



## Preventing metabolic syndrome in morbid obesity with resistance training: Reporting interindividual variability

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### KEYWORDS

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**Abstract** *Background and aims:* Resistant training (RT) improves health markers in obesity, but its effects in morbid obesity are unknown. We aimed to determine the effects of a RT-program in preventing/attenuating the metabolic syndrome (MetS) in patients with morbid obesity. A second aim was to report the interindividual variability in terms of improvements in MetS markers and other related co-variables.

*Methods and results:* Twenty-one adults with obesity or morbid obesity were divided into two groups based on body mass index (BMI): a control obesity (CO,  $n = 7$ ,  $BMI \geq 35 < 40.0 \text{ kg/m}^2$ ) and a morbid obese group (MO,  $n = 14$ ,  $BMI \geq 40 \text{ kg/m}^2$ ). Participants completed a 20-week RT-program (3 sessions/week, 4–8 exercise) using free weights. Participants were assessed for MetS markers (waist circumference, systolic and diastolic blood pressure [BP], fasting glucose, high-density lipoproteins, and triglycerides) and other co-variables (total cholesterol, low-density lipoprotein, one-maximum repetition of biceps curl, and handgrip strength, 6 min walking test). Significant reductions in MetS markers were observed in both CO and MO groups ( $P < 0.05$  to  $P < 0.0001$ ), but significant reductions in diastolic BP and increases in HDL-C were noted only in the MO group ( $P < 0.0001$ ). Changes in waist circumference, and systolic and diastolic BP were significantly greater only in the MO group ( $P < 0.001$ ), but the CO group presented a greater fasting glucose decreases ( $P < 0.0001$ ). The prevalence of non-responders between CO and MO groups was similar in the MetS outcomes.

*Conclusions:* RT promotes greater improvements in overall MetS outcomes waist circumference, BP, and plasma triglycerides in patients with morbid obesity than in obese peers, with no overall differences in the prevalence of non-responders.

*Clinical trial number:* NCT03921853 at [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

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## Introduction

The prevalence of metabolic syndrome (MetS) and cardiovascular disease is expected to rise with the global obesity epidemic [33]. MetS is a cluster of clinical risk factors including abdominal (visceral) obesity, hypertension, elevated serum triglycerides, low serum high-density lipoprotein (HDL) and hyperglycemia [1]. MetS is also associated with a pro-inflammatory state that leads to an altered physiological balance of adipokines, insulin resistance, endothelial dysfunction and a pro-atherogenic profile [31], which overall markedly increases cardiovascular risk and mortality [26].

Morbid obesity is considered a chronic disease highly related to MetS development [6]. Indeed, MetS significantly decreases the life expectancy of individuals with morbid obesity [26], and increases the disease burden and the associated economic healthcare costs [19]. Furthermore, it has recently been reported that body mass index (BMI) and fat distribution have higher associations with inflammation, fat indices, and prevalence of MetS in morbidly obese subjects [18], highlighting the need for the early prevention of MetS in these individuals.

Exercise training (*i.e.*, any traditional endurance or resistant training applied progressively and sustained in the time) is known to be effective in inducing clinically significant weight loss and reducing cardiovascular risk [16], and is also associated with increased muscle mass, decreased body fat, and an improved metabolic profile [*e.g.*, glucose control and lipid levels] [21]. Additionally, exercise training in patients with MetS was also found to be associated with a significant reduction in high-sensitivity C reactive protein and insulin resistance, but was independent of weight loss [7], which is not necessary for improved health in morbidly obese patients. However, considering that cardiorespiratory fitness (CRF) is reported to be a strong predictor of overall health, exercise training may improve CRF in patients with MetS [13,36], and thus CRF-related outcomes such as walking performance can likely be relevant for the health of obese patients at risk of MetS. Additionally, resistance exercise training (RT, an exercise training modality consisting of stimulating muscles using external weights) may help to reduce some health markers such as systolic blood pressure (SBP) in obese patients with MetS risk factors [28]. Indeed, supervised RT improved muscle strength and functional capacity in patients with obesity undergoing bariatric surgery [24]. Nevertheless, whereas, RT has been widely studied in obesity [3], there has been little information on its effects on physical health outcomes in morbid obesity.

Data on the interindividual variability in response to exercise training, in terms of responders and non-responders, is limited in this cohort. However, with regards to overweight, we have shown that individuals with more baseline fat (overweight, obesity) show significant fat reduction with few non-responders [2,3], and we speculate that morbid obese patients have the potential to show greater reductions in both fat and MetS markers

than their peers with less fat. Thus, considering the scarcity of information on the prevention of MetS in morbidly obese patients, as well as the paucity of knowledge about interindividual variability for improving MetS outcomes, we sought to establish the effects of an RT program for preventing or attenuating MetS in patients with morbid obesity. A second aim was to report the interindividual variability in terms of improvements in MetS markers and other related co-variables.

## Methods

### Study design

In an experimental clinical trial, obese and morbid obese patients, who were candidates for bariatric surgery, were invited to participate in a lifestyle study comprising RT over a successive 20-week period. Participants were recruited from the morbid obesity organization "OBEMOB" (Temuco city, Chile), over two months by telephone invitation. The sample size was determined in accordance with the study's feasibility recruitment, and with a previous pilot study determining the effects of an RT program on anthropometric, cardiovascular, metabolic, endurance and muscle strength function in patients with morbid obesity [16]. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethical Committee of the Universidad de La Frontera, Temuco, Chile.

### Patients and recruitment

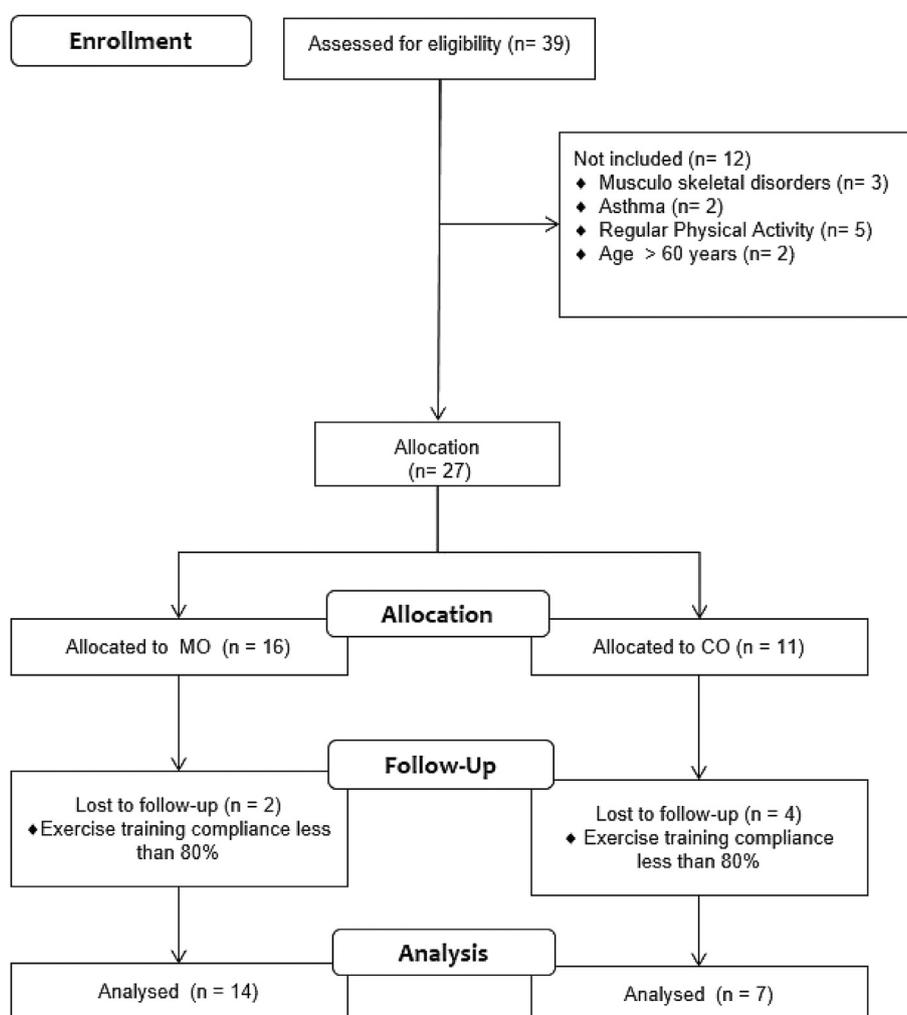
The inclusion criteria were as follows: i)  $>18$  and  $\leq 60$  years of age (65 years is the retirement age for women in Chile), ii) participation in daily activities including walking, physical autonomy, iii) medical authorization by a physician, and iv)  $\text{BMI} \geq 35 \text{ kg/m}^2$ , according to the following classification: class II obesity  $\text{BMI} \geq 35.0\text{--}39.9 \text{ kg/m}^2$ , class III morbid obesity  $\text{BMI} \geq 40 \text{ kg/m}^2$  [9,17]. Exclusion criteria were as follows; i) physical limitations (*e.g.*, restricting injuries of the musculoskeletal system, or dependent on a third person), ii) exercise-related dyspnoea or respiratory alterations, iii) chronic heart disease with any worsening in the last month, and iv) an adherence rate of less than 80% of the total intervention (excluded from the statistical analyses). From the thirty-nine participants ( $\text{♀} = 35$ ;  $\text{♂} = 4$ ) included in the first stage of enrolment, 12 individuals ( $\text{♀} = 12$ ) were excluded because of the exclusion criteria. Thus, twenty-seven participants were randomly allocated to one of the following groups: the group classified as obese (CO,  $n = 16$ ,  $\text{♀} = 14$ ) and the group classified as morbidly obese (MO,  $n = 16$ ,  $\text{♀} = 14$ ). However, during the intervention, four individuals in the CO group and two individuals in the MO group were excluded from the data analysis due to exercise training compliance less than 80%, as stated in the exclusion criteria. Thus, the remaining participants were included in the final analyses:

(CO,  $n = 7$ ; MO,  $n = 14$ ). The study design is described in Fig. 1.

### Resistance training intervention

The 20-week RT program comprised three weekly sessions, each lasting 1 h. All sessions started with a 10-minute warm-up period with continuous walking and joint mobility and flexibility exercises, followed by 5 min of cool-down and stretching, to prevent injuries. Sessions included 4 to 8 RT exercises targeting the following different muscle groups: 1. forearm, 2. knee flexors and 3. extensors, 3. trunk, 4. chest, 5. shoulder elevators, 6. horizontal shoulder flexors and 7. extensors, and 8. plantar flexors. The exercises for each muscle group were performed in 3 sets of as many repetitions (continuous concentric/eccentric voluntary contraction) as possible in 1 min followed by 2 min of passive recovery, as previously reported [5]. Before the RT

program, each participant was evaluated using the subjective modified Borg scale (1–10 points), in order to identify muscle exertion (*i.e.*, the load [kg]) in 1 min of exercise. The recovery period progressed from 2 min (week 1–4) to 1.5 min (week 5–10) maintained to week 20 of RT. The percentage one repetition maximum (1RM) of intensity developed by each exercise was progressively increased from 40 to 55–60%, according to the physiological adaptations of the participants every two weeks. Thus, participants always executed 1 min of exercise, repeated in 3 sets (*i.e.*, 3 min) per exercise, with rest periods. Thus, including warm-up, the 8 exercises, and the cool-down period, the session lasted 1 h. Exercises were performed using dumbbells (Salter, Madrid, Spain), free weights and metal bars, according to the adjustments each week in individual load for participants by exercise. The 1RM strength test intensity was between 20 and 40% of 1RM in a dumbbell test. The program description is described in Table 1.



**MO:** Morbid obesity group  
**CO:** Control obesity group

**Figure 1** Study design.

### Measurements of MetS markers

After 10–12 h of overnight fasting, all patients underwent a baseline assessment (pre-test) between 08:00 and 9:00 am, with measurement of the following variables related to the MetS: fasting glucose, lipid profile (*i.e.*, total cholesterol [TC], low-density lipoprotein-cholesterol [LDL-C], high-density lipoprotein-cholesterol [HDL-C], and triglycerides [TGs]). Additionally, systolic (SBP) and diastolic (DBP) blood pressure was measured on the same day, according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [15]. Waist circumference was assessed with a tape measure graduated in centimeters (Adult SECA™, Seca Corp. Hanover, MD) using a standard protocol [25]. The final (post) measurements were taken 72 h after the last exercise session, in the same order and with the same professional staff as in the baseline assessment.

### Anthropometric parameters

BMI was determined ( $\text{kg}/\text{m}^2$ ) using a calibrated scale for adults (220 kg) (TBS300, Tanita Corp., Tokyo, Japan). The scale was calibrated for each measure according to the manufacturer's instructions, and under standard criteria for the classification of obesity and morbid obesity [35].

### Endurance performance and muscle strength

The day after the metabolic measurements, the physical condition of the participants in both groups was measured by endurance and muscle strength testing. First, a 6-minute walk test (6MWT) was used to estimate CRF, as described previously [8]. The test was performed in a closed space on a flat surface (30-m long), with two reflective cones placed at the ends to indicate the distance. During the test, participants were assisted with instructions by an exercise physiologist.

Second, the maximum dynamic muscular strength was estimated indirectly through the Brzycki formula [11], with fewer than 12 maximum repetitions (1RM) of the bicep curl exercise (1RM<sub>BC</sub>) using a metal Z-style bar. Finally, the mean handgrip strength (HGS) was determined with a dynamometer (Baseline® Hydraulic Hand Dynamometers,

NextGen Ergonomics Inc., Quebec, Canada), according to standard procedures [30].

### Non-responder classification

Following the original studies of exercise interventions [10], the participants who failed to respond to exercise training were categorized as non-responders, and their prevalence was calculated using the typical error (TE) measurement by the following equation:

$$TE = SD_{diff} / \sqrt{2}$$

where  $SD_{diff}$  is the variance (standard deviation) in the difference scores observed between the 2 repeats of each test. A non-responder was defined as someone who failed to demonstrate an increase or decrease (in favour of beneficial changes) that was greater than 2 times the TE from zero. This mean that responders were located after the 2 TE to body mass, waist circumference, SBP/DBP, fasting glucose, and triglycerides, and a non-responder was into this range. By contrast, in HDL-C a non-responder was that participant who decreased more than 2 TE. Thus, a change greater than 2 times the TE in favour of beneficial effects (*i.e.*, responders) indicates a high probability (*i.e.*, 12 to 1 odds) that this response is a true physiological adaptation beyond what might be expected from technical or biological variability. Following this, the TE calculated were as follows according with the main outcomes (body mass 2xTE 6.9 kg, waist circumference 2xTE = 2.0 cm, SBP/DBP 2xTE = 8.0/4.9 mmHg, fasting glucose 2xTE = 7.0 mg/dL, HDL-C 2xTE = 5.0 mg/dL, TG 2xTE = 24.6 mg/dL).

### Data analysis

Data are presented as the mean (95% confidence interval [CI]) in Table 1 and as the mean  $\pm$  SEM in the figures. Normality and homoscedasticity assumptions for all data were analysed using the Shapiro–Wilk test and Levene's test, respectively. Student's *t* test was used to identify differences at baseline. We also calculated the delta change of each outcome and compared the adaptations between both groups. A repeated measures two-way (group, time) analysis of variance was applied to assess the occurrence

**Table 1** Characteristics of resistant training program.

Weeks	Intensity (%1RM)	Reps	Sets (min)	Sets	Rest (min)	Exercises	Warm-up (min)	Cool down (min)	Duration (min)
1–2	40	20–25	1	3	2.0	4	10	5	60
3–4	40–50	25–30	1	3	2.0	5	10	5	60
5–6	45–50	30	1	3	1.5	5	10	5	60
7–8	45–50	30–35	1	3	1.5	5	10	5	60
9–10	50–55	25–30	1	3	1.5	6	10	5	60
11–12	50–55	25–30	1	3	1.5	6	10	5	60
13–14	50–55	30	1	3	1.0	6	10	5	60
15–16	50–55	30–35	1	3	1.0	6	10	5	60
17–18	55	30–35	1	3	1.0	7	10	5	60
19–20	55–60	30–35	1	3	1.0	8	10	5	60

(%1RM) percentage of the one maximum repetition strength test.

of an actual training effect (*i.e.*,  $P < 0.05$  for the interaction [group  $\times$  time] for the different study outcomes). Student's *t* test was applied for each delta comparison. Additionally, Cohen's *d* test was used to detect effect size, using the threshold values of  $\leq 0.49$ , 0.50 to 0.79, and  $\geq 0.80$  for small, moderate, and large effects, respectively [23], with 95% CIs. All statistical analyses were performed with SPSS statistical software version 18 (SPSS™ Inc., Chicago, IL). The alpha level was set at  $P < 0.05$  for statistical significance.

## Results

### Baseline characteristics

At baseline (Table 2 and Figs. 2–4), no differences were found between the CO and MO groups in height, cardiometabolic risk outcomes, HGS or endurance

performance, although subjects in the CO group were significantly older than those in the MO group (47.2 years [95% CI; 32.3, 62.2] and 37.3 years [95% CI; 30.5, 44.1], respectively) ( $P < 0.0001$ ). As expected, body mass was significantly lower in the CO group than in the MO group ( $99.1 \pm 7.6$  vs.  $123.4 \pm 22.8$  kg), as was waist circumference ( $116.9 \pm 5.2$  vs.  $135.9 \pm 15.4$  cm) and BMI ( $37.0 \pm 2.1$  vs.  $46.5 \pm 6.3$  kg/m<sup>2</sup>) ( $P < 0.05$ ). There was significant training-induced effects after intervention in BMI comparing the MO vs. CO group at  $P < 0.0001$ . In addition, the MO group presented significantly greater 1RM<sub>BC</sub> values than the CO group ( $26.0 \pm 8.8$  kg vs.  $19.6 \pm 6.6$  kg).

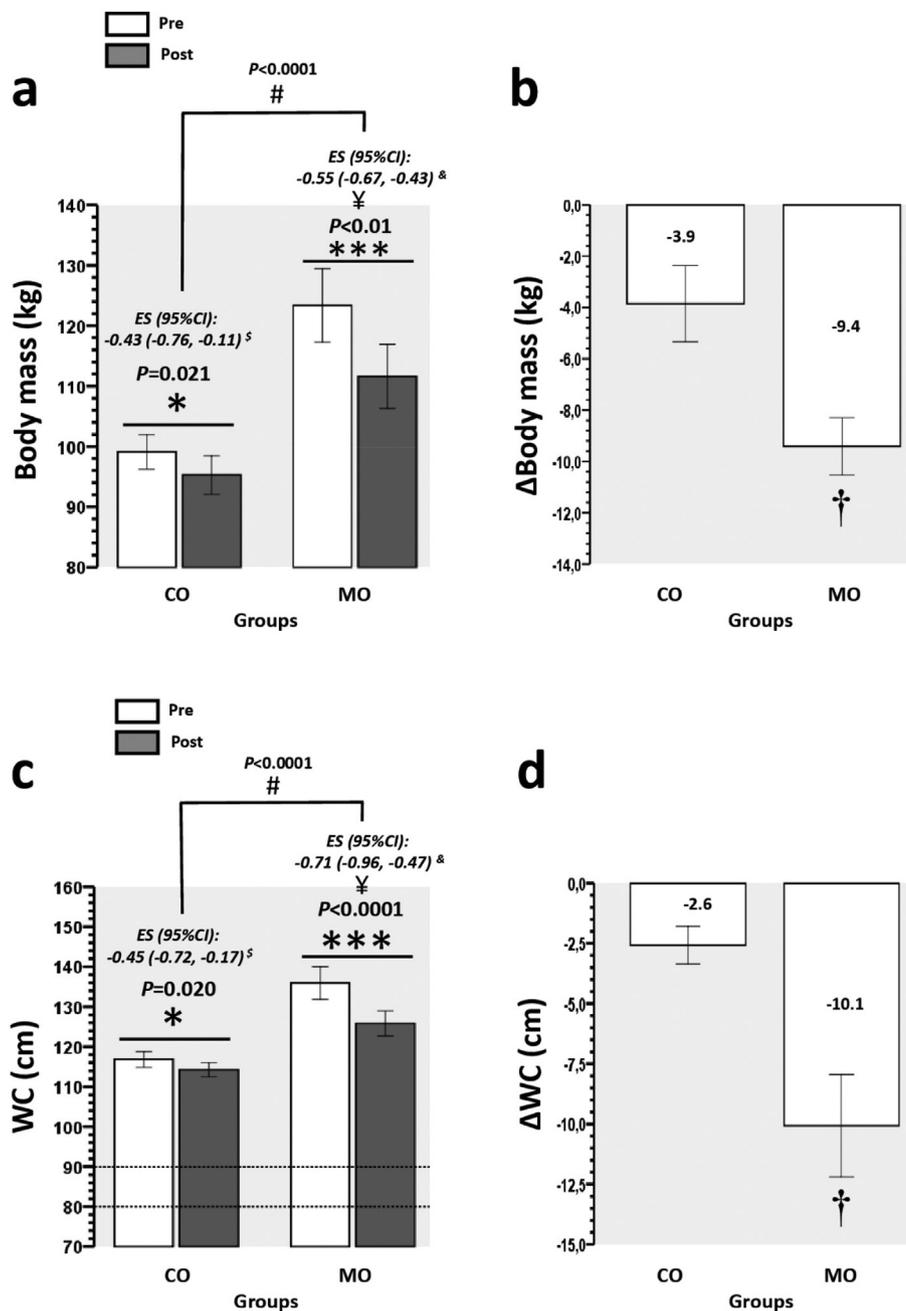
### Anthropometric measurements

Anthropometric outcomes are shown in Fig. 2 (panels a–d). Body mass was significantly reduced both in the CO

**Table 2** Baseline characteristics of the participants.

	Time	CO ( <i>N</i> = 7) Mean (95%CI)	MO ( <i>N</i> = 14) Mean (95%CI)	CO vs. MO† Baseline	ΔCO vs. ΔMO†
<b>Anthropometric</b>					
Age (y)	Pre	47.2 (32.3, 62.2)	37.3 (30.5, 44.1)	$P < 0.0001$	
Height (m)	Pre	1.63 (1.59, 1.67)	1.62 (1.58, 1.66)	$P = 0.511$	
Body mass index (kg/m <sup>2</sup> )	Pre	37.0 (35.0, 38.9)	46.5 (42.9, 50.2)	$P = 0.017$	
	Post	35.6 (32.9, 38.3)	42.3 (39.1, 45.4) <sup>####</sup>		
	<i>P</i> value	$P = 0.056$	$P < 0.0001$		
ΔBMI		−1.4 (−2.6, −0.1)	−4.2 (−5.4, −3.1)		$P < 0.0001$
	ES (95%CI)	−0.48 (−0.85, −0.12) <sup>\$</sup>	−0.70 (−0.85, −0.55) <sup>&amp;</sup>		
<b>Metabolic</b>					
Total cholesterol (mg/dL)	Pre	225.7 (169.8, 281.5)	197.1 (168.2, 226.0)	$P = 0.219$	$P = 0.271$
	Post	213.1 (167.4, 258.7)	189.5 (165.4, 213.6)		
	<i>P</i> value	$P = 0.380$	$P = 0.453$		
ΔTC		−12.5 (−38.2, 13.0)	−7.5 (−31.0, 15.8)		$P = 0.271$
	ES (95%CI)	−0.16 (−0.41, 0.09) <sup>\$</sup>	−0.12 (−0.52, 0.28) <sup>\$</sup>		
Low-density lipoproteins (mg/dL)	Pre	111.7 (81.2, 142.2)	122.5 (99.4, 145.6)	$P = 0.611$	
	Post	106.2 (68.0, 144.4)	114.6 (95.8, 133.4)		
	<i>P</i> value	$P = 0.593$	$P = 0.276$		
ΔLDL-C		−5.4 (−24.5, 13.6)	−7.9 (−24.4, 8.6)		$P = 0.210$
	ES (95%CI)	−0.16 (−0.51, 0.19) <sup>\$</sup>	−0.13 (−0.49, 0.22) <sup>\$</sup>		
<b>Endurance performance</b>					
6MWT (m)	Pre	555.0 (502.4, 607.5)	565.0 (535.0, 595.0)	$P = 0.781$	
	Post	645.7 (540.7, 750.7) <sup>**</sup>	620.8 (591.2, 650.4) <sup>***</sup>		
	<i>P</i> value	$P < 0.001$	$P < 0.0001$		
Δ6Mwt		+90.7 (6.3, 175.0)	+55.8 (40.8, 70.8)		$P = 0.166$
	ES (95%CI)	0.88 (0.24, 1.52) <sup>¥</sup>	1.00 (0.77, 1.23) <sup>¥</sup>		
<b>Muscle strength</b>					
1RM <sub>BC</sub> (kg)	Pre	19.5 (13.4, 25.6)	26.0 (20.9, 31.0)	$P < 0.033$	
	Post	24.7 (15.7, 33.7) <sup>*</sup>	29.2 (25.5, 32.8)		
	<i>P</i> value	$P = 0.020$	$P = 0.036$		
Δ1RM <sub>BC</sub>		+5.1 (0.6, 9.6)	+3.2 (−3.0, 9.5)		$P = 0.391$
	ES (95%CI)	0.52 (0.24, 0.80) <sup>&amp;</sup>	0.50 (−0.09, 1.10) <sup>&amp;</sup>		
Mean HGS (kg)	Pre	37.1 (26.4, 47.8)	38.8 (29.9, 48.6)	$P = 0.391$	
	Post	41.8 (27.1, 56.5) <sup>*</sup>	36.5 (28.0, 44.9)		
	<i>P</i> value	$P = 0.021$	$P = 0.457$		
ΔHGS		+4.7 (−1.4, 10.8)	−2.3 (−10.0, 5.3)		$P = 0.121$
	ES (95%CI)	0.24 (0.01, 0.48) <sup>\$</sup>	−0.06 (−0.40, 0.28) <sup>\$</sup>		

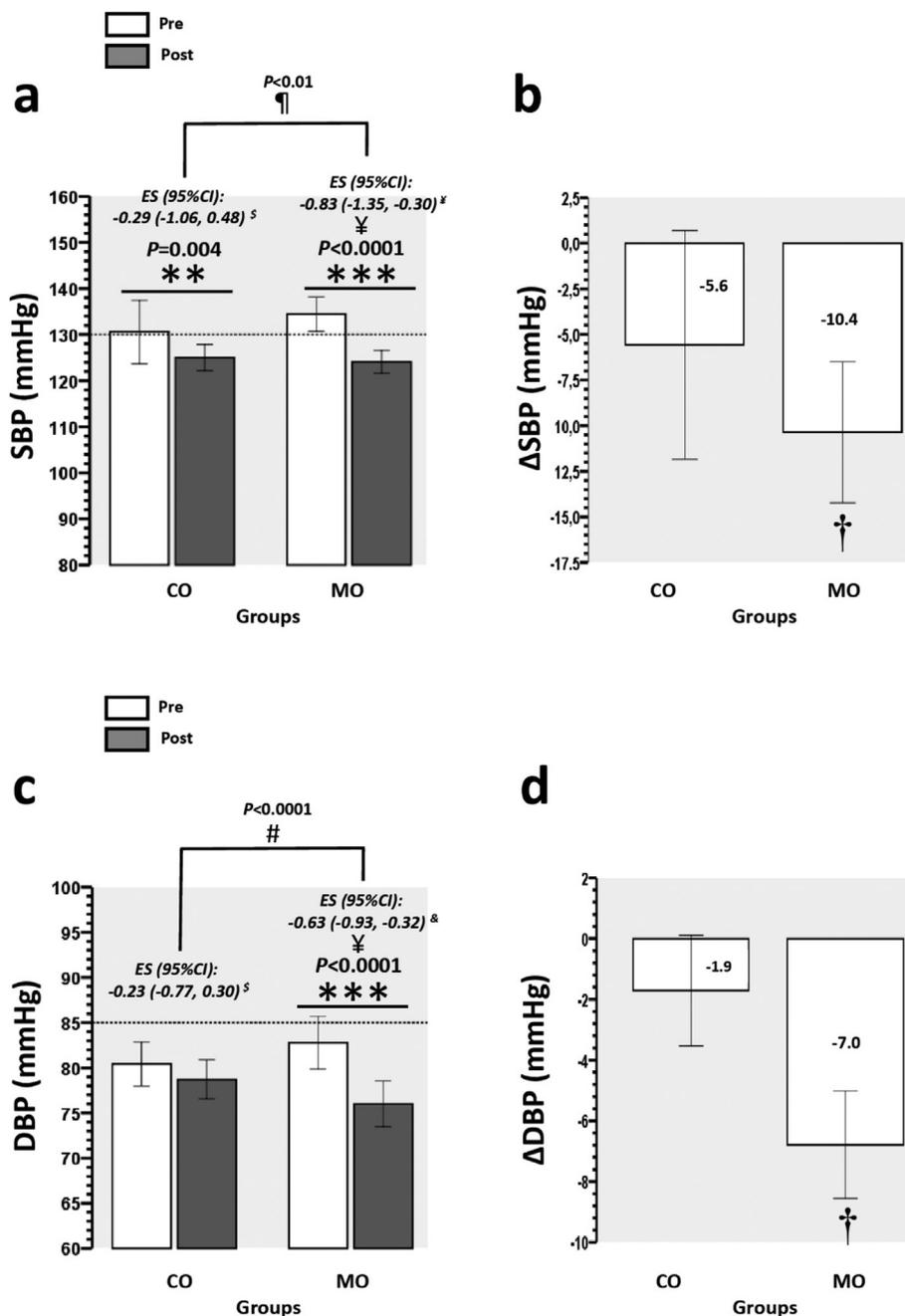
Data are presented in mean and (95%CI). Groups are described as (CO) Control obese group and (MO) Morbid obese group. (6MWT) Six minutes walking test. (1RM<sub>BC</sub>) One maximum repetition strength test of biceps curl. (HGS) Handgrip muscle strength in mean of both arms. (\*) Denotes significant pre-post differences at  $P \leq 0.05$ . (\*\*) Denotes significant pre-post differences at  $P \leq 0.001$ . (\*\*\*) Denotes significant pre-post differences at  $P \leq 0.0001$  by 2-way ANOVA analyses. (#) Denotes interaction groups  $\times$  time statistically significant at  $P < 0.0001$ . (†) Delta changes are compared by Student *t* test. (ES) Cohen *d* Effect size. (\$) Denotes small [ $\leq 0.49$ ] effect size, (&) Denotes medium [0.50 to 0.79] effect size, and (¥) Denotes large statistical [ $\geq 0.80$ ] effect size.



**Figure 2** Body mass and waist circumference pre-post (a and c), and delta changes (b and d) in control obese and morbid obese patients participants of a 20-week resistance training program. Groups are presented as (CO) control obese group, (MO) morbid obese group. (WC) Waist circumference. (\*) Denotes significant pre-post differences at  $P \leq 0.0001$ . (\*\*\*) Denotes significant pre-post differences at  $P \leq 0.0001$ . (#) Denotes interaction groups x time statistically significant at  $P < 0.05$ . (ES) Cohen *d* effect size. (\$) Denotes small [ $\leq 0.49$ ] effect size, (&) Denotes medium [0.50 to 0.79] effect size. (†) Denotes significant differences vs. CO group at  $P < 0.001$ .

(99.1 ± 7.6 vs. 95.3 ± 8.5 kg,  $P < 0.05$ ) and the MO (123.4 ± 22.8 vs. 111.6 ± 19.9 kg,  $P < 0.0001$ ) group after the intervention. There was a major statistical training-induced effects in body mass in the MO group Fig. 2 (panel a). There was a significant training-induced effects in body mass between MO vs. CO group after intervention at  $P < 0.0001$ . Body mass decrease was significantly greater in the MO group than in the CO group when expressed as a delta value ( $\Delta$ Body mass -9.4 kg in the MO group and

-3.9 kg in the CO group,  $P < 0.001$ ). Similarly, waist circumference was significantly reduced in CO (116.9 ± 5.2 vs. 114.3 ± 4.8 cm,  $P < 0.05$ ) and MO (135.9 ± 15.4 vs. 125.9 ± 11.8 cm,  $P < 0.0001$ ) groups. There was a major statistical training-induced effects in waist circumference in the MO group at  $P < 0.0001$ , with additionally greater delta changes observed in the MO group ( $\Delta$ WC -10.1 vs. 2.6 cm, in the MO group and the CO group, respectively,  $P < 0.001$ ), Fig. 2 (panel c and d) respectively.



**Figure 3** Systolic and diastolic BP pre-post (a and c), and delta changes (b and d) in control obese and morbid obese patients participants of a 20-week resistance training program. Groups are presented as (CO) control obese group, (MO) morbid obese group. (SBP) Systolic blood pressure, (DBP) diastolic blood pressure. (\*) Denotes significant pre-post differences at  $P \leq 0.05$ . (\*\*\*) Denotes significant pre-post differences at  $P \leq 0.0001$ . (#, ¶) Denotes interaction groups x time statistically significant at  $P < 0.0001$  and  $P < 0.01$  respectively. (ES) Cohen  $d$  effect size. (\$) Denotes small [ $\leq 0.49$ ] effect size, (&) Denotes medium [0.50 to 0.79] effect size, and (¥) Denotes large statistical [ $\geq 0.80$ ] effect size. (†) Denotes significant differences vs. CO group at  $P < 0.001$ .

### Determinants of MetS

Blood pressure results are shown in Fig. 3 (panels a–d). Both groups showed a significant decrease in SBP (CO:  $130.6 \pm 18.1$  vs.  $125.0 \pm 7.5$  mmHg,  $P < 0.01$  and MO:  $134.4 \pm 13.9$  vs.  $124.1 \pm 9.4$  mmHg,  $P < 0.0001$ ) after the RT program. There was a major statistical training-induced effects in SBP in the MO group at  $P < 0.01$ , Fig. 3 (panel a) and this effect was significantly greater in the MO group

than in the CO group by the delta changes ( $\Delta$ SBP 10.4 vs. 5.6 mmHg, respectively,  $P < 0.001$ ), Fig. 3 (panel b). DBP decreased only in the MO group ( $82.8 \pm 11.0$  vs.  $76.0 \pm 9.5$  mmHg,  $P < 0.0001$ ). There was a major statistical training-induced effects in DBP in the MO group at  $P < 0.0001$ , Fig. 3 (panel c). By delta changes, there were superior effects in DBP in MO group ( $\Delta$ DBP 7.0 vs. 1.9 mmHg to MO and CO group, respectively,  $P < 0.001$ ), Fig. 3 (panel d). Fasting blood glucose was also significantly

decreased following the training program in both groups (CO:  $106.1 \pm 16.1$  vs.  $96.9 \pm 9.9$  mg/dL;  $P < 0.0001$  and MO:  $105.4 \pm 19.2$  vs.  $101.3 \pm 16.8$  mg/dL;  $P < 0.001$ ) (Fig. 4, panel a). There was a major statistical training-induced effects in fasting glucose between MO vs. CO group at  $P = 0.021$ , Fig. 4 (panel a) and the reduction by delta changes was greater in the CO group ( $\Delta$ FGL  $9.3$  vs.  $4.1$  mg/dL,  $P < 0.001$ , Fig. 4, panel b). Regarding HDL-C, there was a significant increase only in the MO group comparing pre vs. post test ( $43.3 \pm 9.4$  vs.  $44.4 \pm 9.7$  mg/dL,  $P < 0.05$ , Fig. 4, panel c), whereas the delta changes were not significantly different between the groups (Fig. 4, panel d). In addition, both the CO ( $148.6 \pm 45.3$  vs.  $132.9 \pm 44.1$  mg/dL) and the MO ( $141.9 \pm 53.6$  vs.  $113.1 \pm 42.5$  mg/dL) group showed significant decreases in triglycerides at  $P < 0.0001$ , Fig. 4 (panel e). There was a major statistical training-induced effects in triglycerides in the MO vs. CO group at  $P < 0.0001$ , Fig. 4 (panel e) with a greater effect by delta changes observed in the MO group ( $\Delta$ TG  $-28.9$  vs.  $-15.7$  mg/dL,  $P < 0.001$ , Fig. 4 (panel f). No significant changes were observed in total cholesterol or LDL-C in either group (Table 2).

### Endurance performance and muscle strength

Data on endurance performance and muscle strength are shown in Table 2. Endurance performance, determined by the distance walked during the 6MWT significantly improved in both groups (CO:  $555 \pm 57$  m vs.  $646 \pm 114$  m;  $P < 0.001$  and MO:  $565 \pm 52$  m vs.  $621 \pm 51$  m;  $P < 0.0001$ ), with no significant differences between the groups (Table 2). Regarding muscle strength, both groups showed a significant improvement in  $1RM_{BC}$  (CO:  $19.6 \pm 6.6$  vs.  $24.7 \pm 9.7$  kg and MO:  $26.0 \pm 8.8$  vs.  $29.2 \pm 6.4$  kg;  $P < 0.05$ ), whereas HGS was significantly increased only in the CO group ( $37.1 \pm 11.6$  vs.  $41.9 \pm 15.9$  kg,  $P < 0.05$ ). The observed changes in  $1RM_{BC}$  and HGS were not significantly different between the groups.

### Prevalence of non-responders

There were significant differences in the prevalence of non-responders in the context of body mass between the CO and MO groups (71.4 vs. 21.4%, respectively,  $P < 0.05$ ) (Fig. 5, panels a and b), and a trend towards the same in terms of waist circumference (85.4 vs. 42.8%, respectively,  $P = 0.061$ ) (Fig. 5, panels c and d) and BMI (71.4 vs. 28.6%, respectively,  $P = 0.061$ ). No significant differences were observed in the prevalence of non-responders in the other assessed outcomes (Figs. 6 and 7). The odds ratio (OR) of the non-responder prevalence revealed a high risk (>2-fold) for body mass (OR: 3.3) and waist circumference (OR: 2.0) (see Fig. 5).

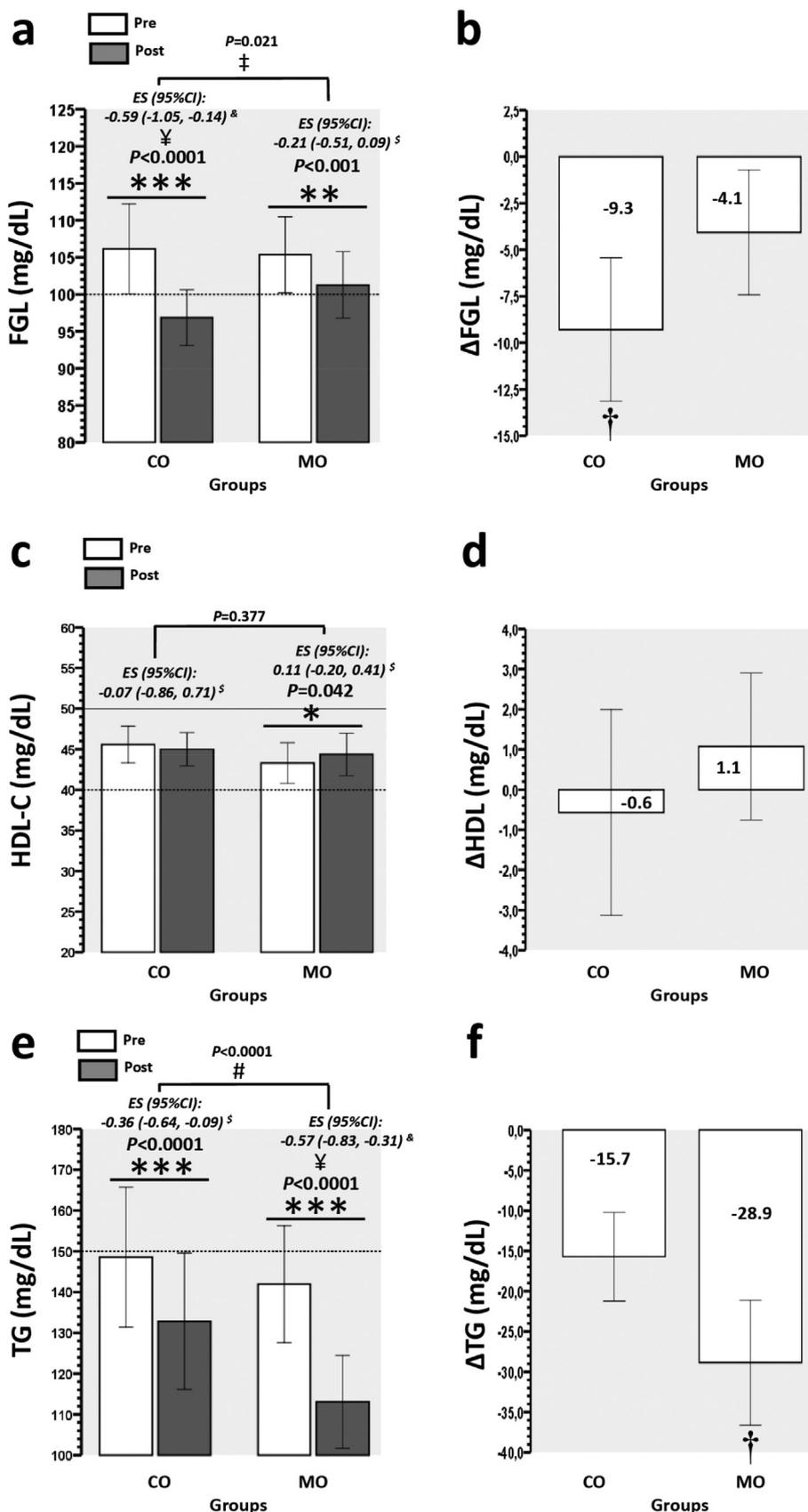
### Discussion

The aim of the present study was to determine the effects of a RT program in preventing/attenuating MetS in patients with morbid obesity. A second aim was to report the prevalence of

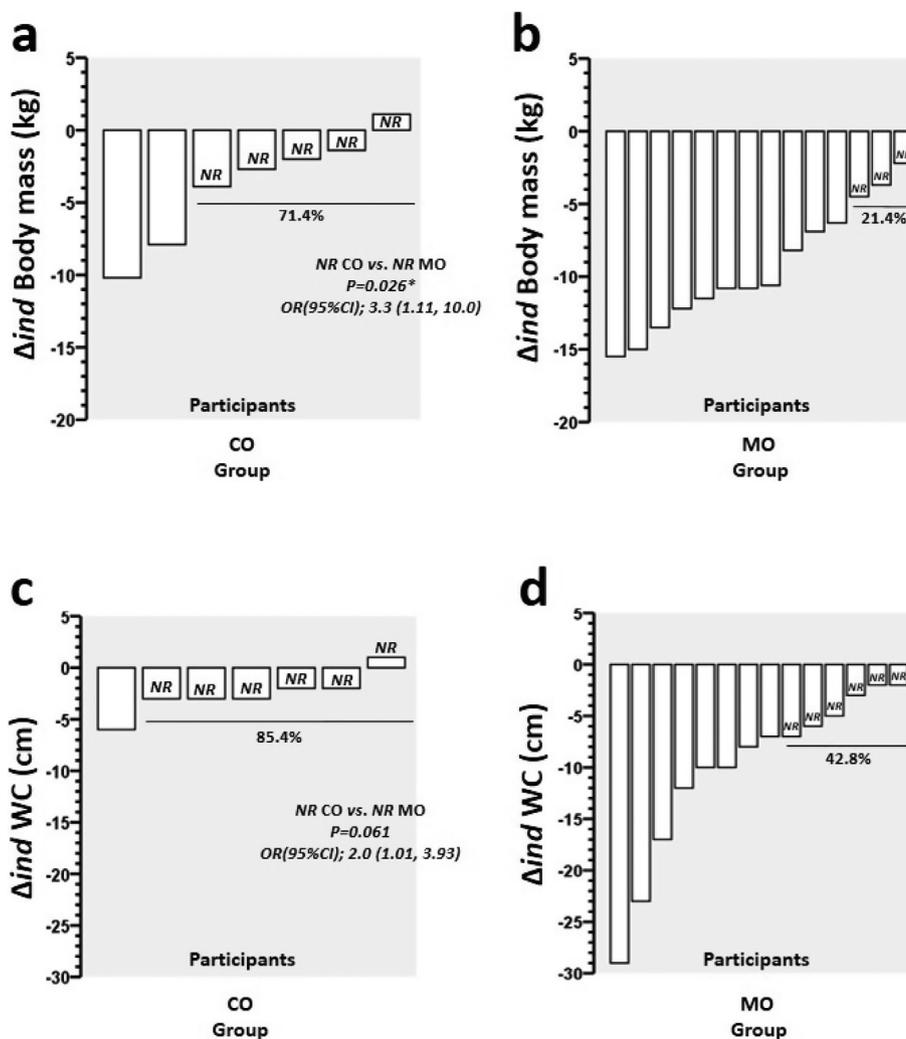
non-responders in terms of improvements in MetS markers and related co-variables. The main results of the study are that determinants of MetS including waist circumference, SBP, DBP, fasting glucose, and triglycerides, are all significantly reduced following a 20-week RT program in both subjects with obesity or morbid obesity. Also, there was no overall difference in the prevalence of non-responders in terms of improvements in MetS outcomes (in exception of body mass which is not considered a MetS criteria) after the 20-week intervention. These findings were observed in parallel with decreases in body mass  $\Delta -3.9$ ,  $\Delta -9.4$  kg, increases in the distance walked in the 6MWT  $\Delta +90.7$ ,  $\Delta +55.8$  m, and increases in muscle strength tested by the  $1RM_{BC}$   $\Delta +5.1$ ,  $\Delta +3.2$  kg for the CO and MO group, respectively, although handgrip strength increased only in the CO group  $\Delta +4.7$  kg (see Table 2).

In a previous study in obese men [27], the authors reported that a 12-week RT program (3 times weekly, 60 min/session, 17 strength exercises at 60–70% 1RM intensity) did not significantly modify the anthropometric parameters body mass  $\Delta +0.3$  kg and fat mass  $\Delta -0.5\%$ , but did lead to significant decreases in both SBP  $\Delta -12.3$  and DBP  $\Delta -11.2$  mmHg, and also an increase in muscle strength in the 1RM bench press  $\Delta +17.3$  kg, [33.3%] and leg press  $\Delta +55.5$  kg, [+31.7%]. Another study in young men with overweight and obesity [32] found that 12 weeks of RT (3 sessions per week, 2–3 sets, 12–15 repetitions at 100% of 8–12RM to 100% of 6–8RM) significantly reduced the total and trunk fat mass while increasing the fat-free mass (i.e., muscle). Interestingly, while this RT study failed to change fasting glucose levels, it improved insulin sensitivity measured by the euglycemic-hyperinsulinemic clamp  $\Delta +1.6$ , improving thus glucose control. In the present study, we observed more robust body mass reductions in morbid obese patients  $\Delta -9.4$  kg with a longer training period than the aforementioned studies (8 weeks more), and similar decreases in SBP and DBP in the MO group  $\Delta -10.4$  and  $-7.0$  mmHg. These results show that irrespective of the RT configuration, a larger volume of exercise can promote additional benefits for the MetS in this patient population.

A recent study investigated the preservation of muscle mass after intentional weight loss in overweight and obese older adults using a 10-week RT program (3 sessions per week, 2–3 sets of 50 s, 10 exercises) in combination with a hypocaloric diet [i.e., 600 kcal below estimated energy needs] [37]. The authors found body mass reduction by diet alone  $\Delta -2.1$  kg, exercise  $\Delta -2.6$  kg, or the combination of both  $\Delta -2.0$  kg. Interestingly, the authors noted a significant increase in fat-free mass  $\Delta +0.2$  kg after the combined strategy, which was not detected in the groups on diet or RT alone [37]. It is widely accepted that RT prevents muscle mass loss in association with either diet or after bariatric by-pass surgery, promoting a negative energy balance and thus contributing to body weight maintenance and an overall reduction in MetS risk factors [14]. Thus, independently of weight loss, this RT program benefit patients with morbid obesity by improving relevant cardiometabolic risk factors for MetS, such as waist



**Figure 4** Fasting glucose (a), high-density lipoproteins (c), triglycerides (e), and delta changes (b, d and f) in control obese and morbid obese participants of a 20-week resistance training program. Groups are presented as (CO) control obese group, (MO) morbid obese group. (FGL) Fasting glucose, (HDL-C) high-density lipoproteins, and (TG) triglycerides. (\*) Denotes significant pre-post differences at  $P \leq 0.05$ . (\*\*) Denotes significant



**Figure 5** Individual delta of pre-post changes ( $\Delta ind$ ) of body mass (**a, b**) and waist circumference (**c, d**) in control obese and morbid obese participants of a 20-week resistance training program. Groups are presented as (CO) control obese group, (MO) morbid obese group. ( $\Delta WC$ ) delta waist circumference. (\*) Denotes significant pre-post differences at  $P \leq 0.05$  between non-responders CO vs. non-responders MO group. (OR) Odds ratio of non-response.

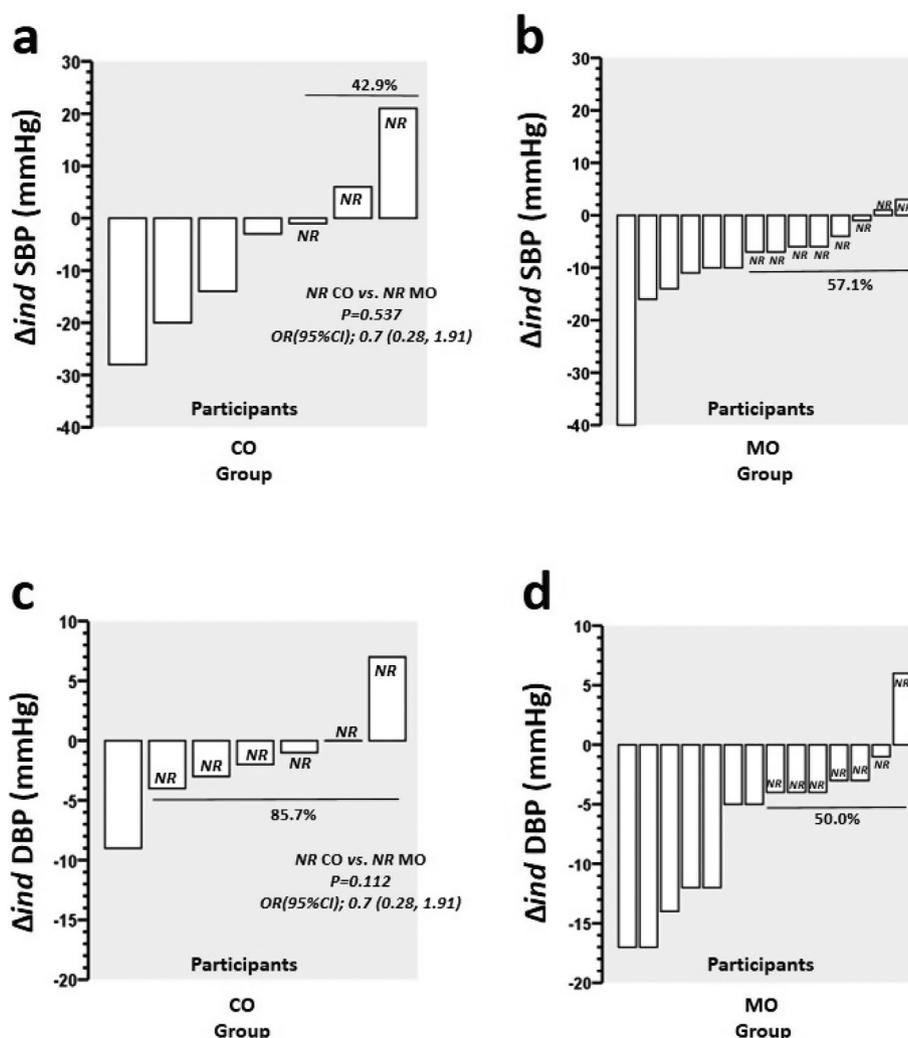
circumference  $\Delta -10.1$  cm, SBP/DBP  $\Delta -10.4/-7.0$  mmHg, and decrease triglycerides  $\Delta -28.9$  mg/dL, and as this findings were in addition with increases the  $1RM_{BC}$  muscle strength, we speculate that potential muscle mass increases as shown previously in older adults with obesity [38] can be related.

A study comparing aerobic training and RT in overweight and obese men [22] showed that 12 weeks of RT (5 sessions per week, 4 sets of 8–12 repetitions at 10-RM) in 5 muscle groups significantly decreased waist circumference  $\Delta -2.6$  cm, do not modified fasting glucose, increased HDL-C  $\Delta 4.2$  mg/dL, but increased triglycerides  $\Delta 9.8$  mg/dL. These results were in additional increases in the resting respiratory exchange ratio as compared with aerobic training, which reflects improved fat oxidation capacity. Thus, our 20-week RT program in morbid obese show

greater effects in improving cardiometabolic risk factors for avoiding MetS. On the other hand, our results report more improvements in the distance walked in the 6MWT and in the  $1RM_{BC}$  can be attributed to both fat mass loss and improved muscle function. Indeed, it has been previously shown that endurance performance and muscle strength improvements are key factors for continuing the adherence to exercise in obesity state [34].

Burd et al. demonstrated that four sets of low-load, high-volume resistance exercise (a low relative  $1RM$  intensity  $\sim 30\%$   $1RM$ ) with a high number of repetitions or until reaching volitional failure, is as effective as high-load ( $90\%$   $1RM$ ), low-volume resistance exercise in eliciting skeletal muscle myofibrillar protein synthesis secondary to sustained activation of mTOR-induced protein synthesis [12]. Likewise, although muscle mass was not directly

pre-post differences at  $P \leq 0.001$ . (\*\*\*) Denotes significant pre-post differences at  $P \leq 0.0001$ . (‡, #) Denotes interaction groups x time statistically significant at  $P < 0.0001$ , and  $P < 0.01$  respectively. (ES) Cohen  $d$  effect size. (\$) Denotes small [ $\leq 0.49$ ] effect size, (&) Denotes medium [0.50 to 0.79] effect size. (†) Denotes significant differences vs. CO group at  $P < 0.001$ .

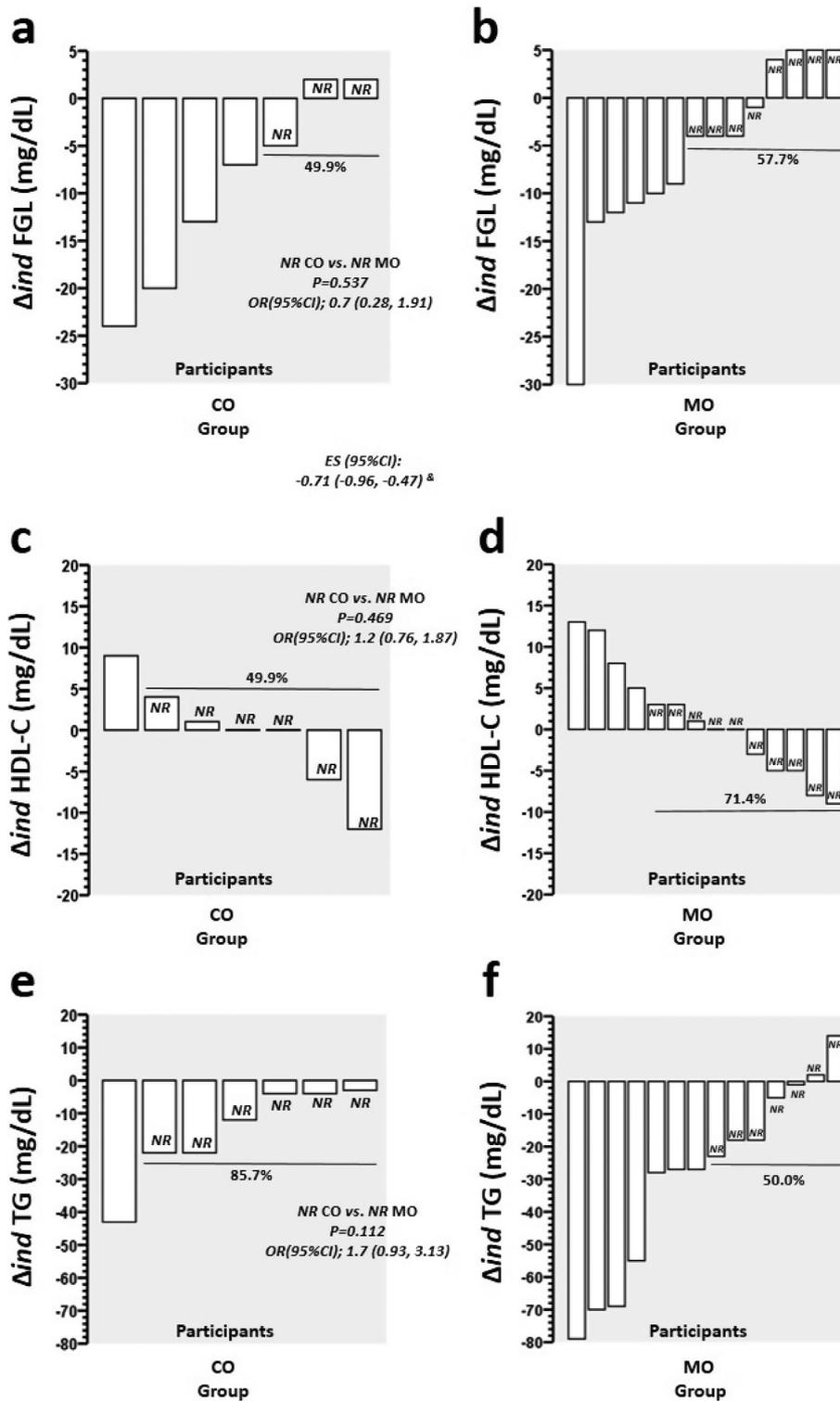


**Figure 6** Individual delta of pre-post changes ( $\Delta_{ind}$ ) of the systolic (a, b), and diastolic BP (c, d) in control obese and morbid obese patients participants of a 20-week resistance training program. Groups are presented as (CO) control obese group, (MO) morbid obese group. ( $\Delta$ SBP) delta systolic BP. ( $\Delta$ DBP) delta diastolic BP. (OR) Odds ratio of non-response.

measured in the present study, increases in the  $1RM_{BC}$  in the MO group suggest that RT contributes to preserve muscle mass in these participants. It is important to note that although subjects in the MO group were characterized by morbid obesity, their metabolic profile was not severely altered, with borderline values for fasting glycemia, resting blood pressure, total cholesterol and LDL-C. That said, we observed that these parameters were profoundly affected following the intervention in both groups, and with further improvements in fasting glucose and HDL-C observed only in the MO group. In addition, we have found at level of the waist circumference, SBP/DBP, fasting glucose, and triglycerides a superior training-induced effects in favour of the MO group. These changes highlight the choice of RT-programs in order of promoting additional beneficial changes for improving MetS outcomes together with improving traditional outcomes such as decreasing weight in this major seek group.

With the exception of body mass, we found no differences in the prevalence of non-responders between

control obese and morbid obese patients for improving MetS outcomes. In body composition outcomes [20], has previously reported that 7.2% of participants were non-responders for a decrease in waist circumference. In other studies, and at cardiovascular level [29], reported that after 6-months of RT (8–12 repetitions, 8 exercises, 70–85% of  $1RM$ , 3 days/week) there was a 60.9% of participants non-responders to decrease SBP, and a 59.1% to decrease DBP. More recently, we showed that the prevalence of non-responders for changes in DBP was different between pre-hypertensive patients (11.4%) and healthy subjects (68.8%) [4]. At metabolic outcomes, previous studies have shown that the prevalence of non-responders for reducing fasting glucose after 12-weeks under a similar RT protocol was of 47% [2] in comparison with the present study (CO 49.4; MO group 57.7%), being the nonresponders prevalence in agreement with previous findings. Little information is available for non-responders for HDL-cholesterol and triglycerides, where this study is adding.



**Figure 7** Individual delta of pre-post changes ( $\Delta ind$ ) of fasting glucose (**a, b**), high-density lipoprotein (**c, d**), and triglycerides (**e, f**) in control obese and morbid obese patients participants of a 20-week resistance training program. Groups are presented as (CO) control obese group, (MO) morbid obese group. ( $\Delta FGL$ ) delta fasting glucose. ( $\Delta HDL-C$ ) delta high-density lipoprotein. ( $\Delta TG$ ) delta triglycerides. (OR) Odds ratio of non-response.

### Strengths and limitations

The limitations of the present study were the increased age in the MO group, and the small final sample in the control group. A strength of this study was that we

included not only MetS markers but also other anthropometric, metabolic, endurance performance, and muscle strength outcomes that are relevant to this morbid obesity cohort and for clinicians managing additional morbidity control in bariatric surgery patients.

In summary, RT promotes a higher degree of improvement in MetS risk factors such as waist circumference, blood pressure and plasma triglycerides in the morbid obese than in obese control peers (with the exception of fasting glucose), with no differences in the prevalence of non-responders for improving MetS risk factors.

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## Conflict of interest disclosure statement

The authors declare no conflict of interest.

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## References

- Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 2009;120(16):1640–5. <https://doi.org/10.1161/CIRCULATIONAHA.109.192644>.
- Álvarez C, Ramírez-Campillo R, Ramírez-Vélez R, Izquierdo M. Effects and prevalence of nonresponders after 12 weeks of high-intensity interval or resistance training in women with insulin resistance: a randomized trial. *J Appl Physiol* 2017a;122(4):985–96.
- Álvarez C, Ramírez-Campillo R, Ramírez-Vélez R, Izquierdo M. Prevalence of non-responders for glucose control markers after 10 weeks of high-intensity interval training in adult women with higher and lower insulin resistance. *Front Physiol* 2017b;8:479.
- Álvarez C, Ramírez-Campillo R, Cristi-Montero C, Ramírez-Vélez R, Izquierdo M. Prevalence of non-responders for blood pressure and cardiometabolic risk factors among prehypertensive women after long-term high-intensity interval training. *Front Physiol* 2018;9(1443). <https://doi.org/10.3389/fphys.2018.01443>.
- Álvarez C, Ramírez R, Flores M, Zúñiga C y, Celis-Morales CA. Efectos del ejercicio físico de alta intensidad y sobrecarga en parámetros de salud metabólica en mujeres sedentarias, pre-diabéticas con sobrepeso u obesidad. *Rev Med Chile* 2012;140(10):1289–96.
- Baffi CW, Wood L, Winnica D, Strollo Jr PJ, Gladwin MT, Que LG, et al. Metabolic syndrome and the lung. *Chest* 2016;149(6):1525–34. <https://doi.org/10.1016/j.chest.2015.12.034>.
- Balducci S, Zanuso S, Nicolucci A, Fernando F, Cavallo S, Cardelli P, et al. Anti-inflammatory effect of exercise training in subjects with type 2 diabetes and the metabolic syndrome is dependent on exercise modalities and independent of weight loss. *Nutr Metab Cardiovasc Dis* 2010;20(8):608–17.
- Bellet RN, Adams L, Morris NR. The 6-minute walk test in outpatient cardiac rehabilitation: validity, reliability and responsiveness—a systematic review. *Physiotherapy* 2012;98(4):277–86.
- Booth HP, Charlton J, Gulliford MC. Socioeconomic inequality in morbid obesity with body mass index more than 40 kg/m<sup>2</sup> in the United States and England. *SSM-Popul Health* 2017;3:172–8.
- Bouchard C, Blair SN, Church TS, Earnest CP, Hagberg JM, Hakkinen K, et al. Adverse metabolic response to regular exercise: is it a rare or common occurrence? *PLoS One* 2012;7(5):e37887. <https://doi.org/10.1371/journal.pone.0037887>.
- Brzycki M. Strength testing—predicting a one-rep max from reps-to-fatigue. *J Phys Educ Recreat Dance* 1993;64(1):88–90.
- Burd NA, West DW, Staples AW, Atherton PJ, Baker JM, Moore DR, et al. Low-load high volume resistance exercise stimulates muscle protein synthesis more than high-load low volume resistance exercise in young men. *PLoS One* 2010;5(8):e12033. <https://doi.org/10.1371/journal.pone.0012033>.
- Cardinal BJ, Park EA, Kim M, Cardinal MK. If exercise is medicine, where is exercise in medicine? Review of US medical education curricula for physical activity-related content. *J Phys Act Health* 2015;12(9):1336–43.
- Clark JE. Diet, exercise or diet with exercise: comparing the effectiveness of treatment options for weight-loss and changes in fitness for adults (18–65 years old) who are overfat, or obese; systematic review and meta-analysis. *J Diabetes Metab Disord* 2015;14(1):31.
- Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, et al. Seventh report of the joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension* 2003;42(6):1206–52. <https://doi.org/10.1161/01.HYP.0000107251.49515.c2>.
- Delgado-Floody P, Caamaño-Navarrete F, Jerez-Mayorga D, Martínez-Salazar C, García-Pinillos F, Latorre-Román P. Adaptaciones al ejercicio físico en el perfil lipídico y la salud cardiovascular de obesos mórbidos. *Gac Med Mex* 2017;153(7):781–6.
- Dixon JB, Zimmet P, Alberti KG, Rubino F, Epidemiology, I.D.F.T.o., and Prevention. Bariatric surgery: an IDF statement for obese type 2 diabetes. *Diabet Med* 2011;28(6):628–42.
- Dusanov S, Heggen E, Tonstad S. Characteristics of metabolic syndrome in morbidly obese subjects. *Metab Syndr Relat Disord* 2016;14(10):500–6. <https://doi.org/10.1089/met.2016.0062>.
- Fontaine KR, Redden DT, Wang C, Westfall AO, Allison DB. Years of life lost due to obesity. *JAMA* 2003;289(2):187–93.
- Gremeaux V, Drigny J, Nigam A, Juneau M, Guilbeault V, Latour E, et al. Long-term lifestyle intervention with optimized high-intensity interval training improves body composition, cardiometabolic risk, and exercise parameters in patients with abdominal obesity. *Am J Phys Med Rehabil* 2012;91(11):941–50.
- Han TS, Lean ME. A clinical perspective of obesity, metabolic syndrome and cardiovascular disease. *JRSM Cardiovasc Dis* 2016;5:2048004016633371.
- Ho SS, Dhaliwal SS, Hills AP, Pal S. The effect of 12 weeks of aerobic, resistance or combination exercise training on cardiovascular risk factors in the overweight and obese in a randomized trial. *BMC Public Health* 2012;12:704. <https://doi.org/10.1186/1471-2458-12-704>.
- Hopkins WG, Marshall SW, Batterham AM, Hanin J. Progressive statistics for studies in sports medicine and exercise science. *Med Sci Sport Exerc* 2009;41(1):3–13. <https://doi.org/10.1249/mss.0b013e31818cb278>.
- Huck CJ. Effects of supervised resistance training on fitness and functional strength in patients succeeding bariatric surgery. *J Strength Cond Res* 2015;29(3):589–95.
- Aronne LJ. Classification of obesity and assessment of obesity-related health risks. *Obes Res* 2002;10(S12):105S–15S.
- Isomaa B, Almgren P, Tuomi T, Forsén B, Lahti K, Nissen M, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 2001;24(4):683–9.
- Klimcakova E, Polak J, Moro C, Hejnova J, Majercik M, Viguerie N, et al. Dynamic strength training improves insulin sensitivity without altering plasma levels and gene expression of adipokines in subcutaneous adipose tissue in obese men. *J Clin Endocrinol Metab* 2006;91(12):5107–12.
- Lemes ÍR, Ferreira PH, Linares SN, Machado AF, Pastre CM, Netto J. Resistance training reduces systolic blood pressure in metabolic syndrome: a systematic review and meta-analysis of randomised controlled trials. *Br J Sports Med* 2016;50(23):1438–42.
- Moker EA, Bateman LA, Kraus WE, Pescatello LS. The relationship between the blood pressure responses to exercise following training and detraining periods. *PLoS One* 2014;9(9):e105755.
- Puh U. Age-related and sex-related differences in hand and pinch grip strength in adults. *Int J Rehabil Res* 2010;33(1):4–11.

- [31] Ritchie S, Connell J. The link between abdominal obesity, metabolic syndrome and cardiovascular disease. *Nutr Metab Cardiovasc Dis* 2007;17(4):319–26.
- [32] Roberts CK, Croymans DM, Aziz N, Butch AW, Lee CC. Resistance training increases SHBG in overweight/obese, young men. *Metabolism* 2013;62(5):725–33. <https://doi.org/10.1016/j.metabol.2012.12.004>.
- [33] Shin JA, Lee JH, Lim SY, Ha HS, Kwon HS, Park YM, et al. Metabolic syndrome as a predictor of type 2 diabetes, and its clinical interpretations and usefulness. *J Diabetes Investig* 2013;4(4):334–43.
- [34] Strasser B, Schobersberger W. Evidence for resistance training as a treatment therapy in obesity. *J Obesity* 2010;2011.
- [35] Sturm R. Increases in morbid obesity in the USA: 2000–2005. *Public Health* 2007;121(7):492–6.
- [36] Tjønnå AE, Ramos JS, Pressler A, Halle M, Jungbluth K, Ermacora E, et al. EX-MET study: exercise in prevention of metabolic syndrome—a randomized multicenter trial: rationale and design. *BMC Public Health* 2018;18(1):437.
- [37] Verreijen AM, Engberink MF, Memelink RG, Van der Plas SE, Visser M, Weijs PJ. Effect of a high protein diet and/or resistance exercise on the preservation of fat free mass during weight loss in overweight and obese older adults: a randomized controlled trial. *Nutr J* 2017;16(1):10.
- [38] Villareal DT, Smith GI, Sinacore DR, Shah K, Mittendorfer B. Regular multicomponent exercise increases physical fitness and muscle protein anabolism in frail, obese, older adults. *Obesity* 2011;19(2):312–8.