Original Article

Effects of repeated yearly exposure to exercise-training on blood pressure and metabolic syndrome evolution

Felix Morales-Palomo^a, Miguel Ramirez-Jimenez^a, Juan F. Ortega^a, Pedro L. Lopez-Galindo^b, Juan Fernandez-Martin^b, and Ricardo Mora-Rodriguez^a

Objective: To study if repeated yearly training programs consolidate the transient blood pressure (BP) improvements of one exercise program into durable adaptations.

Methods: Obese middle-age individuals with metabolic syndrome (MetS) underwent high-intensity aerobic interval training during 16 weeks (November to mid-March) in 3 consecutive years [training group (TRAIN); $N=23$]. Evolution of MetS components was compared with a matched-group that remained sedentary [control group (CONT); $N=26$].

Results: At the end of the first training program (0–4 months), TRAIN lowered systolic arterial pressure, blood glucose, waist circumference and MetS Z-score below CONT (-8.5 ± 2.5 mmHg; -19.9 ± 2.6 mg/dl; -3.8 ± 0.1 cm and -0.3 ± 0.1 , respectively, all $P < 0.05$). With detraining (month 4–12) TRAIN adaptations relapsed to the levels of baseline (month 0) except for BP. A second exercise program (month 12–16) lowered blood glucose and waist circumference below CONT (-19.0 ± 2.0 mg/dl; -4.1 ± 0.1 cm). After detraining (month 16–24) BP, blood glucose and Z-score started below CONT values (-6.8 ± 0.9 mmHg; -24.6 ± 2.5 mg/dl and -0.4 ± 0.05 , respectively, all $P < 0.05$) and those differences enlarged with the last training program (month 24–28). Ten-year atherosclerotic cardiovascular disease risk estimation increased only in CONT (8.6 ± 1.1 – $10.1 \pm 1.3\%$; year 2–3; $P < 0.05$).

Conclusion: At least two consecutive years of 4-month aerobic interval training are required to chronically improve MetS (Z-score). The chronic effect is mediated by BP that does not fully return to pretraining values allowing a cumulative improvement. On the other hand, sedentarism in MetS patients during 3 years increases their predicted atherosclerotic diseases risk.

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Keywords: arterial pressure, cardiovascular diseases, high-intensity interval training, metabolic syndrome X

Abbreviations: AIT, high intensity aerobic interval training; ANOVA, analysis of variance; CVD, cardiovascular disease; CONT, control group; HDL-c, HDL cholesterol; LDL-c, LDL cholesterol; MetS, metabolic syndrome; TRAIN, training group

INTRODUCTION

Metabolic syndrome (MetS) is cluster of anthropometric, metabolic and cardiovascular abnormalities that occur in concurrence at a higher rate than what would be expected by chance alone. In addition, the overall cardiovascular risk associated with MetS is greater than the sum of the risks of each of its components [1]. One-third of patients with essential hypertension also have MetS [2]. The addition of the other MetS factors to hypertension increase their risk of suffering cardiovascular and renal diseases. A program of intense aerobic exercise training reduces cardiovascular risk in MetS patients by lowering arterial blood pressure (BP), blood lipids and abdominal obesity [3,4]. We and others have studied different exercise methods (continuous vs. interval) to discern which result in the largest benefit for the health of MetS patients. Studies of 8–16 weeks of training using high intensity aerobic interval training (AIT) reveal that this type of training improves endothelial function above isocaloric continuous training [5], reduces BP [4], improves heart diastolic function [6], induces mitochondrial biogenesis [4,7], improves cardiorespiratory fitness [8] and insulin sensitivity [9].

Habitually, the effects of exercise training are tested 48–72 h after the last exercise bout to measure the chronic rather than the acute effect of the last training bout. Thus, the literature provides information of the health improvements derived from an exercise training program during the 2–3 days after the last training bout. However, it is unclear if those responses would last to be considered chronic adaptations. There are few studies addressing the effects of exercise discontinuity (short-term detraining) in the decay of health parameters improved by exercise training. To our knowledge, there are only three studies of this type in obese-MetS patients [4,10,11]. In those studies, it is suggested that some health-related training adaptations are retained during 1 month of detraining [BP, waist

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^aExercise Physiology Lab at Toledo, University of Castilla-La Mancha and ^bServicio de Salud de Castilla-La Mancha (SESCAM), Toledo, Spain

Correspondence to Ricardo Mora-Rodriguez, Exercise Physiology Lab at Toledo, University of Castilla-La Mancha, 45071 Toledo, Spain. Tel: +34 925268800; e-mail: ricardo.mora@uclm.es

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circumference, HDL cholesterol (HDL-c)], whereas others rapidly decay to pretraining values (cardiorespiratory fitness, maximal fat oxidation and blood triglycerides).

Ideally, MetS patient should include exercise into their lifestyles and endure it all year-round. However, low initial fitness levels, low motivation/commitment, seasonal holidays, travel, musculoskeletal injuries, upper respiratory tract infections preclude training continuity resulting in the 21–58% levels of attrition reported depending on the duration of the exercise programs [12]. Thus, the study of detraining time-course in health variables may derive important information. On the other hand, scarce information is available regarding the regaining of those adaptations upon retraining [13], and to our knowledge, none in obese-MetS populations. The athletic performance literature suggests that upon detraining, recovery of the trained levels in maximal oxygen consumption, lactate threshold or running economy requires longer than the duration of detraining [14,15]. However, when exercise-training to improve health, rather than to improve athletic performance, those physiological variables are not maximized to the level found in the athletic population, and, thus, the decay with detraining may be of less magnitude. Conversely, the recovery rates with retraining may be quicker in the population that exercise-train for improving health. This may explain why some investigators report that older adults show resilience to exercise detraining [16].

The retention of some adaptations during detraining [4,10,11] and the recovery of the ones that relapse to pretraining values with retraining is largely undetermined. To address this question, we designed a study in which MetS patients underwent the same dose of exercise-training in three consecutive years while following their physiological responses during training–detraining–retraining in comparison with a sedentary control group (CONT).

The main purpose of this study is to determine if there is a cumulative effect of several short-term, yearly exercise-training programs in BP and in the composed MetS Z-score which is the best index of health deviation/normalization in this population [17]. Another purpose is to determine which MetS factors are more resilient and which more prone to the decay with detraining. Identification of those fast-decaying factors allows to devise combination strategies (medicine and exercise) to target those factors. Our hypothesis is that long-standing health improvements that reflect in MetS Z-score will necessitate from several short-term, yearly exercise-training programs. Our main outcome is MetS Z-score followed by BP as a related secondary outcome.

METHODS

Participants

Forty-nine middle-aged (54 ± 8 years) obese patients ($n = 42$ men and $n = 7$ women) with BMI of 33 ± 4 kg/m² and MetS completed this study. MetS was defined as the presence of three of the following five risk factors; elevated waist circumference, elevated BP, elevated fasting blood glucose, elevated triglycerides or reduced HDL-c [18]. Exclusion criteria included untreated cardiovascular or renal disease, or any condition associated with exercise intolerance. All patients provided written, witnessed,

informed consent of the protocol approved by the Virgen de la Salud Hospital's Ethics Committee in accordance with the world medical association Declaration of Helsinki.

Experimental design

We used a nonrandomized pretest posttest CONT experimental design. Patients were recruited, screened, and completed the treatments and testing in the order presented in Fig. 1. Patients were studied during three consecutive years (2013–2016). Knowing that seasons may affect MetS factors incidence [19] testing was conducted in the same time of the year (November–mid-March). Patients were divided into two group of similar characteristics in age, weight, BMI and number of MetS factors (Table 1). One group [training group (TRAIN); $N = 23$] underwent supervised AIT with a frequency of 3 times per week during 16 weeks. Training consisted on pedaling for 10 min as warm up at 70% of maximal heart rate (HR_{max}) followed by 4×4 -min intervals at 90% of HR_{max} interspersed with 3-min active recovery at 70% HR_{max} and a 5-min cool-down period for a total of 43-min workout. Exercise intensity was increased as training adaptations developed to maintain target heart rate (HR) ([20], Seego; Realtrack Systems, Almeria, Spain). Participants were required to attend at least 90% of all the exercise sessions. The CONT ($N = 26$) remained sedentary for the duration of the study. All patients were advised to maintain their normal dietary habits during the whole study. They were requested to fill out a 3-day nutritional diary that was analyzed using a software (CESNID v1.0; Barcelona, Spain) and feedback provided monthly during the intervention months.

Clinical investigation

Patients arrive to the laboratory before (November) and after the 16-week intervention (mid-March to compensate for missing training in Christmas) in the morning after an overnight fast. Nude body weight (Hawk; Metler, Toledo, Ohio, USA), height (Stadiometer; Secca 217, Hamburg, Germany) and waist circumference (no elastic measuring tape) were assessed by the same researcher. Then, resting BP was measured after 15 min of supine resting using a calibrated ECG gated electro-sphygmomanometer (Tango; Suntec Medical, Morrisville, North Carolina, USA) as the average of three measurements. Following, a 5-cm³ blood sample was drawn from an antecubital vein for the determination of blood glucose and lipids [i.e. triglycerides, total cholesterol (TC), HDL-c and LDL cholesterol (LDL-c)]. In the TRAIN, all tests were scheduled at least 48 h after the last exercise training session to avoid measuring the acute effects of the last exercise bout rather than the chronic effects of the exercise training program.

Blood analyses

Plasma glucose was analyzed using the glucose oxidase peroxidase method with intraassay and interassay coefficient of variation (iCV) of $0.9 \pm 1.2\%$. HDL-c using accelerator selective detergent method (iCV; $1.7 \pm 2.9\%$). Blood triglycerides with glycerol-3-phosphate oxidize method (iCV; $0.8 \pm 1.7\%$). Total serum cholesterol by an enzymatic method with a single aqueous reagent (iCV; $1.1 \pm 1.4\%$). LDL-c was calculated as proposed by Friedewald [21]. All

FIGURE 1 CONSORT schematic representation of the study procedures.

the above analyses were run in an automated Mindray BS 400 Chemistry Analyzer (Mindray Medical Instrumentation, Shenzhen, China).

Metabolic syndrome Z-score and predicted 10-year atherosclerotic cardiovascular disease risk

The MetS Z-score is a continuous score that comprises the five MetS variables. Sex-specific Z-score equations were used to account for variations from the MetS harmonized definition [18]. Z-scores were calculated to assess the evolution to the norm of MetS risk factors [3]. The sum of the Z-scores for each MetS components was divided by five to compile the MetS risk score with units of SD [22]. Ten-year cardiovascular risk percentage was determined using the

atherosclerotic cardiovascular disease (ASCVD) algorithm [23] that includes as predicting factors; race, sex, age, TC, HDL-c, SBP, treatment for hypertension, diabetes status and smoking status.

Statistical analysis

Data are presented as mean $\pm$ SEM and descriptive data as mean $\pm$ SD (Table 1). Shapiro–Wilks test revealed that data were normally distributed. Preintervention differences between groups were studied using *t* test for independent samples. To evaluate the effects of the interventions a two-way (Group $\times$ Time) mixed-model analysis of variance was used using sex and age as covariant. When an interaction existed, Bonferroni post-hoc test was performed to identify the time point in which treatments significantly differed.

TABLE 1. Participant characteristics prior to interventions

	TRAIN, N = 23	CONT, N = 26	P value
Women, (%)	14%	14%	–
Age	53 ± 9	55 ± 6	0.141
Weight (kg)	95.8 ± 13.4	92.6 ± 13.0	0.519
BMI (kg/m ²)	33.0 ± 3.8	32.2 ± 3.72	0.554
MetS factors (number)	3.81 ± 0.75	3.56 ± 0.93	0.301
Medication (user in %)			Chi square value
Antihypertensive	57%	51%	0.874
Cholesterol lowering	24%	21%	0.512
Triglyceride lowering	10%	15%	0.351
Glucose lowering	19%	23%	0.668
1 medication	33%	35%	0.414
2 medications	24%	22%	0.552
3 medications	10%	9%	0.235

Data presented as mean ± SD. CONT, control group; MetS, metabolic syndrome; TRAIN, training group.

Effect size is presented based on the following criteria; more than 0.70 large effect; 0.30–0.69 moderate effect; 0.30 or less small effect. SPSS v22 (IBM Corporation, Armonk, New York, USA) was used for statistical analysis with statistical significance set at $P \leq 0.05$ or less.

RESULTS

Control group response

In the CONT, there was no differences within each year between tests performed in November and mid-March. The tendency for MetS components was to be maintained or to worsen over the 3-year follow-up. SBP and DBP remained at the same values between year 1 and year 3 (135.6 ± 2.4 vs. 134.8 ± 1.4 mmHg, effect size = 0.07 and 81.6 ± 1.7 vs. 81.2 ± 1.2 mmHg, effect size = 0.05, respectively; all $P = 1.00$; Fig. 2a and b). Blood glucose triglyceride concentrations and waist circumference tended to increase from years 1 to 3 (126.8 ± 5.7 to 136.7 ± 6.9 mg/dl, effect size = 0.29; 169.3 ± 13.7 to 204.1 ± 22.5 mg/dl, effect size = 0.36 and 108.5 ± 1.5 to 109.7 ± 1.4 cm, effect size = 0.15, respectively; all $P > 0.05$; Fig. 2c, d and f). These increases were not enough to increase MetS Z-score (Fig. 3b). Cholesterol and BMI maintained their values from years 1 to 3 (Table 2). However, the 10-year ASCVD risk score increased in year 3 above year 2 (effect size = 0.28; $P = 0.04$; Fig. 3a).

Training group responses

SBP and DBP were both significantly reduced after the first exercise program (Fig. 2a and b). Even after 7.5 months of detraining (months 12 and 24), SBP and DBP before exercise-training were lower in years 2 and 3 than in year 1 (139.2 ± 3.3 to 130.6 ± 3.4 to 128.4 ± 3.0 and 85.1 ± 2.1 to 79.8 ± 2.2 to 77.3 ± 1.5 mmHg, respectively; all $P < 0.01$; Fig. 2a and b). Glucose was reduced with training in the first year but relapse to levels of pretraining and was maintained at similar levels during the 3 years (114.0 ± 3.7 to 112.1 ± 4.4 mg/dl, effect size = 0.10; $P = 1.00$, years 1–3; Fig. 2c). Waist circumference (Fig. 2f), BMI and body weight (Table 2) decline significantly after the first year of training and less with successive training in years 2 and 3.

Triglycerides and cholesterol (total; HDL-c and LDL-c) were not affected by training remained similar in years 1 and 3 (Fig. 2d and e, and Table 2). After the first training program (month 4) ASCVD risk score decreased, but it relapsed with detraining to pretraining values and that level was maintained during years 2 and 3 (Fig. 3a). Training lowered Z-scores every year, but levels returned to preexercise levels with detraining in years 1 and 2. However, before the onset of training in year 3 (month 24) values remained lower than at the same time in year 2 (0.56 ± 0.10 vs. 0.29 ± 0.11 , effect size = 0.55; $P = 0.11$; Fig. 3b). This difference from year 2 was expanded at the end of training (month 28; $P < 0.05$).

Comparison between training and control groups

At the beginning of year 1, there were not differences between TRAIN and CONT in SBP, DBP (139.2 ± 3.3 vs. 135.6 ± 2.4 mmHg, effect size = 0.25; 85.1 ± 2.1 vs. 81.6 ± 1.7 mmHg, effect size = 0.36), blood glucose (114.0 ± 3.7 vs. 126.8 ± 5.7 mg/dl, effect size = 0.54), triglycerides (116.6 ± 8.9 vs. 169.3 ± 13.7 mg/dl, effect size = 0.94), HDL-c (39.8 ± 2.4 vs. 47.5 ± 2.8 mg/dl, effect size = 0.61) and waist circumference (107.5 ± 1.7 vs. 108.5 ± 1.5 cm, effect size = 0.13; all $P > 0.05$; Fig. 2). After the first training program (month 4) there were reductions in SBP, blood glucose and waist circumference in the TRAIN that resulted in values significantly lower than in the CONT at that time point. HDL-c levels were higher in the CONT than in the TRAIN in year 2 (41.0 ± 2.7 vs. 49.8 ± 2.7 mg/dl; effect size = 0.67; $P < 0.05$; Fig. 2e). In addition, blood glucose and waist circumference were lower in TRAIN than CONT at the end of the second training program (month 16). At the end of year 3, TRAIN displayed significantly lower values than CONT in SBP, DBP, blood glucose and triglycerides (128.3 ± 3.0 vs. 134.8 ± 1.4 mmHg; effect size = 0.61; 70.3 ± 1.5 vs. 81.2 ± 1.2 mmHg; effect size = 0.60; 112.0 ± 4.4 vs. 136.7 ± 6.9 mg/dl, effect size = 0.88 and 126.6 ± 10.3 vs. 204.1 ± 22.4 mg/dl, effect size = 0.93, respectively; all $P < 0.05$; Fig. 2a–d). TRAIN was lower than CONT in Z-score as well (0.29 ± 0.11 vs. 0.65 ± 0.08 , effect size = 0.77; $P = 0.01$; Fig. 3b).

FIGURE 2 Metabolic syndrome components during 3 consecutive years of a 16-week program of aerobic interval training (training group; $N=23$) or sedentary lifestyle (control group; $N=26$). Data are mean $\pm$ SEM. *Significant difference between training and control groups at that time point ($P < 0.05$). **Significant different from year 1 within each group ($P < 0.05$). ***Significant different from year 2 within each group ($P < 0.05$). ****Significant Baseline vs. 16-week in that intervention year ($P < 0.05$).

DISCUSSION

We conducted this study to determine which training health adaptations attained by a 16-week training program persist upon 7.5 months of detraining and if yearly exercise training is needed to consolidate transient improvements in BP and other health-related variables into durable health adaptations. We chose to study a population of middle-age (54 ± 8 years) abdominally obese individuals, all with three or more criteria of MetS because of their elevated risk of suffering cardiovascular [24] and metabolic diseases [18] and because of their high prevalence of hypertension [2]. Our first observation is that MetS patients not following exercise training (i.e. CONT) increase the estimated 10-year ASCVD risk (effect size = 0.28; $P = 0.043$; Fig. 3a). This deterioration took place despite being under medical supervision following the latest guidelines for pharmacological management of MetS [25]. This underlines the clinical importance of providing supervised exercise training to this population to reduce their progression in the risk of suffering CVDs.

MetS Z-score summarizes in one number the extent of the deviation from a healthy value of the five MetS components. The positive short-term effects of an exercise training program on MetS Z-score had been previously reported [3,26,27]. However, to our knowledge, this is the first study to seek for the chronic effect of exercise training on MetS Z-score. We found that two yearly 16-week intense aerobic exercise programs were required for MetS Z-score to be chronically reduced (effect size = 0.57; $P = 0.038$; Fig. 3b). We deem this reduction as chronic because despite that 7.5 months of detraining elapsed between the end of training in year 2 and the beginning of training in year 3, Z-score remained at the level of the end of exercise (month 16; Fig. 3b). MetS Z-score before training in year 3, was reduced by 55% from the onset of the study, which likely constitutes a relevant health improvement in the TRAIN. In fact, an epidemiological study, gathering data from more than 3500 MetS individuals reveals a high association between MetS Z-score and the risk of suffering, type 2 diabetes, myocardial infarction, cardiovascular and all-cause death [17].

FIGURE 3 (a) Predicted 10-year atherosclerotic cardiovascular disease risk, and (b) metabolic syndrome Z-score during 3 consecutive years of a 16-week program of aerobic interval training (training group; $N=23$) or sedentary lifestyle (control group; $N=26$). Data are mean $\pm$ SEM. *Significant difference between training and control groups at that time point ($P<0.05$). ** Significant different from year 1 within each group ($P<0.05$). ***Significant different from year 2 within each group ($P<0.05$). ****Significant Baseline vs. 16-week in that intervention year ($P<0.05$).

The contribution of each MetS components to the improvement in MetS Z-score vary with studies. For instance, Bateman *et al.* [26] (i.e. STRRIDE study) found reductions in triglycerides, waist circumference and BP when combining aerobic and resistance training. In contrast, cross-sectional data from the Aerobics Center

Longitudinal Study (ACLS at Cooper Clinic) show reductions in all but blood glucose and SBP despite increases in individual cardiorespiratory level [28]. In our data, pivotal to the chronic reduction in MetS Z-score was the sharp drop in SBP and DBP after the first training program, and the fact that pressures did not completely relapse back to the initial levels after detraining (Fig. 2a and b). In addition, there was a maintenance in blood glucose and waist circumference that seems more relevant when observing that those tended to increase in the sedentary CONT (Fig. 2c–f). Thus, the reduction in Z-score before training started in year 3, was led by the decreased BP with contributions of blood glucose and waist circumference.

A portion of the improvements in MetS Z-score in TRAIN could be derived from the progressive loss of body weight during the consecutive yearly exercise-programs (Table 2). It is well established that diet-induced body weight loss reduces resting BP in MetS patients [29,30]. However, we and others reported that exercise training have a significant BP lowering effect despite minor body weight loss (1.3–2 kg; [4,5]). Nonetheless, simultaneous [31] or sequential [3] combination of exercise training and weight loss results in larger or longer-maintained reductions in SBP than when applying exercise alone. Being aware of the likely effect of body weight on BP, we closely matched the CONT and TRAIN in body weight, BMI (Table 2) and waist circumference (Fig. 2f), so that any of the effects observed could be related only to the yearly exercise treatment. However, the TRAIN reduced their body weight and BMI significantly in year 1 (Table 2). This may have influenced the sharp lowering of BP after treatment in year 1 that resulted in the reduction in MetS Z-score. However, the reduction in body weight in TRAIN ($\sim 3\%$) seems an effect intrinsic to the exercise program not a result of dieting, as caloric intake did not change according to their dietary log analysis.

We observed that 3 years of repeated exercise exposure prevented the increase in the Framingham-predicted 10-year ASCVD risk index [23] that, however, rose in the CONT patients. Like the MetS Z-score, the Framingham CVD risk score is a composite index for people between 30–74 years old that includes as predictors, blood lipids (cholesterol and HDL-c), SBP, age, sex, smoking, diabetes, and treatment for hypertension. It has some common components with MetS Z-score, though it does rely more

TABLE 2. Blood lipids, body weight and BMI in the training and control groups during 3 consecutive years of 16-weeks follow-up testing

	Year 1		Year 2		Year 3	
	Baseline	16 weeks	Baseline	16 weeks	Baseline	16 weeks
CONT						
Total cholesterol (mg/dl)	185.2 $\pm$ 6.4	184.5 $\pm$ 6.5	196.6 $\pm$ 8.7	196.6 $\pm$ 8.7	188.3 $\pm$ 6.9	188.3 $\pm$ 6.9
LDL-c (mg/dl)	106.9 $\pm$ 7.0	106.9 $\pm$ 6.9	111.6 $\pm$ 8.0	111.6 $\pm$ 8.0	106.2 $\pm$ 7.0	106.2 $\pm$ 7.1
Body weight (kg)	92.5 $\pm$ 2.4	92.5 $\pm$ 2.4	93.6 $\pm$ 2.5	93.6 $\pm$ 2.5	94.3 $\pm$ 2.3	94.3 $\pm$ 2.5
BMI (kg/m ²)	32.3 $\pm$ 0.7	32.4 $\pm$ 0.7	32.7 $\pm$ 0.7	32.8 $\pm$ 0.7	32.9 $\pm$ 0.7	33.0 $\pm$ 0.7
TRAIN						
Total cholesterol (mg/dl)	193.3 $\pm$ 6.7	196.1 $\pm$ 6.5	197.5 $\pm$ 7.6	182.3 $\pm$ 7.1 ^a	191.0 $\pm$ 7.5	190.3 $\pm$ 7.1
LDL-c (mg/dl)	130.2 $\pm$ 5.7*	133.7 $\pm$ 5.9*	127.9 $\pm$ 6.2	114.9 $\pm$ 6.2 ^a	123.0 $\pm$ 6.3	122.2 $\pm$ 5.2
Body weight (kg)	95.0 $\pm$ 2.9	92.6 $\pm$ 2.5 ^a	93.2 $\pm$ 2.6	92.3 $\pm$ 2.4	92.7 $\pm$ 2.4	91.7 $\pm$ 2.6
BMI (kg/m ²)	32.9 $\pm$ 0.8	32.1 $\pm$ 0.7 ^a	32.3 $\pm$ 0.7	32.0 $\pm$ 0.7	32.1 $\pm$ 0.8	31.8 $\pm$ 0.8

Data are presented as mean $\pm$ SEM for 49 metabolic syndrome patients divided into the TRAIN and control groups. CONT, control group; LDL-c, LDL cholesterol; TRAIN, training group.

^aSignificantly different from baseline in that year.

*Significant different from control group at that time point ($P<0.05$).

heavily on cholesterol, whereas it does not account for disarrangements in glucose metabolism. Although when comparing at 3 years, there were no statistical differences between CONT and TRAIN, it was evident that exercise training restrained the increase in the 10-year ASCVD risk index observed in their sedentary counterparts (i.e. CONT).

In addition to BP, other health parameters responded in a larger magnitude to the same dose of training during the first year of exposure to training. This seemed to be the case for blood glucose and waist circumference (Fig. 2c and f). Likewise, the largest reduction in body weight and BMI occurred the first year of training (Table 2). In contrast, blood lipid profile did not respond to training with unchanged blood triglycerides, HDL-c (Fig. 2d and e) or LDL-c and TC (Table 2). Nevertheless, although TC remained unchanged with TRAIN, there was a trend for HDL-c to increase (Fig. 2d), whereas LDL-c decreased (Table 2) with training from 1 to 3 years. Thus, using an atherosclerotic index (i.e. HDL-c/TC or LDL-c/HDL-c) the effects of exercise were evidently positive with TRAIN.

This 3-year intervention longitudinal study in diagnosed MetS patients, has some limitations. A similar percentage of the patients in each group were taking medication being the most prevalent antihypertensive, followed by statins and hypoglycemic agents with a few taking medication to lower blood triglycerides (Table 1). To study the pure effect of exercise training ideally all patients should have suppressed medication during the study. However, our ethical committee deemed inappropriate to withhold antihypertensive and other medication during the study in patients with increased CVD risk. It is currently unclear if exercise training lowers BP through mechanisms different to medication, so a possible interaction between medication and exercise training could have existed in our data resulting in an overestimation of the effects of exercise in the TRAIN. Physicians rarely adjust or withhold medication when MetS patients start an exercise program. So, we support that our experimental situation better resembles their clinical situation.

In summary, we studied if repeated exposure to an exercise training dose is needed to consolidate transient improvements in health parameters into durable health adaptations in MetS patients. We found that indeed at least two yearly intense aerobic training programs are required to chronically improve MetS Z-score. The chronic effect was mediated mostly by BP that does not fully return to pre-training values with detraining, accounting for the cumulative improvement. On the other hand, 3 years of sedentarism in MetS patients worsens their ASCVD risk despite being medicated. Our results strongly argue for inclusion of at least 4 month per year of intense exercise training program into the therapy to treat MetS.

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Conflicts of interest

There are no conflicts of interest.

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Reviewers' Summary Evaluations**Reviewer 1**

This study shows that several, short-term yearly exercise-training programs are capable of consolidating transient improvements in health parameters into durable health adaptations (i.e., improvement in Z score) in patients with metabolic syndrome. The paper brings to the attention the problem that several factors (low initial fitness levels, low motivation/commitment, seasonal holidays, travel, etc.) may preclude training continuity all life long. This applies to several chronic diseases, and not only metabolic syndrome, which would benefit from regular exercise training.

Hence, the finding that some benefits of exercise are maintained even after shorter, more feasible, yet yearly, training periods would represent an important advancement.

Reviewer 2

The strength of the study is the design with 4 months exercise training each year during a three consecutive years and comparison with a matched sedentary group. The effect was a lower blood pressure in the trained group. This effect would have been more convincing, if 24-h blood pressure had been measured after each of the training periods.