\dot{V}O_{2\max}$ , maximal  $\dot{V}O_2$ .

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reduced  $\dot{V}O_{2\max}$  [maximal  $\dot{V}O_2$  (oxygen uptake)] and impaired insulin and glucose handling [4,5]. Endothelial dysfunction has proven to be a key early event in atherosclerosis, and can be detected several years ahead of plaque formation and thrombosis, and is an independent predictor of cardiovascular disease and mortality [6,7]. Freedman et al. [8] reported that 58% of obese children and adolescents (5–17 years old) had at least one of the major cardiovascular risk factors normally observed at old age. Furthermore, a 57-year follow-up study reported that adults that were overweight during adolescence had a 2.3-fold risk of morbidity and mortality from cardiovascular diseases, independently of adult weight [9]. More recently, studies [10–12] have reported beneficial effects of exercise training and diet on endothelial function in overweight/obese children and adolescents. It is difficult, however, to assess the separate effects of the training and diet, particularly because none of the studies have used a homogenous exercise training regimen.

Unanimously better, but affordable, prevention and treatment strategies to improve worldwide-scale health outcomes are called upon to slow down the current epidemic of being overweight [2]. It is now well-established that physical activity reduces, but does not currently prevent, the epidemic of obesity from either reaching global proportions or taxing public health and economy [13]. Despite the recent advances in understanding the biology underlying improved cardiovascular health with exercise training, several questions remain unresolved. For instance, the optimal programme, e.g. when to initiate, whom to prescribe exercise to and which exercise-intensity is required, and the actual design of the treatment programme remain to be determined.

The aim of the present study was to compare the effects of a multidisciplinary approach (MTG) and intensity-controlled aerobic interval training (AIT) on cardiovascular risk factors in overweight adolescents.

## MATERIALS AND METHODS

A total of 62 overweight and obese adolescents from Trøndelag County in Norway, referred for medical treatment at St Olav's Hospital, Trondheim, Norway, were invited to participate in the study. Of these, 54 adolescents (28 girls and 26 boys; mean age, 14 years) agreed to participate. They were randomized and stratified [according to age, gender and BMI (body mass index)] to either AIT ( $n=28$ ; 14 girls and 14 boys; mean age,  $13.9 \pm 0.3$  years) or MTG ( $n=26$ ; 14 girls and 12 boys; mean age,  $14.2 \pm 0.3$  years). The randomization code was developed using a computer random number generator to select random permuted blocks. The unit of Applied Clinical Research at the Norwegian University of Science and Technology carried out all of the randomization procedures to secure complete blinded randomization.

All adolescents and parents provided written informed consent, and the Regional Committee for Medical Research Ethics approved the protocol. The research has been carried out in accordance with the Declaration of Helsinki (2000). The study trial has been registered at ClinicalTrials.gov (<http://clinicaltrials.gov>) under the trial number NCT00184236.

Baseline characteristics are shown in Table 1.

## Anthropometric measurements

BMI was calculated, and dual-energy X-ray absorptiometry (Dexa; Hologic Discovery) scanning was used to determine body composition.

## Testing of $\dot{V}O_{2\max}$ and $Hf_{\max}$ (maximal heart frequency)

Subjects were informed about the test and instructed to exercise to their maximum limit. Familiarization with the treadmill, warm-up and the  $\dot{V}O_{2\max}$  ramp procedure using MetaMax II (Cortex) have been described in detail previously [14]. A levelling-off of  $\dot{V}O_2$  despite increased workload and a respiratory exchange ratio  $> 1.05$  were used as criteria for reaching the true  $\dot{V}O_{2\max}$ , and this was achieved in all individuals in the present study. For an estimate of stroke volume during maximal exercise, oxygen pulse ( $\dot{V}O_{2\max}/Hf_{\max}$ ) was calculated using pre- and post-test  $\dot{V}O_{2\max}$  and  $Hf_{\max}$  data respectively.  $\dot{V}O_{2\max}$  [in  $\text{ml} \cdot \text{min}^{-1} \cdot \text{Lm}_b^{-0.75}$  (where  $\text{Lm}_b$  is lean body mass)] was used as a supplement in the results as empirical studies have shown that  $\dot{V}O_2$ , depending upon the group studied, should be expressed in relation to  $\text{Lm}_b^{-0.75}$  over a wide range of body weights [15]. Otherwise, changes in  $\dot{V}O_{2\max}$  may be due to changes in body weight and not improved fitness.

## Endothelial function and BP (blood pressure)

Endothelial function was measured as FMD (flow-mediated dilation) using high-resolution vascular ultrasound (14 MHz echo Doppler probe; Vivid 7 System, GE Vingmed Ultrasound) according to current guidelines [16]. A detailed description of the procedure for measuring FMD and BP has been reported recently [17]. Shear rate was calculated as blood flow velocity (cm/s) divided by the diameter (cm), as reported previously [18]. As no group differences were found, these data are not presented. All ultrasound images were analysed in a random order, using EchoPAC™ (GE Vingmed Ultrasound) by an investigator blinded to the study groups.

## Training groups

AIT was performed as walking/running 'uphill' on a treadmill twice a week for 3 months. AIT subjects warmed-up for 10 min at 70% of  $Hf_{\max}$  before performing  $4 \times 4$  min intervals at 90–95% of  $Hf_{\max}$ , with a

**Table 1** Variables related to the overweight adolescents during the experimental period

Values are means  $\pm$  S.E.M., except baseline values which are means  $\pm$  S.D. \* $P < 0.05$  and \*\* $P < 0.01$ , significantly better compared with baseline within the group; § $P < 0.05$ , significantly better compared with the respective time in the MTG group. 1RM; one repetition maximum; nm, not measured.

Variable	MTG			AIT		
	Baseline	3 Months ( $n = 22$ )	12 Months ( $n = 14$ )	Baseline	3 Months ( $n = 20$ )	12 Months ( $n = 13$ )
<b>Body composition</b>						
Weight (kg)	94.3 $\pm$ 15.3	95.4 $\pm$ 1.4	96.1 $\pm$ 1.7	94.1 $\pm$ 23.3	94.4 $\pm$ 1.4	94.4 $\pm$ 1.7
Height (cm)	168 $\pm$ 8.6	169 $\pm$ 0.4**	171 $\pm$ 0.5**	169 $\pm$ 10.6	170 $\pm$ 0.4**	173 $\pm$ 0.5**
BMI (kg/m <sup>2</sup> )	33.3 $\pm$ 4.5	33.1 $\pm$ 0.4	32.9 $\pm$ 0.5	33.2 $\pm$ 6.1	32.5 $\pm$ 0.4**	31.4 $\pm$ 0.5
Waist (cm)	101.4 $\pm$ 10.8	104.2 $\pm$ 1.6	100.1 $\pm$ 2.3	105.3 $\pm$ 10.5	104.9 $\pm$ 1.7	98.1 $\pm$ 2.2*
Total fat (%)	41.1 $\pm$ 4.7	40.8 $\pm$ 0.5	39.1 $\pm$ 0.6	40.6 $\pm$ 5.3	39.3 $\pm$ 0.5**	38.6 $\pm$ 0.7**
Fat weight (kg)	34.8 $\pm$ 7.8	35.1 $\pm$ 1.1	34.7 $\pm$ 1.3	34.5 $\pm$ 12.2	33.6 $\pm$ 1.1**	32.1 $\pm$ 1.5
Fat weight trunk (kg)	17.7 $\pm$ 5.3	17.9 $\pm$ 0.6	17.1 $\pm$ 0.8	18.3 $\pm$ 7.2	17.0 $\pm$ 0.6**	16.8 $\pm$ 0.8
Lm <sub>b</sub> (kg)	56.1 $\pm$ 8.7	57.9 $\pm$ 0.6**	58.8 $\pm$ 0.8	55.9 $\pm$ 11.8	57.9 $\pm$ 0.6**	60.0 $\pm$ 0.8
<b>BP</b>						
SBP (mmHg)	125.0 $\pm$ 12.9	122.5 $\pm$ 1.5*	119.8 $\pm$ 2.1**	128.8 $\pm$ 12.8	119.4 $\pm$ 1.6**	120.9 $\pm$ 2.0**
DBP (mmHg)	65.5 $\pm$ 8.6	67.3 $\pm$ 1.6	66.2 $\pm$ 2.1	70.4 $\pm$ 7.5	64.9 $\pm$ 1.6**	65.5 $\pm$ 2.0*
MAP (mmHg)	85.3 $\pm$ 9.5	85.8 $\pm$ 1.4	84.1 $\pm$ 1.8	89.9 $\pm$ 8.6	82.7 $\pm$ 1.4**	83.7 $\pm$ 1.7**
<b>Exercise variables</b>						
$\dot{V}_{O_2 \max}$ (ml $\cdot$ kg <sup>-1</sup> of body weight $\cdot$ min <sup>-1</sup> )	32.3 $\pm$ 4.8	32.3 $\pm$ 0.8	31.9 $\pm$ 1.0	32.3 $\pm$ 5.8	35.3 $\pm$ 0.8**§	36.0 $\pm$ 1.1*§
$\dot{V}_{O_2 \max}$ (ml $\cdot$ min <sup>-1</sup> $\cdot$ Lm <sub>b</sub> <sup>-0.75</sup> )	148.8 $\pm$ 17.4	146.8 $\pm$ 4.0	139.7 $\pm$ 4.5	145.9 $\pm$ 20.1	161.4 $\pm$ 4.4**§	164.5 $\pm$ 11.9*§
Peak oxygen pulse (ml/beat)	15.1 $\pm$ 2.6	15.6 $\pm$ 0.7*	14.3 $\pm$ 0.8	14.8 $\pm$ 3.9	17.2 $\pm$ 1.0**§	18.3 $\pm$ 1.4*§
Maximal leg strength (1RM) (kg)	166.3 $\pm$ 30.0	171.3 $\pm$ 9.1	nm	161.3 $\pm$ 31.1	173.8 $\pm$ 9.1*	nm

3 min active recovery at 70% of Hf<sub>max</sub> between each interval, and a 5 min cool-down period, giving a total of 40 min. At all exercise training sessions, an instructor supervised the adolescents. Only a 30 min meeting with general nutritional advice was given at inclusion; no other advice about diet and exercise training was given to the AIT group. Following the 3 months of training, the adolescents were encouraged to perform at least two interval sessions each week at home or at a gym. Adolescents met for one session every second week for 6 months, and one session each month for the last 3 months before the 12 month follow-up testing.

Subjects randomized to MTG had a 12 month regimen (at St. Olav's Hospital, Trondheim, Norway) consisting of group meetings every 2 weeks involving a physician, psychologist, physiotherapist and clinical nutritional physiologist. The multidisciplinary programme was to be tested at St. Olav's University Hospital as a potential effective treatment of obese adolescents that had been 'given up' by their family physician and, therefore, referred to medical treatment at St. Olav's Hospital. The MTG group had a total of 21 h of treatment during the first 3 months of intervention. During the 3 month intervention, the MTG group had three activity sessions and three group conversations, each lasting 3 and 4 h respectively; this frequency continued through the whole intervention. Attendance criteria for inclusion to analyse the 3 month follow-up in both groups was set to be a minimum of 80%.

## Blood analyses

If not otherwise stated, all blood analyses were performed using standard local procedures. oxLDL (oxidized low-density lipoprotein) and adiponectin were measured in plasma using specific ELISAs (Mercodia), the total nitrite (NO<sub>2</sub><sup>-</sup>) concentration was quantified using a commercially available assay for NO detection (R&D Systems), and plasma insulin was analysed by RIA (Linco Research). HOMA (homoeostasis model assessment) was used to estimate  $\beta$ -cell function (HOMA%B) and overall insulin sensitivity (HOMA%S). This computer model gives a value for insulin sensitivity expressed as HOMA2-%S (where 100% is normal), which is simply the reciprocal of HOMA2-IR (insulin resistance) [19].

## Diet registration

The food diary used in the present study has a list of 277 drinks, food items and dishes, grouped together according to a typical Norwegian diet. Each food group is supplemented with open-ended alternatives. Food amounts are presented in predefined household units or as portions estimated from photographs in a photographic booklet, as described in detail elsewhere [20] (not recorded at 12 month follow-up).

## Leisure time physical activity

Leisure time physical activity was recorded 1 week before the training intervention and 1 week before

**Table 2** Blood variables related to the overweight adolescents during the experimental period

Values are means  $\pm$  S.E.M., except baseline values which are means  $\pm$  S.D. \* $P < 0.05$  and \*\* $P < 0.01$ , significantly better compared with baseline within the group; § $P < 0.05$ , significantly better compared with the respective time in the MTG group. HbA<sub>1c</sub>, glycated haemoglobin; HOMA% $\Delta$ S, insulin sensitivity estimated by HOMA; HOMA%B,  $\beta$ -cell function estimated by HOMA; nm; not measured.

Blood variable	MTG			AIT		
	Baseline	3 Months ( $n = 22$ )	12 Months ( $n = 14$ )	Baseline	3 Months ( $n = 20$ )	12 Months ( $n = 13$ )
Insulin (pmol/l)	173.0 $\pm$ 101	140.0 $\pm$ 17.4*	156.8 $\pm$ 20.2	186.4 $\pm$ 134	132.1 $\pm$ 17.2*	123.8 $\pm$ 23.4*
Insulin (2 h glucose load) (pmol/l)	634.7 $\pm$ 456	372.2 $\pm$ 72.9*	412.2 $\pm$ 85.4*	634.7 $\pm$ 558	461.5 $\pm$ 76.6*	294.3 $\pm$ 102.0*
Fasting glucose (mmol/l)	5.1 $\pm$ 0.32	5.0 $\pm$ 0.07	4.9 $\pm$ 0.1*	5.2 $\pm$ 0.44	4.9 $\pm$ 0.07**	4.9 $\pm$ 0.11**
2 h Post-glucose load (mmol/l)	5.5 $\pm$ 1.26	5.22 $\pm$ 0.19	5.34 $\pm$ 0.23	6.3 $\pm$ 1.51	5.57 $\pm$ 0.20*	5.22 $\pm$ 0.25
HOMA% $\Delta$ S (%)	41.0 $\pm$ 19.5	51.2 $\pm$ 9.03*	55.86 $\pm$ 10.09*	42.1 $\pm$ 26.3	66.0 $\pm$ 9.38*	59.7 $\pm$ 10.84*
HOMA%B (%)	170.9 $\pm$ 43.7	175.5 $\pm$ 15.6	188.3 $\pm$ 20.0	174.4 $\pm$ 56.0	173.2 $\pm$ 16.3	215.6 $\pm$ 22.0
HbA <sub>1c</sub> (%)	5.76 $\pm$ 0.17	5.63 $\pm$ 0.03**	5.78 $\pm$ 0.04	5.77 $\pm$ 0.24	5.63 $\pm$ 0.03**	5.76 $\pm$ 0.05
HDL-cholesterol (mmol/l)	1.23 $\pm$ 0.29	1.14 $\pm$ 0.04	1.25 $\pm$ 0.05	1.13 $\pm$ 0.29	1.24 $\pm$ 0.04*	1.24 $\pm$ 0.05
Triacylglycerols (mmol/l)	1.36 $\pm$ 0.80	1.24 $\pm$ 0.07	1.05 $\pm$ 0.09*	1.34 $\pm$ 0.83	1.19 $\pm$ 0.07	1.10 $\pm$ 0.09
Adiponectin ( $\mu$ g/ml)	8.05 $\pm$ 1.5	9.6 $\pm$ 1.10	nm	6.5 $\pm$ 1.3	8.28 $\pm$ 0.62	nm
NO ( $\mu$ mol/l)	97.1 $\pm$ 17.9	76.7 $\pm$ 4.0	nm	78.1 $\pm$ 16.6	80.8 $\pm$ 6.6§	nm
oxLDL (units/l)	34.0 $\pm$ 6.66	36.5 $\pm$ 3.0	nm	34.2 $\pm$ 10.5	34.8 $\pm$ 2.6	nm

the 3 month follow-up (not including organized training) by all participants wearing an accelerometer (ActigraphAM7164), and daily and total counts were registered (not measured at 12 month follow-up).

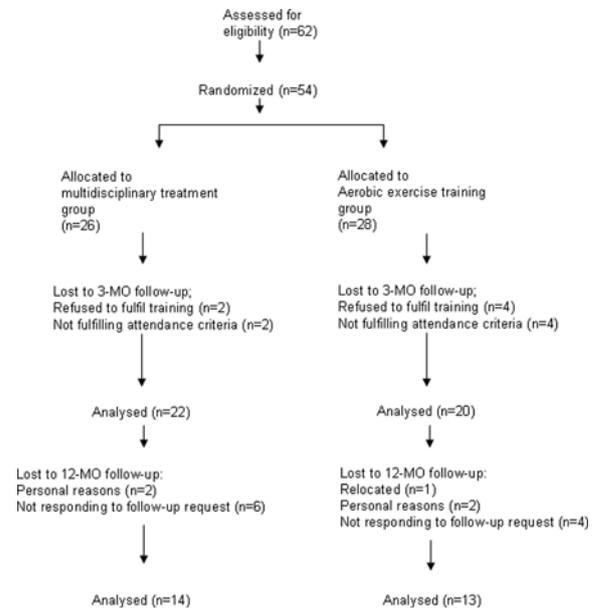
### Statistical analysis

The primary outcome variable was  $\dot{V}O_{2\max}$ . Prior experience suggests an S.D. of approx. 2–3 [21]. No formal sample size calculation was done, but with ten subjects in each group, a standardized within-group difference of 1.0 may be detected using a paired Student's  $t$  test with 80% power, at a significance level of 5% [22]. Clinically, this corresponds to a detectable difference in  $\dot{V}O_{2\max}$  of 3 ml  $\cdot$  kg<sup>-1</sup> of body weight  $\cdot$  min<sup>-1</sup>. For descriptive purposes, values are expressed as means  $\pm$  S.D. or means  $\pm$  S.E.M. when group differences are of main interest. A linear mixed model, allowing for repeated measurements, was used to model group differences. To confirm within-group changes we used the non-parametric Wilcoxon signed rank test. With respect to overweight, distribution of the risk factors was analysed using McNemar's test. Reported  $P$  values refer to within-group changes relative to baseline, unless otherwise specified.  $P < 0.05$  was considered as statistically significant. No correction for multiple analyses was made. SPSS<sup>®</sup> 14.0 was employed in all analyses.

## RESULTS

### Baseline characteristics

Baseline characteristics were similar in the two groups (Table 1 and 2). As shown in Figure 1, 12 subjects

**Figure 1** Flow chart of the study design

3-MO, 3 months; 12-MO, 12 months.

dropped out of the project before the 3 month follow-up, and an additional 15 subjects dropped out of the project between the 3 and 12 month follow-up. Data for the drop-outs did not differ from the adolescents who completed the study with regards to endothelial function, weight, BMI, fat percentage,  $\dot{V}O_{2\max}$ , maximal leg strength, and both fasting insulin and glucose, and insulin and glucose after the glucose test.

**Table 3** Dietary habits from last representative weekValues are means  $\pm$  S.E.M.  $\S P < 0.05$ , significantly better compared with the other group.

	MTG		AIT	
	Baseline	3 Months ( $n = 22$ )	Baseline	3 Months ( $n = 20$ )
Total nutrition (g)	7509 $\pm$ 443	7678 $\pm$ 292	6872 $\pm$ 667	6760 $\pm$ 284 $\S$
Total energy consumption (kJ)	28 534 $\pm$ 1586	26 273 $\pm$ 407	24 408 $\pm$ 2231	22 123 $\pm$ 884 $\S$
Protein intake (g)	286 $\pm$ 15	267 $\pm$ 5	234 $\pm$ 20	239 $\pm$ 9 $\S$
Fat intake (g)	255 $\pm$ 20	237 $\pm$ 5	212 $\pm$ 21	178 $\pm$ 15 $\S$
Saturated and <i>trans</i> -fat intake (g)	118 $\pm$ 10	107 $\pm$ 3	97 $\pm$ 11	79 $\pm$ 6 $\S$
<i>Trans</i> -fat intake (g)	5.4 $\pm$ 0.5	5.5 $\pm$ 0.2	4.2 $\pm$ 0.5	3.5 $\pm$ 0.3 $\S$
Mono-unsaturated fat (g)	80 $\pm$ 6	77 $\pm$ 2	70 $\pm$ 7	62 $\pm$ 5 $\S$
Polyunsaturated fat (g)	34.2 $\pm$ 2.8	34.7 $\pm$ 0.8 $\S$	28.2 $\pm$ 2.6	28.0 $\pm$ 2.0
Unsaturated/saturated fat ratio	0.95 $\pm$ 0.04	0.99 $\pm$ 0.02	0.99 $\pm$ 0.04	1.11 $\pm$ 0.03 $\S$
Cholesterol (g)	896 $\pm$ 99	752 $\pm$ 22	777 $\pm$ 117	718 $\pm$ 51
Carbohydrate (g)	810 $\pm$ 48	739 $\pm$ 16	719 $\pm$ 71	639 $\pm$ 25 $\S$
Starch (g)	428 $\pm$ 23	455 $\pm$ 8	358 $\pm$ 28	312 $\pm$ 14 $\S$
Mono-/di-saccharide (g)	369 $\pm$ 30	277 $\pm$ 13	352 $\pm$ 53	316 $\pm$ 20
Food fibre (g)	59.7 $\pm$ 3.5	60.8 $\pm$ 1.9 $\S$	46.5 $\pm$ 3.6	46.5 $\pm$ 3.6

### Body composition, BP and diet

AIT decreased BMI by 0.7 and 1.8 kg/m<sup>2</sup> after 3 and 12 months respectively (Table 1). Subjects in both groups had an increase in height during the experimental period (Table 1), while body weight remained unchanged. AIT decreased the percentage of fat by 1.3 and 2% at 3 and 12 months respectively, and total fat decreased by 0.9 and 2.4 kg (Table 1). No changes were observed in the MTG group (Table 1). AIT decreased trunk fat weight by 1.3 and 1.5 kg after 3 and 12 months respectively, but no change was observed in the MTG group.  $L_{m_b}$  increased by 2.0 and 1.8 kg in the AIT and MTG groups respectively, after 3 months (Table 1).

SBP (systolic BP) decreased by 9.4 and 2.5 mmHg after 3 months of AIT and MTG respectively. After 12 months, a 7.9 and 5.2 mmHg decrease was observed following AIT and MTG respectively (Table 1). DBP (diastolic BP) decreased by 5.5 mmHg after 3 months of AIT, but no change was observed in the MTG group. In addition, after 12 months, DBP was still decreased by 4.9 mmHg in the AIT group compared with baseline values, but no change was observed in the MTG group (Table 1). MAP (mean arterial BP) decreased by 7.2 mmHg after 3 months of AIT compared with at baseline, but no change was observed in the MTG group. After 12 months, MAP was still 6.2 mmHg lower than baseline in the AIT group, but remained unchanged in the MTG group (Table 1).

Interestingly, at 3 months, subjects in the AIT group had a significantly better diet than those in the MTG group; however, the intake of polyunsaturated fat and fibre was higher and the intake of mono-/di-saccharides was lower in the MTG group compared with the AIT group. In addition, the unsaturated/saturated fat

ratio in the diet was increased in both groups during the experimental period. The main dietary factors are summarized in Table 3.

### Aerobic capacity, daily activity, peak oxygen pulse and leg strength

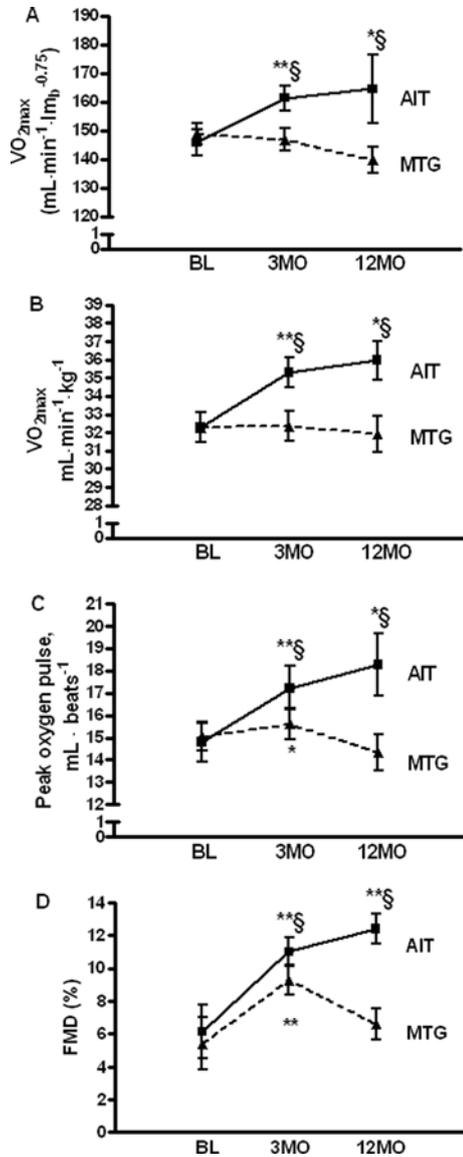
After 3 months,  $\dot{V}O_{2\max}$  increased by 15.5 ml  $\cdot$  min<sup>-1</sup>  $\cdot$   $L_{m_b}^{-0.75}$  after AIT, whereas no change was observed after MTG. At 12 months of follow-up,  $\dot{V}O_{2\max}$  was 18.7 ml  $\cdot$  min<sup>-1</sup>  $\cdot$   $L_{m_b}^{-0.75}$  higher than at baseline in the AIT group, but unchanged in the MTG group (Figure 2A). Both groups had a non-significant increase in total pedometer counts recorded after 3 months of training (results not shown). Peak oxygen pulse at 3 months increased by 2.4 ml/beats in the AIT group and 0.5 ml/beats in the MTG group. At 12 months, the AIT group had a 3.5 ml/beats increase, whereas no change was observed in the MTG group (Figure 2C). Maximal leg strength increased by 11.8 kg in the AIT group after 3 months compared with baseline, whereas no change was observed in the MTG group (Table 1).

### FMD

After 3 months, AIT and MTG increased FMD by 5.1 and 3.9% respectively. At 12 months, AIT had an FMD that was 6.3% higher than baseline values, whereas the FMD values in the MTG group had returned to baseline levels (Figure 2D).

### Blood analysis

NO, which is the main substrate regulating endothelial function, increased significantly after 3 months of AIT compared with MTG (Table 2), whereas oxLDL,



**Figure 2**  $\dot{V}O_{2\max}$  (A and B), peak oxygen pulse (C) and endothelial function (D) in adolescents assigned to the two groups at baseline, and after 3 and 12 months

$\dot{V}O_{2\max}$  was measured in  $\text{mL} \cdot \text{min}^{-1} \cdot \text{Lm}_b^{-0.75}$  in (A) and  $\text{mL} \cdot \text{kg}^{-1}$  of body weight  $\cdot \text{min}^{-1}$  in (B). In (D), endothelial function was measured as FMD of the brachial artery. \* $P < 0.05$  and \*\* $P < 0.01$  compared with baseline (BL) within the group; § $P < 0.05$  compared with the MTG group. 3MO, 3 months; 12MO, 12 months.

which negatively regulates the bioavailability of NO, was unchanged in both groups (Table 2). Circulating adiponectin, an adipocyte-secreted hormone that is associated with improved insulin sensitivity and the amelioration of the metabolic syndrome, increased by 1.9 and 0.9  $\mu\text{g}/\text{mL}$  after 3 months of AIT and MTG respectively (Table 2). After 3 months, HDL (high-density lipoprotein)-cholesterol increased by 0.11 mmol/l in the AIT group and decreased by 0.09 mmol/l in the

group (Table 2). At 3 months, fasting glucose decreased by 0.3 mmol/l in the AIT group, but did not change in the MTG group (Table 2). After 12 months, fasting glucose decreased by 0.3 mmol/l in AIT and 0.2 mmol/l in the MTG group (Table 2). A 2 h post-glucose load after 3 months decreased by 0.73 mmol/l in the AIT group but not in the MTG group (Table 2). Insulin decreased by 54.3 and 33 pmol/l after 3 months of AIT and MTG respectively. After 12 months, insulin was 62.6 pmol/l lower than baseline in the AIT group, whereas no change was observed in the MTG group (Table 2). HOMA analysis demonstrated that insulin sensitivity after 3 months was increased by 23.9 and 10.7% in the AIT and MTG groups respectively. Furthermore, at 12 months, insulin sensitivity was still 17.6 and 14.9% higher than at baseline (Table 2) in the AIT and MTG groups respectively.

### Overall changes

Table 4 summarizes the overall changes after the two interventions, and demonstrates that AIT had a more robust change in cardiovascular risk factors compared with MTG.

### DISCUSSION

The main findings of the present study are that 3 months of high-intensity AIT improved several known cardiovascular risk factors, including BMI, fat percentage,  $\dot{V}O_{2\max}$ , MAP and HDL, and reduced fasting glucose more than that observed after a multidisciplinary treatment regimen in obese adolescents. Additionally, the results after 12 months indicate that AIT improved or maintained the physiological changes to a better degree than MTG.

### 'Cost-effectiveness'

One may argue that it is of no surprise and that it is expected that endurance training would have a greater effect on cardiovascular risk factors within such a short period of time as 3 months. Therefore we performed a follow-up of some of the important variables after 12 months and still found that those subjects that had performed endurance training had more robust physiological improvements than that observed after the multitreatment strategy. Furthermore, the MTG used in the present study is a treatment strategy that was initiated in adolescents where no other treatment had been successful, and it includes both nutritional advice as well as exercise training. One could therefore expect a more robust outcome after 12 months of treatment when compared with a very simple treatment strategy existing of only (effective) endurance training. However, as most of the cardiovascular risk factors, including fat metabolism, are actually related to the level of aerobic fitness, it may

**Table 4** Number of subjects in each group that had positive changes in risk factors after the experimental period

Values are the number of risk factors/patients. \* $P < 0.05$  and \*\* $P < 0.01$ , significantly better compared with baseline within group; § $P < 0.05$ , significant difference the between groups.

	3 Months		12 Months	
	MTG ( $n = 22$ )	AIT ( $n = 20$ )	MTG ( $n = 14$ )	AIT ( $n = 13$ )
Total reduction in risk factors ( $n$ )	8/15**	11/15**§	9/15**	12/15**§
Risk factor ( $n$ )				
Weight	9/22	10/20	8/14	7/13
BMI	10/22	14/20	8/14	10/13*
Waist	11/22	12/20	8/14	11/13*
Percentage fat	9/22	17/20**	7/14	11/13*
Fat weight (trunk)	12/22	16/20**	10/14	10/13*
Fasting glucose	11/22	14/20	8/14	12/13**
Insulin	15/22	15/20*	10/14	10/13*
Insulin sensitivity	16/22*	15/20*	9/14	12/13**
HDL-cholesterol	9/22	16/20**	9/14	10/13*
$\dot{V}O_{2\max}$	16/22	19/20**	3/14	12/13**
Peak oxygen pulse	15/22	19/20**	8/14	11/13*
FMD	15/22	15/20**	9/14	12/13**
SBP	16/22*	17/20**	10/14	11/13*
DBP	10/22	14/20	6/14	10/13*
MAP	15/22	17/20**	8/14	10/13*

not be that surprising after all, and it may be that future treatment strategies in obese adolescents should focus upon increasing aerobic fitness more today. Interestingly, informal comments from the adolescents in the AIT group indicated that they found it motivating to have a varied procedure to follow during each training session, and that the feeling of actually getting in better shape also motivated them to continue after the 3 month experimental period. Long-term follow-up studies are needed to determine how long this effect lasts.

### Exercise capacity and cardiac output

Of all of the established risk factors, low aerobic exercise capacity appears to be the strongest predictor of mortality [23]. The high-intensity exercise in the AIT group was set to 90% of  $Hf_{\max}$  and was performed as AIT because this training method has previously yielded the greatest improvements in aerobic capacity over a relatively short time in healthy individuals [24], and in patients with coronary artery disease [14], intermittent claudication [25], the metabolic syndrome [12] and post-infarction heart failure [21]. The rationale behind interval training is that most evidence suggests that it is the pumping capacity of the heart (i.e. stroke volume) that limits  $\dot{V}O_{2\max}$ , and the interval design allows for rest periods that make it possible for the adolescents to complete short work periods at higher intensities, which thereby challenge the heart's pumping ability more than what would be possible by continuous exercise. Maximal stroke volume

during exercise increased more after AIT, indicated by the maximal oxygen pulse, and probably contributes to the greater increase in  $\dot{V}O_{2\max}$  in this group compared with MTG. Even though the adolescents trained on average for only 1 h a week, a relatively large increase in  $\dot{V}O_{2\max}$  was observed after AIT (11%), confirming the effectiveness of the training method. To increase  $\dot{V}O_{2\max}$  in MTG, more or different physical activity than the standard treatment used is required. Interestingly, although obesity and aerobic capacity are strong and independent prognostics markers of cardiovascular mortality, the link between aerobic capacity and mortality appears to be stronger [26,27]. This suggests that treatment should target improvement in aerobic capacity rather than weight loss. The results of the present study demonstrate that AIT partly or fully reverses several of the traditional cardiovascular risk factors, suggesting that this may be a promising treatment strategy. However, despite the results reported in the present study, the interval protocol may not be readily acceptable to the general population of overweight and obese individuals. On the other hand, an exercise intensity of 90% of  $Hf_{\max}$  corresponds to a heart rate that is approx. 20 beats/min below the maximum and below  $\dot{V}O_{2\max}$ . This implies that the subjects would have tolerated higher exercise intensities (but with shorter durations), and that most adolescents walked 'uphill' on the treadmill to avoid running and, thereby, reduce the risk of skeletal muscle injuries due to increased mechanical load at high running speeds.

## BMI

Only AIT induced a significant reduction in BMI after 3 months, but it was small, despite a significant decrease in fat mass. This may be explained by an increase in  $Lm_b$  and, thereby, unchanged total body mass. Both growth and exercise training are factors increasing muscle mass in adolescents. This confirms that BMI is an inadequate measure for detecting changes in body composition in adolescents losing weight [11]. As stated previously, adiposity is associated with increased risk of cardiovascular disease [1,8], and using waist circumference as a measure has been shown to have a stronger association with cardiovascular disease risk factors than BMI [28,29].

## Losing body fat: the misunderstanding of exercise intensity

At both 3 and 12 months, percentage body fat decreased only after AIT. This is consistent with the findings by Woo et al. [11], who reported that exercise training decreased fat mass substantially compared with dietary changes. However, most studies [11,30] have used lower exercise intensities than in the present study. When training volumes are equalized between groups, high-intensity training appears to be the most effective training method to reduce weight both in adolescents [31,32] and adults [12]. In line with this, high-intensity physical activity, but not moderate-intensity physical activity, can predict body fat [32,33]. The present study supports the notion that high-intensity training is effective in getting a more favourable body composition.

It is a widely held misunderstanding that, although percentage fat metabolism may be higher during moderate-intensity exercise, this does not necessarily mean that total fat metabolism is higher. Not only is the total energy expenditure greater in the higher intensity exercise, but the amount of fat metabolized is also larger per unit of time [34]. With even higher intensities (90%), post-exercise oxidation appears to be mainly supplied by fat during the first hours of recovery [35]. This should be emphasized when designing exercise programmes for overweight and obese individuals.

## FMD

AIT improved FMD more both at 3 and 12 months compared with MTG. This was not surprising considering the superiority of AIT over MTG in improving most of the other cardiovascular risk factors. For instance, HDL, blood glucose and insulin changed in a positive direction only after AIT, all of which are known to directly influence the bioavailability of NO, the main regulator of endothelial function [36]. It has been suggested that obesity is related to increased levels of inflammation in the vessel wall [37]. Interestingly, both groups had a substantial increase in an anti-inflammatory factor, adiponectin, also linked with improved insulin sensitivity,

improved endothelial function and amelioration of the metabolic syndrome in adults [12,37]. These observations could indicate that adiponectin has a central role in the improvements in FMD in the two groups. A recent study from our laboratory [12] has demonstrated that both AIT and moderate exercise increased the levels of adiponectin, and it may be that the reason for increased levels after MTG is due to the exercise training performed. In addition, both groups had an improved unsaturated/saturated fat ratio in their diet and also improved insulin sensitivity, both of which may also contribute to improved endothelial function [12,38]. The reason for the dramatic decline in FMD from 3 to 12 months in the MTG group is not fully understood, but may be linked to a general decline in other physiological variables towards baseline values (Table 4).

We have demonstrated, in line with other studies [11,30] and a comprehensive review [26], that regular exercise training improves endothelial function independent of weight loss. This suggests that obesity is not valid as a cardiovascular risk factor if the subjects are physically fit. This led Gaesser [27] to hypothesize that fatness, instead of being a contributor to early cardiovascular morbidity and mortality, reflects a lack of physical activity and low  $\dot{V}O_{2\max}$ .

## Dietary habits and blood profile

Interestingly, AIT was better compared with MTG in improving the diet of the subjects after the 3 month experimental period. This is somehow surprising considering the fact that the AIT group only received some general advice with regard to their diet compared with a comprehensive theoretical and practical supervision in the MTG group. The reason for this finding is not fully understood, but could be a positive motivational side effect of improving their aerobic capacity. This is confirmed by informal comments from the adolescents in the AIT group indicating that they became more conscious of their dietary behaviour after just 3 months. Blood glucose at 3 months was only reduced in the AIT group and was consistent with the lower intake of carbohydrates compared with the MTG group, despite a lower intake of mono-/di-saccharides in the latter group after the experimental period. It is also well known that GLUT-4 increases in proportion to increased insulin sensitivity after endurance training, which also probably contributes to the lowering of blood glucose [39].

## Limitations of the present study

The relatively small number of adolescents included in the present study has probably made it hard to detect any group differences. It is also important to note that the study was not 'an intention to treat study' but rather 'an effect of treatment study', and the study should therefore be regarded as 'a proof-of-concept study'. Another clear limitation of the present study is the large drop-out

between 3 and 12 months, although the drop-outs did not differ from the adolescents who completed the study with regard to endothelial function, weight, BMI, percentage fat,  $\dot{V}O_{2\max}$ , maximal leg strength, and both fasting insulin and glucose and insulin and blood glucose. The number of drop-outs in the present study was consistent with previous follow-up studies (1 year) [40,41]. In addition, hormonal changes, especially in girls as it is known that oestrogen improves endothelium-dependent dilation, were not accounted for. Furthermore, it is hard to be conclusive on which factor(s) in the MTG contributed to improved cardiovascular function as several variables were manipulated at the same time. However, from the results in the AIT group, one may speculate that it was the exercise part in the MTG that had most influence upon cardiovascular function.

## Conclusions

The novel finding of the present proof-of-concept study was that 3 months of twice weekly high-intensity exercise sessions reduced several known cardiovascular risk factors, including FMD,  $\dot{V}O_{2\max}$ , insulin, fasting glucose and fat mass, more than that observed after a multitreatment strategy in obese adolescents. Follow-up for 12 months confirmed that AIT improved or maintained these risk factors to a better degree than MTG. The present results are provocative and should encourage larger multicentre studies to be undertaken using the same endurance protocol as reported in the present study.

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