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### Body fat loss and compensatory mechanisms in response to different doses of aerobic exercise—a randomized controlled trial in overweight sedentary males

Mads Rosenkilde,<sup>1</sup> Pernille Auerbach,<sup>1</sup> Michala Holm Reichkender,<sup>1</sup> Thorkil Ploug,<sup>1</sup> Bente Merete Stallknecht,<sup>1</sup> and Anders Sjødin<sup>2</sup>

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**Rosenkilde M, Auerbach P, Reichkender MH, Ploug T, Stallknecht BM, Sjødin A.** Body fat loss and compensatory mechanisms in response to different doses of aerobic exercise—a randomized controlled trial in overweight sedentary males. *Am J Physiol Regul Integr Comp Physiol* 303: R571–R579, 2012. First published August 1, 2012; doi: 10.1152/ajpregu.00141.2012.—The amount of weight loss induced by exercise is often disappointing. A diet-induced negative energy balance triggers compensatory mechanisms, e.g., lower metabolic rate and increased appetite. However, knowledge about potential compensatory mechanisms triggered by increased aerobic exercise is limited. A randomized controlled trial was performed in healthy, sedentary, moderately overweight young men to examine the effects of increasing doses of aerobic exercise on body composition, accumulated energy balance, and the degree of compensation. Eighteen participants were randomized to a continuous sedentary control group, 21 to a moderate-exercise (MOD; 300 kcal/day), and 22 to a high-exercise (HIGH; 600 kcal/day) group for 13 wk, corresponding to ~30 and 60 min of daily aerobic exercise, respectively. Body weight (MOD: –3.6 kg,  $P < 0.001$ ; HIGH: –2.7 kg,  $P = 0.01$ ) and fat mass (MOD: –4.0 kg,  $P < 0.001$  and HIGH: –3.8 kg,  $P < 0.001$ ) decreased similarly in both exercise groups. Although the exercise-induced energy expenditure in HIGH was twice that of MOD, the resulting accumulated energy balance, calculated from changes in body composition, was not different (MOD: –39.6 Mcal, HIGH: –34.3 Mcal, not significant). Energy balance was 83% more negative than expected in MOD, while it was 20% less negative than expected in HIGH. No statistically significant changes were found in energy intake or nonexercise physical activity that could explain the different compensatory responses associated with 30 vs. 60 min of daily aerobic exercise. In conclusion, a similar body fat loss was obtained regardless of exercise dose. A moderate dose of exercise induced a markedly greater than expected negative energy balance, while a higher dose induced a small but quantifiable degree of compensation.

exercise; body weight regulation; compensatory mechanisms; energy balance

ALTHOUGH A MODERN SEDENTARY lifestyle along with overeating has been put forward as “Big Two” factors in the etiology of obesity (3, 10, 29), the outcomes of structured exercise programs designed to promote weight loss are often modest (42, 58). This has led to the general (mis)conception that exercise,

in itself, is a poor weight management strategy (20, 42, 49). Apart from a potential lack of compliance, the discrepancy between predicted and observed weight loss is likely due to a combination of physiological and behavioral compensatory changes affecting energy balance. These compensatory changes cause the accumulated energy balance during an exercise intervention to be less negative than would be theoretically predicted from the exercise-induced energy expenditure (ExEE), i.e., the total amount of energy expenditure that is caused by the exercise intervention (12, 32, 34).

Body energy stores are protected against long-term negative energy balance resulting from caloric restriction by a greater than predicted reduction in resting energy expenditure (REE) (28), a decrease in nonexercise activity thermogenesis (NEAT) (40, 45), an increase in the metabolic efficiency of physical activity (16, 35), and an increase in hedonic (21) and hormonal mediators of appetite (53). During a diet-induced weight loss, it is generally accepted that fat mass and fat free mass (FFM) decrease proportionally (25). In contrast, FFM is at least preserved (5) or sometimes even increased (20, 48) during exercise-induced weight loss. Even when body weight is only marginally affected, exercise may lead to a negative energy balance resulting in a healthy loss of fat mass (14, 43).

In the elegant DREW study (12) on dose-response effects of exercise in postmenopausal overweight women, Church et al. (12) reported a substantial discrepancy between observed and predicted weight loss with increasing exercise dose. It was suggested that compensatory changes with increasing amounts of exercise attenuate weight loss. Activity behavior based on registration of step counts and energy intake (EI) based on food records were not significantly affected; nevertheless, increased EI was suggested as the likely compensatory change. Others have suggested that decreased NEAT occurs as a compensatory response to a strenuous exercise regime (52, 56) and results in less than expected weight loss. In addition, dietary composition also seems to play a role; a high-fat diet, compared with a low-fat diet, seems to induce a less negative energy balance during a short-term (7 days) structured aerobic exercise regime in lean young men (52). Thus, several factors seem to impact the compensatory response to aerobic exercise.

Although it is well known that habitual exercise reduces body fat, and in particular, in the abdominal region (47), it is poorly understood how different doses of increased ExEE impacts on compensatory responses (i.e., increased EI and/or

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reduced NEAT). We have found no long-term randomized controlled exercise interventions closely monitoring exercise compliance, which have investigated changes in body composition assessing accumulated energy balance and quantifying the degree of compensation. Therefore, the primary aim of the present study was to examine the effects of increasing doses of aerobic exercise on body weight and composition. Secondly, accumulated energy balance and the degree of compensation were assessed on the basis of changes in body composition. Additionally, we wanted to identify potential underlying mechanisms, i.e., EI, dietary macronutrient composition, NEAT, and REE, which could explain any apparent compensation.

## MATERIALS AND METHODS

The Four-IN-onE project (<http://fine.ku.dk>) on metabolic and cultural health in moderately overweight men was conducted between December 2009 and July 2011. The study adhered to the declaration of Helsinki, was approved by the Ethical Committee of Copenhagen (H-4-2009-089), and was registered at [clinicaltrials.gov](http://clinicaltrials.gov) (identifier: NCT01430143).

**Study subjects.** We recruited young (20–40 yr) Caucasian males, with no first-degree relatives with Type 2 diabetes, from the Copenhagen area. At a screening visit, 64 subjects that were moderately overweight (BMI: 25–30 kg/m<sup>2</sup>, fat percentage  $\geq$ 25%), sedentary [not engaged in regular exercise, maximal oxygen consumption

( $\dot{V}O_{2\max}$ )  $\leq$ 45 ml O<sub>2</sub>·kg body mass<sup>-1</sup>·min<sup>-1</sup>], healthy (blood pressure  $\leq$ 140/90 mmHg, fasting blood glucose  $\leq$ 6.1 mmol/l, no regular medication), not engaged in dieting to lose weight and willing to adhere to the protocol were found eligible for randomization (Fig. 1). Subjects signed an informed consent after receiving detailed oral and written information regarding the study. Withdrawal of consent or insufficient training compliance resulted in exclusion from the study. Participants received a payment for successful participation in the study.

**Study design.** The study was a randomized controlled trial, including a 13-wk exercise intervention of moderate (MOD) or high (HIGH) dose, and a control group (CON) that maintained a sedentary lifestyle. Subjects in CON were offered consultations regarding “healthy” lifestyle changes after completion of the study. The randomization procedure was done in three blocks (from January 2010 to February 2011), and in the beginning of each block, identical group allocations were available.

Subjects in MOD and HIGH were instructed to perform aerobic exercise (e.g., running and cycling) corresponding to a training-induced energy expenditure (TrEE) of 300 or 600 kcal/day, respectively, i.e., the energy expenditure only associated with the exercise bout. Missed sessions (unless due to injury or illness) were to be compensated for during the following sessions. Three times per week, sessions were intense, i.e., higher than 70% of  $\dot{V}O_{2\max}$ , based on the heart rate (HR) reserve method (31). Exercise intensity at the remaining sessions was self-selected.

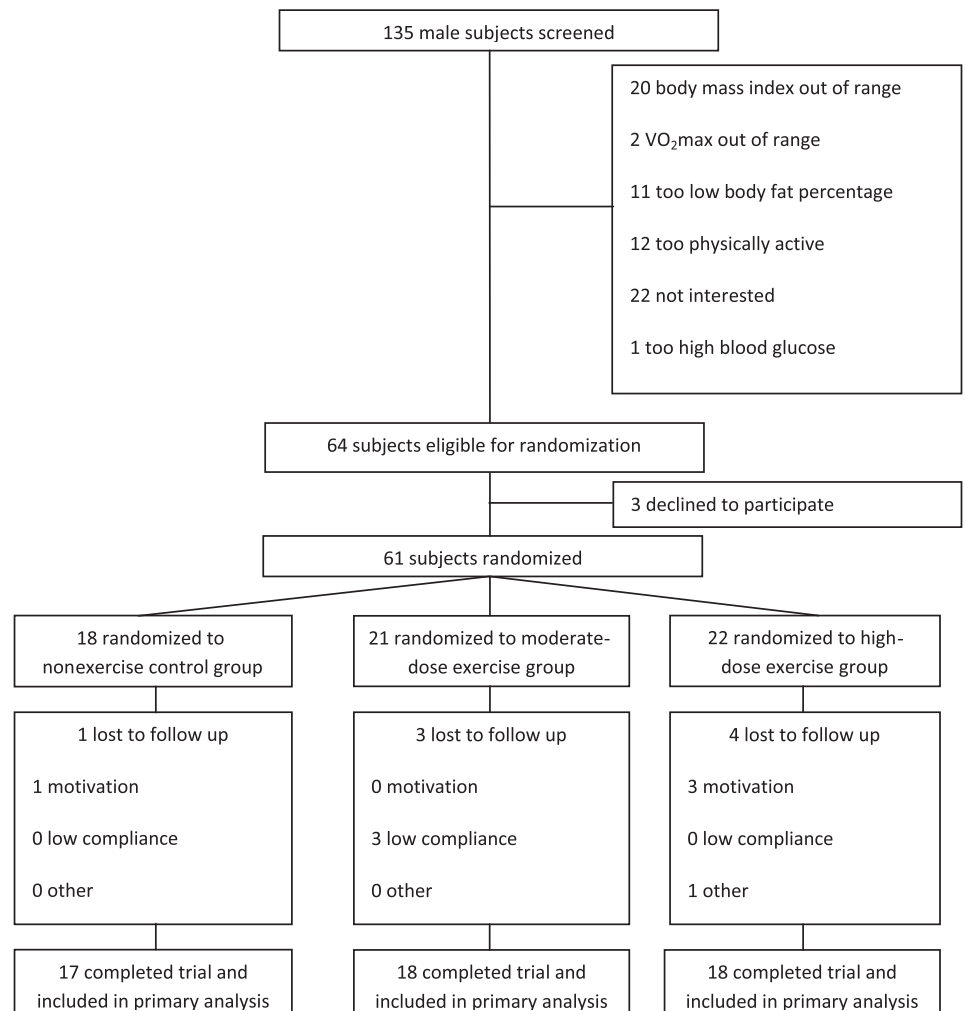


Fig. 1. Participant flow chart.

Exercise was individually prescribed on the basis of body mass, resting and maximal HR, and  $\dot{V}O_{2\max}$ , and these variables were subsequently entered into a HR monitor (RS400; Polar Electro OY, Kempele, Finland) that was used to monitor the training intervention. After 2, 6, and 10 wk, individual exercise target HR and training time were recalculated depending on changes in  $\dot{V}O_{2\max}$  and body weight. To verify and control exercise sessions, subjects wore HR monitors during all exercise sessions that stored exercise HR, number, and duration of exercise sessions, and calculated TrEE (13).

To promote high compliance to the exercise regimen, subjects were required to report their performed training (including HR monitor files) to the research staff for supervision every second day during the 2 first weeks and every 4th day thereafter, throughout the intervention.

Subjects were excluded if they deviated more than 20% from the prescribed exercise dose. Additionally, two of the following three criteria had to be met: 1) at least 80% of the intervention days should include exercise, 2) 80% of exercise sessions should include registration of HR, and 3) less than 20% of days without training due to illness or injury. All subjects had free access to a fitness center, but subjects in CON group only gained access after participation in the study.

We attempted to 'blind' subjects to the appetite/EI part of the study, and thus, they were informed that the aim of the project was to investigate the effects of different doses of exercise on metabolic parameters. Additionally, they were told not to impose any dietary restrictions during study participation but to select food items without restraint.

**Measurements.** All subjects underwent a 3-wk baseline test regimen after which subjects were randomized to CON, MOD, or HIGH. Follow-up testing started after 10-wk intervention and continued for 3 wk, during which subjects adhered to the intervention protocol as randomized.

Body weight and composition were measured after an overnight fast. Weight was measured on an electronic scale, height was measured using a stadiometer, and body composition was assessed using dual-energy X-ray absorptiometry (DPX-IQ X-ray bone densitometer 4.7e; Lunar Corporation, Madison, WI, USA).

Resting energy expenditure was assessed in a supine position using a respiratory calorimetry system (Oxycon Pro, Jaeger, Würzburg, Germany). Respiratory gas exchange was measured for 30 min after 25 min of rest. The first 10 min was discarded, and REE was calculated using the Weir equation (55).

$\dot{V}O_{2\max}$  was assessed using an electronically braked bicycle (Lode Excalibur, Groeningen, Netherlands) and respiratory calorimetry. Workload was increased with 25-W increments every minute after warm-up until exhaustion, and attainment of  $\dot{V}O_{2\max}$  was accepted using previously defined criteria (46).

Total physical activity was assessed using Actigraph GT1-M (Actigraph, Pensacola, FL, USA), which measured total daily activity counts for three consecutive days at baseline and in the 6th and 11th wk after randomization. Subjects were instructed to wear the monitor throughout the day and were allowed to take off the monitor when showering. Accelerometry data were downloaded as 1-min epochs, and activity measures were considered valid if at least 2 out of 3 days had activity counts throughout the day (except for the sleeping period). In the exercise groups, nonexercise activity was assessed by subtracting activity counts obtained during prescribed exercise from total activity counts (38). Activity counts obtained at the 6th and 11th wk were averaged and then pooled for further analysis. Data derived from the Actigraph were analyzed using a conservative approach, in which activity counts, rather than energy expenditure, were assessed in the analysis.

Habitual EI was calculated from food records on the same weekdays at baseline and in *week 11*. All subjects were told to carefully weigh and record all foods and drinks consumed for 3 days. The recordings were processed using appropriate software (Dankost 3000; Dankost, Copenhagen, Denmark).

Diets were provided to the subjects for ad libitum consumption during an 8-day period at baseline and at the 13th week. The diets were provided in a randomized double-blinded order and consisted of four consecutive days of either high-carbohydrate or low-carbohydrate diet, respectively, to objectively evaluate whether an increase in EI in the end of the exercise intervention was dependent on the dietary macronutrient composition. The diets comprised similar type of meals with similar energy density and palatability but differed in macronutrient composition: high-carbohydrate diet: 65% carbohydrate, and 20% fat, 15% protein; and low-carbohydrate diet: 35% carbohydrate, 50% fat, and 15% protein. All food components within a single meal were interchangeable, since they had the same macronutrient composition. Approximately double the expected daily energy needs were provided to allow ad libitum feeding. Subjects were instructed to select freely from the food items provided and to eat until comfortably satiated. All leftovers were returned and weighed, and energy intake was subsequently calculated. Ad libitum EI during the last 3 days of each feeding regimen and pooled data from all 8 diet days were analyzed.

**Calculations.** The accumulated energy balance was calculated from changes in body energy stores. Over a longer period, changes in body composition reflect changes in energy balance; thus, the accumulated gain or loss of different body tissues should reflect energy balance over the exercise intervention. We define the accumulated balance as the energy balance reflected by changes in body fat and FFM and assume that a gain of 1-kg fat mass or 1-kg FFM corresponds to 12,000 and 1,780 kcal, respectively (18). We assumed that a loss of 1 kg fat mass or 1 kg FFM corresponds to 9,417 and 884 kcal, respectively (19).

ExEE was calculated from measured TrEE. Here 15% of excess postexercise energy expenditure was added (4), but a conservative sedentary physical activity level ( $REE \times 1.2$ ) was removed:  $ExEE = (TrEE \times 0.15) + (TrEE - \text{training duration} \times REE \times 1.2)$ .

The degree of compensation in response to the increase in ExEE was assessed through a compensation index: Degree of compensation =  $(ExEE - AEB)/ExEE \times 100\%$ .

This index provides an estimation of the degree of compensation. When the degree of compensation equals zero, then changes in body composition (calculated as accumulated energy balance) equals the amount of calories spent due to exercising (ExEE) during the given time frame. A change in body composition, indicating a less negative energy balance than what could be expected is defined as (positive) compensation and, correspondingly, a larger than expected negative energy balance is referred to as a negative compensation.

Linear regression at baseline ( $n = 61$ ) based on observed REE and FFM was used to derive an equation to predict REE at follow-up. Residuals between observed and predicted REE were calculated to estimate adaptations in REE that could not be attributed to changes in FFM (39).

**Statistical analysis.** The study was primarily an efficacy study, and results are presented as per-protocol analyses. Descriptive baseline data are tabulated as means  $\pm$  SE. Between-group differences were assessed using analysis of covariance with group baseline values and group assignment as covariates. The differences in follow-up values among the randomization groups are presented as adjusted least-square means with two-sided 95% confidence intervals (CI), and all pairwise comparisons were adjusted using the Tukey procedure. Within-group differences were tested using *t*-tests. Data that did not comply with the criteria for the statistical model (i.e., unequal variance) were log transformed.

An intention-to-treat analysis, including subjects that were excluded or dropped out after randomization, was also conducted for changes in body composition, for the degree of compensation, and for compensatory changes. If the subject dropped out of the intervention, the baseline values were carried forward (i.e., last observation carried forward). If the subject were excluded due to compliance issues, the post value was analyzed as randomized.



Table 1. Baseline characteristics of 61 randomized subjects and 53 completers

Characteristics	All randomized (n = 61)	CON (n = 17)	MOD (n = 18)	HIGH (n = 18)
Age, mean (SD), yr	29 (6)	31 (6)	30 (7)	28 (5)
Anthropometric variables, mean (SD)				
Weight, kg	91.8 (7.8)	92.8 (8.5)	93.2 (8.1)	91.3 (7.2)
Body Mass Index, kg/m <sup>2</sup>	27.9 (1.8)	28.0 (2.3)	28.6 (1.8)	27.6 (1.4)
Fat mass, kg	28.4 (4.8)	29.0 (6.0)	30.0 (4.6)	27.4 (4.2)
Fat free mass, kg	63.4 (5.8)	63.9 (2.8)	63.3 (6.9)	64.0 (5.7)
Waist circumference, cm	95 (5)	96 (6)	97 (5)	94 (6)
Diet registration, mean (SD)				
Habitual energy intake, kcal/day	2690 (560)	2670 (490)	2550 (440)	2820 (680)
E% carbohydrate*, †	47 (8)	48 (9)	48 (9)	47 (5)
E% fat*, †	31 (6)	31 (8)	29 (6)	31 (5)
E% protein*, †	16 (3)	16 (3)	16 (3)	16 (4)
E% alcohol*, †	6 (7)	5 (8)	6 (8)	6 (5)
Ad libitum diet delivery, mean (SD)‡				
High-CHO, kcal/day	2640 (600)	2740 (630)	2600 (750)	2540 (490)
High-CHO, kcal·day <sup>-1</sup> ·kg <sup>-1</sup> body wt	29 (7)	30 (7)	28 (9)	28 (6)
Low-CHO, kcal/day	3170 (670)	3240 (770)	3090 (710)	3150 (630)
Low-CHO, kcal/day body wt	35 (8)	35 (8)	34 (9)	35 (8)
Pooled caloric intake 8 days, kcal/day	2920 (580)	3010 (620)	2860 (650)	2840 (520)
Pooled caloric intake 8 days, kcal/day body wt	32 (7)	33 (6)	31 (8)	31 (6)
Resting variables, mean (SD)				
Resting energy expenditure, kcal/day§	1810 (178)	1809 (157)	1832 (226)	1833 (169)
Respiratory exchange ratio*	0.87 (0.09)	0.86 (0.07)	0.87 (0.11)	0.87 (0.10)
Resting heart rate, bpm	56 (7)	55 (7)	56 (8)	56 (6)
Exercise test variables, mean (SD)				
$\dot{V}O_{2max}$ , ml·kg <sup>-1</sup> ·min <sup>-1</sup>	35.1 (4.9)	35.9 (4.8)	34.6 (4.1)	36.2 (5.3)
Respiratory exchange ratio	1.25 (0.06)	1.24 (0.06)	1.26 (0.07)	1.24 (0.05)
Maximal heart rate, bpm	185 (8)	186 (9)	185 (7)	187 (9)
Peak power output, W	247 (40)	257 (45)	250 (33)	249 (37)

\*5 subjects were not analyzed because of lack of compliance with food records; †Percentages may not sum to 100 because of rounding; ‡4 subjects did not receive diet delivery due to time constraints; §5 Subjects were not analyzed due to equipment malfunction. bpm, beats per minute; CHO, carbohydrate; CON, control group; E%, percentage contribution to total energy intake; HIGH, high-dose exercise group; H-CHO, high-carbohydrate diet, L-CHO, low carbohydrate diet; MOD, moderate-dose exercise group;  $\dot{V}O_2$ , volume oxygen consumed.

Power and sample size calculations were based on changes in fat mass. Approximately  $3 \times 20$  persons were necessary to detect a 25% reduction in fat mass in the intervention groups compared with CON. With a coefficient of variation of 20%, a statistical power of 80% is obtained. A level of  $P \leq 0.05$  was considered significant. Statistical analyses were conducted in SAS Enterprise Guide 4.2 (SAS Institutes, Cary, NC, USA).

## RESULTS

Of the 64 subjects eligible for inclusion, 3 subjects withdrew their consent during baseline testing, and 61 subjects were randomized (CON,  $n = 18$ ; MOD,  $n = 21$ ; HIGH,  $n = 22$ ). Return rate to follow-up was 82 to 94% across groups. With-

drawal of informed consent ( $n = 2$ ) or insufficient training compliance ( $n = 6$ ) resulted in subsequent exclusion of eight subjects (Fig. 1). The baseline data for the study population are presented in Table 1. During the intervention, average adherence to the prescribed exercise was 99% for MOD (CI: 96, 102) and 96% for HIGH (CI: 93, 99%) ( $P = 0.14$ ), and there was no difference in exercise intensity and number of exercise sessions conducted per week ( $P > 0.12$ ) (Table 2). The intervention resulted in an increase in  $\dot{V}O_{2max}$  of 18% for MOD (CI: 12–25) and 17% for HIGH (CI: 11–21) (Table 2). This was a larger increase for both exercise groups compared

Table 2. Descriptive training data for subjects who completed the exercise intervention

	CON (n = 17)	MOD (n = 18)	HIGH (n = 18)
Training adherence, mean (SD)			
Training energy expenditure, kcal/session†	n.a.	335 (8)	653 (10)\$
Exercise sessions/wk	n.a.	6.2 (0.6)	6.2 (0.4)
Duration, min/session	n.a.	29.9 (8.2)	55.2 (6.6)\$
Exercise intensity, % $\dot{V}O_{2max}$	n.a.	66.2 (6.6)	67.3 (6.5)
Intervention length, days	76 (14)	72 (4)	74 (5)
Days without training	n.a.	8 (6)	8 (4)
Sick days	n.a.	1 (2)	3 (6)
Exercise test variables, mean change (95% CI)			
$\dot{V}O_{2max}$ , ml·kg <sup>-1</sup> ·min <sup>-1</sup>	1.3 (-1.0; 3.5)	7.7 (5.4; 9.9)**	7.0 (5.1; 8.8)**
Respiratory exchange ratio	0 (-0.05; 0.04)	-0.05 (-0.01; -0)*	-0.03 (0; -0.07)
Maximal heart rate, bpm	-2 (-8; 5)	-7 (-1; -13)*	-6 (-0; -12)*
Peak power output, W	1 (-27; 30)	24 (-1; 48)#	46 (21; 71)**\$

CI, confidence interval. †Data are based on variables that are adjusted for changes in body composition and  $\dot{V}O_{2max}$  in the MOD and HIGH group. \* $P < 0.05$  within group. # $P < 0.05$  compared with control (CON). \$ $P < 0.05$  compared with MOD.

with CON (MOD:  $6.0 \text{ ml O}_2 \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ , CI: 2.7, 9.2,  $P < 0.001$ ; HIGH:  $5.8 \text{ ml O}_2 \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ , CI: 2.5, 9.0,  $P < 0.001$ ) (Table 2).

Body weight and composition remained unchanged in CON ( $P > 0.36$ ). There was a modest decrease in body weight in both MOD (4%; CI: 2–5) and HIGH (3%; CI: 1–4), and a substantial reduction in body fat in MOD (14%; CI: 10–18) and HIGH (13% CI: 10–17). Compared with CON, both body weight (MOD:  $-3.6 \text{ kg}$ , CI:  $-5.7$ ;  $-1.5 \text{ kg}$ ,  $P < 0.001$ ; HIGH:  $-2.7 \text{ kg}$ , CI:  $-4.8$ ;  $-0.6$ ,  $P = 0.01$ ) and fat mass (MOD:  $-4.0 \text{ kg}$ , CI:  $-5.6$ ;  $-2.3 \text{ kg}$ ,  $P < 0.001$ ; HIGH:  $-3.8 \text{ kg}$ , CI:  $-5.6$ ;  $-2.1$ ,  $P < 0.001$ ) decreased in MOD and HIGH. A tendency toward an increase in FFM was observed in HIGH compared with CON ( $1.0 \text{ kg}$ , CI:  $-0.1$ ,  $2.2$ ,  $P = 0.06$ ) (Fig. 2A). In the intention-to-treat population, similar changes were observed except for the change in FFM ( $0.9 \text{ kg}$ , CI:  $-0.2$ ,  $1.9$ ;  $P = 0.12$ ).

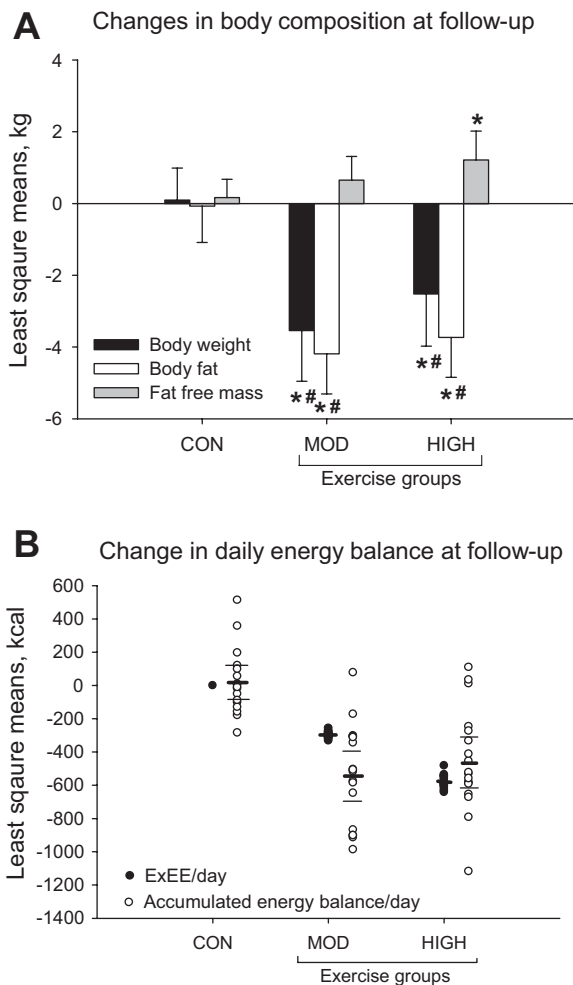


Fig. 2. Effects of the intervention on the degree of compensation *A*: changes (follow-up minus baseline) in body composition over the intervention in the control (CON,  $n = 17$ ), moderate-dose exercise (MOD,  $n = 18$ ), and high-dose exercise group (HIGH,  $n = 18$ ) as measured by DEXA scan. *B*: energy balance per day during the intervention in CON ( $n = 17$ ), MOD ( $n = 18$ ), and HIGH ( $n = 18$ ). Data are least square means, and error bars represent 95% confidence intervals. \* $P < 0.01$  within group. # $P < 0.01$  compared with control (CON). Abbreviations: CON, control group; DEXA, dual-energy X-ray absorptiometry; ExEE: exercise-induced energy expenditure; HIGH, high-dose exercise group; MOD, moderate-dose exercise group.

The changes in body energy stores indicated that both exercise regimes resulted in substantial negative accumulated energy balance compared with CON (MOD:  $-39.6 \text{ Mcal}$ , CI:  $-57.1$ ;  $-22.0$ ,  $P < 0.001$ ; HIGH:  $-34.3 \text{ Mcal}$ , CI:  $-51.9$ ;  $-16.7$ ,  $P < 0.001$ ) over the course of the intervention. Thus, average daily accumulated energy balance was  $-550 \text{ kcal}$  in MOD (CI:  $-770$ ;  $-320$ ,  $P < 0.001$ ) and  $-470 \text{ kcal}$  in HIGH (CI:  $-690$ ;  $-240$ ,  $P < 0.001$ ) compared with CON (Fig. 2B). The average daily ExEE was  $300 \text{ kcal}$  (CI: 290, 305) for MOD and  $580 \text{ kcal}$  (CI: 560, 600) for HIGH, which corresponded to doubled ExEE in HIGH compared with MOD (193%, CI: 187: 200,  $P < 0.001$ ), as intended in the study design (Fig. 2B). The changes in accumulated energy balance and ExEE resulted in a 20% (CI:  $-6$ : 46) degree of compensation in HIGH and a  $-83\%$  (CI:  $-134$ :  $-33$ ) degree of compensation in MOD. Accordingly, the moderate dose of exercise resulted in a negative accumulated energy balance considerably in excess of what could be expected from the accumulated ExEE. The degree of compensation differed substantially between MOD and HIGH (104%, CI: 159, 49,  $P < 0.001$ ).

REE increased more in HIGH compared with both MOD (205 kcal/day, CI: 89, 322,  $P < 0.001$ ) and CON (129 kcal/day, CI: 11, 247,  $P = 0.03$ ) (Fig. 3A). REE also increased more in HIGH compared with MOD when corrected for changes in FFM ( $2.9 \text{ kcal} \cdot \text{day}^{-1} \cdot \text{kg}^{-1}$  FFM, CI: 0.03, 5.7,  $P = 0.05$ ). At baseline, REE was regressed against FFM [REE (kcal/day) =  $928.14 + 14.055 \times \text{FFM}$ ,  $R = 0.5$ ,  $P < 0.001$ ], and at follow-up, the observed REE was greater than the predicted REE in HIGH compared with both MOD (192 kcal/day, CI: 81, 305,  $P < 0.001$ ) and CON (115 kcal/day, CI: 1, 228,  $P = 0.05$ ). With intention-to-treat analysis, a difference between predicted and observed REE was still observed between HIGH and MOD (141 kcal/day CI: 31, 251,  $P = 0.009$ ), but not between MOD and CON (95 kcal/day, CI:  $-19$ , 211,  $P = 0.12$ ).

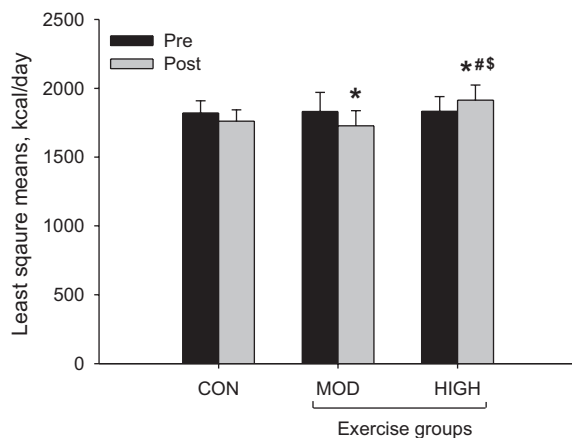
Total physical activity (total activity counts as detected by accelerometry) increased for both MOD ( $13.9 \times 10^3$  counts/day, CI: 2.8, 25.0,  $P = 0.01$ ) and HIGH ( $19.3 \times 10^3$  counts/day, CI: 8.1, 30.6,  $P < 0.001$ ) compared with CON, which was also apparent within the intention-to-treat population. When the exercise component (activity counts during exercise sessions) was subtracted from the total activity counts, there was no significant difference in nonexercise activity between any of the groups (Fig. 2B). However, nonexercise activity was numerically increased by 37% in MOD compared with CON ( $8.8 \times 10^3$  counts/day, CI:  $-1.0$ , 18.7,  $P = 0.09$ ).

There was no difference in habitual EI as a response to the intervention between or within groups (Table 3). Furthermore, the intervention did not change the relative contribution of dietary macronutrients between or within the groups ( $P > 0.13$ , Table 3). No changes between or within groups were observed when ad libitum EI was expressed as total EI or relative to body weight during a high-carbohydrate or low-carbohydrate diet, or combined over 8 days (Table 3).

## DISCUSSION

Over the course of the exercise intervention, engagement in daily aerobic exercise induced a clinically meaningful weight loss (14% body fat reduction) in sedentary, moderately overweight men. Although one group of men (HIGH) increased their ExEE twice as much as the other (MOD), body weight

### A Resting energy expenditure at baseline and follow-up



### B Activity behavior over the course of the intervention

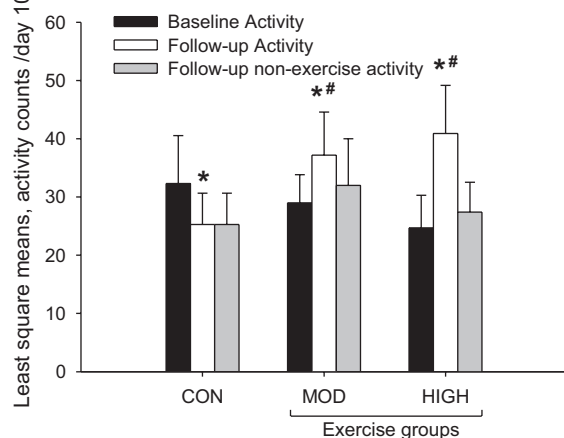


Fig. 3. Effects of the intervention on components of energy expenditure. *A*: resting energy expenditure measured by indirect calorimetry at baseline (black bars) and after the intervention (gray bars). *B*: activity behavior measured by actigraphy before the intervention (black bars) and after the intervention (white bars), and nonexercise activity after the intervention (gray bars). Data are least square means, and error bars represents 95% confidence intervals. \* $P < 0.05$  within group. # $P < 0.05$  compared to CON. \$ $P < 0.001$  compared with MOD. Resting energy expenditure: CON,  $n = 15$ ; MOD,  $n = 16$ ; HIGH,  $n = 13$ . Activity behavior: CON,  $n = 15$ ; MOD,  $n = 16$ ; HIGH,  $n = 17$ . CON, control group; HIGH, high-dose exercise group; MOD, moderate-dose exercise group.

and fat mass losses were similar in both groups. On the basis of our calculations, the accumulated negative energy balance was  $\sim 20\%$  less than could be explained by the exercise intervention in HIGH, whereas it was  $\sim 80\%$  greater than expected in MOD.

The concept of compensation in response to an exercise intervention is not new. Bouchard et al. (7, 8) showed that highly controlled exercise (ExEE: 1,000 kcal/day) for  $\sim 100$  days under conditions of a maintained EI resulted in fat mass reduction ranging from 3 to 12 kg in young, moderately overweight men, suggesting large variability in compensation even when attempts were made to limit potential compensation to factors influencing EE. Recent studies (12, 34) have predicted expected weight loss using a static estimate of 7,700 kcal/kg body wt lost based on the assumption of a 70:30

relationship between fat and lean tissue lost. Using this method, Church et al. (12) reported a dose-dependent attenuation of predicted weight loss with increasing amounts of aerobic exercise in overweight and obese postmenopausal women. This finding is in line with our results, suggesting a threshold in which further increase of exercise does not necessarily induce a more negative accumulated energy balance and, therefore, no additional weight loss or loss of fat mass should be expected. However, this threshold appears to have large individual variation (6, 12, 34) and is likely to depend on sex (15, 23) and the type of exercise (14). King et al. (34) reanalyzed the concept of compensation in response to their earlier supervised exercise intervention in overweight and obese men and women, focusing on changes in body composition. The degree of compensation in response to the increased ExEE was not quantified. However, since the fat mass contribution of body weight lost clearly exceeded 70% in both compensators and noncompensators (33), it is evident that previously reported data have overestimated the degree of compensation in response to exercise. Thus, the compensation index, which is based on changes in fat mass and FFM rather than on weight, represents in our opinion a more precise estimate when the impact of exercise interventions (increased ExEE) on energy balance is quantified.

In the present trial, both exercise regimes (30 as well as 60 min of daily aerobic exercise) led to identical negative accumulated energy balance when calculated from actual changes in body composition over the intervention period. The resulting weight loss in the present trial comprised exclusively of fat mass, demonstrating that even a modest exercise-induced weight loss can be a meaningful “healthy” weight loss (11, 47). Current guidelines for physical activity varies somewhat between countries, but in the adult population,  $\sim 150$  min of physical activity per week (54, 59) or 30 min/day (44) is generally recommended to benefit health, while higher doses of physical activity are often recommended to obtain weight loss or to prevent weight gain (27). However, we observed a greater than predicted negative accumulated energy balance in moderately overweight men exercising only 30 min/day, suggesting a “bonus effect”. Somewhat surprisingly, we found no additional benefit from doubling the exercise dose. Therefore, we challenge the basis for the current recommendations regarding exercise for weight management. A deeper understanding of the mechanisms responsible for lower or greater than predicted change in accumulated energy balance in response to exercise is of interest when recommendations regarding exercise for weight management in different groups are compiled in the future.

Resting energy expenditure is an essential part of total EE, and it decreases in response to caloric restriction, often beyond what would be expected as a result of decreased FFM (28). In this study, exercise was shown to protect FFM and will thereby attenuate any decrease in REE. The decrease in REE observed in MOD is most likely related to the lack of increase in FFM in combination with the negative energy balance (17, 28, 35), whereas the increase in REE in HIGH clearly was driven by the increase in FFM (51). Hence, changes in REE cannot help to explain the difference in compensation between MOD and HIGH found in the present study.

The regulation of NEAT in response to exercise is not well understood, and it is probably influenced by age (22, 26), sex

Table 3. Dietary outcomes for subjects who completed the intervention

Intervention Group	No. of Participants	Mean (SD)	Mean (95% CI)		Pairwise <i>P</i> Value
		Follow-Up Value	Within-Group Change	Between-Group Comparison CON vs. Intervention Groups	
<i>Habitual EI based on diet registrations, kcal/day</i>					
CON	15	2670 (630)	0 (−440; 430)		
MOD	16	2570 (510)	20 (−370; 400)	−60 (−660; 540)	0.57
HIGH	17	2950 (760)	130 (−370; 640)	300 (−280; 880)	0.45
<i>H-CHO, kcal/day</i>					
CON	16	2540 (580)	−200 (−480; 90)		
MOD	16	2580 (630)	−20 (−250; 200)	140 (−210; 490)	0.69
HIGH	18	2560 (480)	20 (−210; 250)	120 (−240; 480)	0.61
<i>H-CHO, kcal·day<sup>−1</sup>·kg body wt<sup>−1</sup></i>					
CON	16	27 (6)	−2.3 (−5.4; 0.7)		
MOD	16	29 (7)	0.6 (−1.9; 3.1)	2.3 (−1.4; 6.1)	0.29
HIGH	18	29 (6)	1.0 (−1.5; 3.5)	2.6 (−1.1; 6.3)	0.20
<i>L-CHO, kcal/day</i>					
CON	16	3050 (730)	−190 (−420; 40)		
MOD	16	2990 (580)	−100 (−340; 150)	50 (−310; 410)	0.98
HIGH	18	3010 (680)	−140 (−370; 90)	20 (−310; 410)	0.98
<i>L-CHO, kcal·day<sup>−1</sup>·kg body wt<sup>−1</sup></i>					
CON	16	33 (7)	−2.1 (−4.7; 0.5)		
MOD	16	34 (7)	−0.1 (−2.8; 2.5)	1.6 (−2.5; 5.3)	0.60
HIGH	18	34 (8)	−0.7 (−3.5; 2.2)	1.3 (−2.6; 5.6)	0.68
<i>Diet 8-day, kcal/day</i>					
CON	16	2870 (640)	−150 (−340; 50)		
MOD	16	2830 (550)	−30 (−240; 170)	70 (−210; 360)	0.81
HIGH	18	2820 (440)	−10 (−190; 160)	90 (−190; 360)	0.73
<i>Diet 8-day, kcal·day<sup>−1</sup>·kg body wt<sup>−1</sup></i>					
CON	16	31 (6)	−1.7 (−3.8; 0.3)		
MOD	16	32 (6)	0.5 (−1.7; 2.7)	1.8 (−1.2; 4.8)	0.32
HIGH	18	32 (6)	0.7 (−1.3; 2.8)	2.0 (−0.9; 5.0)	0.22

Diet 8-day, pooled caloric intake from H-CHO and L-CHO. EI, energy intake; E%, percentage contribution to total energy intake.

(57), and type of exercise (30, 56). Exercise that is not too strenuous might increase or at least not lead to a decrease in NEAT (2, 56) but lower NEAT after an exercise regime has been associated with lower than predicted loss of fat mass in some individuals (39), suggesting a potential causal effect under certain conditions. The larger than expected negative accumulated energy balance in MOD could potentially be explained by an increase in NEAT. Although not statistically significant, we found 37% higher ( $P = 0.09$ ) nonexercise activity in MOD compared with CON at follow-up. Determination of changes in free-living NEAT is a technical challenge (36), and clearly, we are limited by the accelerometer-based approach. Nonexercise activity thermogenesis has, furthermore, been reported to vary considerably from day to day (37), and our samplings are limited to a few days, and, in addition, we cannot pick up small ambulatory movements and fidgeting using accelerometers (36, 37).

It is also well recognized that habitual EI is difficult to measure due to unintentional, as well as potential intentional restrictions in food intake, underreporting, and considerable variability in EI between days. Nevertheless, there is some indication that EI increased in HIGH, driving the small but quantifiable degree of compensation. We applied two different methods for assessing changes in EI and, although not statis-

tically significant, the methods showed similar tendencies toward a numerical increase in EI. A similar potential compensation as seen in HIGH, probably explained by an increase in homeostatic and/or hedonic drive to eat, has been demonstrated in previous exercise interventions comparable to the intervention in HIGH (33, 41).

Several limitations could affect the interpretation of the study. One apparent limitation is that the study is statistically powered to calculate the degree of compensation, while it is not powered to detect small, but relevant, changes in the compensatory mechanisms, largely due to the variation associated with these measures (accuracy). Furthermore, the calculation of the degree of compensation was based on previously published assumptions for energy equivalents for gain or loss in fat mass and FFM. However, there is no consensus in the literature for absolute values derived for the synthesis or liberation of energy during breakdown/oxidation of fat mass and FFM (24, 50).

We conclude that a similar meaningful loss of body fat was obtained regardless of exercise dose. On the basis of our calculations of accumulated energy balance, 30 min of daily exercise resulted in a greater than expected negative energy balance, whereas 60 min of daily exercise induced a small, but quantifiable, amount of compensation. Thus, the degree of



compensation in response to an increase in ExEE as a result of introduction of regular endurance exercise is dependent on exercise dose. The number of subjects in the present study was sufficient for assessment of energy balance but not to adequately elucidate the compensatory mechanisms involved. However, on the basis of the present findings, we propose that the introduction of a moderate dose of exercise may actually lead to an increase in NEAT without any increase in EI resulting in a “bonus effect,” whereas a higher dose of exercise may lead to an increase in EI and, thereby, a degree of compensation and less than expected loss of FM.

### Perspectives and Significance

Obesity, as a result of long-term positive energy balance, is a major risk factor for many preventable diseases, such as coronary heart disease and Type 2 diabetes. Although well recognized as an important means for weight loss maintenance (9), the role of habitual endurance training in weight loss is scrutinized, and it has been suggested that exercise leads to compensatory responses. In the current study, we show that despite that one group undertook twice the amount of endurance training, the reduction in body weight and, more importantly, in body fat was the same as the weight loss and was equal among the two groups (a healthy weight loss). Surprisingly, the reduction with the moderate-dose exercise was far greater than what could be explained by the increased energy expenditure from the training itself (no compensation). Thus, when addressing obesity reduction and compensatory changes in response to exercise in the future, using weight loss as the only determinant for success is inadequate (47). Well-controlled, long-term “cost-benefit studies” that are designed to find the most efficacious feasible exercise interventions for healthy weight loss and to address the identification of potential compensatory responses in different groups of overweight individuals are needed.

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### DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

### AUTHOR CONTRIBUTIONS

Author contributions: M.R., T.P., B.M.S., and A.S. conception and design of research; M.R., P.L.A., M.H.R., T.P., and B.M.S. performed experiments; M.R. and A.S. analyzed data; M.R., T.P., B.M.S., and A.S. interpreted results of experiments; M.R. prepared figures; M.R. and A.S. drafted manuscript; M.R., B.M.S., and A.S. edited and revised manuscript; M.R., P.L.A., M.H.R., T.P., B.M.S., and A.S. approved final version of manuscript.

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