



Effects of a 4-month active weight loss phase followed by weight loss maintenance on adaptive thermogenesis in resting energy expenditure in former elite athletes

Catarina L. Nunes¹ · Filipe Jesus¹ · Ruben Francisco¹ · Mark Hopkins² · Luís B. Sardinha¹ · Paulo Martins³ · Cláudia S. Minderico¹ · Analiza M. Silva¹

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Abstract

Purpose Despite adaptive thermogenesis (AT) being studied as a barrier to weight loss (WL), few studies assessed AT in the resting energy expenditure (REE) compartment after WL maintenance. The aim of this study was twofold: (1) to understand if AT occurs after a moderate WL and if AT persists after a period of WL maintenance; and (2) if AT is associated with changes in body composition, hormones and energy intake (EI).

Methods Ninety-four participants [mean (SD); BMI, 31.1(4.3)kg/m²; 43.0(9.4)y; 34% female] were randomized to intervention (IG, *n* = 49) or control groups (CG, *n* = 45). Subjects underwent a 1-year lifestyle intervention, divided in 4 months of an active WL followed by 8 months of WL maintenance. Fat mass (FM) and fat-free mass (FFM) were measured by dual-energy X-ray absorptiometry and REE by indirect calorimetry. Predicted REE (pREE) was estimated through a model using FM, FFM. EI was measured by the “intake-balance” method.

Results For the IG, the weight and FM losses were – 4.8 (4.9) and – 11.3 (10.8)%, respectively (*p* < 0.001). A time–group interaction was found between groups for AT. After WL, the IG showed an AT of –85(29) kcal.d^{–1} (*p* < 0.001), and remained significant after 1 year [AT = – 72(31)kcal.d^{–1}, *p* = 0.031]. Participants with higher degrees of restriction were those with an increased energy conservation (*R* = – 0.325, *p* = 0.036 and *R* = – 0.308, *p* = 0.047, respectively). No associations were found between diet adherence and AT. Following a sub-analysis in the IG, the group with a higher energy conservation showed a lower WL and fat loss and a higher initial EI.

Conclusion AT in REE occurred after a moderate WL and remained significant after WL maintenance. More studies are needed to better clarify the mechanisms underlying the large variability observed in AT and providing an accurate methodological approach to avoid overstatements. Future studies on AT should consider not only changes in FM and FFM but also the FFM composition.

Keywords Energy balance · Metabolic adaptation · Resting energy expenditure

Introduction

Despite lifestyle interventions aimed weight loss (WL) being abundant in the literature, there is a lack of information regarding one’s ability to maintain their new and lower weight. Indeed, most people struggle with maintaining a weight-reduced state, often regaining their lost weight over time [1, 2].

During WL, changes in energy expenditure (EE) components are expected to occur as a consequence of changes in FM and FFM [3], such as decreases in resting and non-resting energy expenditure [4, 5]. However, it has been shown that some changes in components of EE occur to a greater

✉ Analiza M. Silva
analiza@fmh.ulisboa.pt

¹ Exercise and Health Laboratory, CIPER, Faculdade Motricidade Humana, Universidade Lisboa, Estrada da Costa, 1499-002 Cruz-Quebrada, Portugal

² School of Food Science and Nutrition, Faculty of Environment, University of Leeds, Leeds, UK

³ Laboratory of Sport Psychology, Faculdade de Motricidade Humana da Universidade de Lisboa, 1499-002 Cruz-Quebrada, Portugal

extent than would be predicted based on changes in body composition stores [6]. This mass-independent decrease in any of the EE components, such as resting EE (REE), physical activity EE (PAEE), and thermic effect of food (TEF), beyond what we predicted from changes in FM and FFM is defined as adaptive thermogenesis (AT) [7, 8].

While AT after WL has been widely studied and discussed [6], the lack of concordance among methodologies employed to assess AT and/or how REE is predicted was recently highlighted [9]. AT has been studied as a possible barrier especially in WL maintenance, contributing to weight regain [10–12]. Moreover, its influence on long-term weight management has been recently questioned, as some authors found that this “phenomenon” seems to be attenuated or even disappeared after a period of weight stabilization [13–17]. Regarding moderate WL, while some studies suggest that a disproportionate decrease in REE appears during WL and may persist during the weight-reduced state [10, 18], others have found no evidence of AT in any of the EE components [19, 20]. In addition, the limited number of studies available assessing AT during a WL maintenance typically employs weak-to-moderate designs, being mostly observational studies or controlled trials without a control group [6].

Therefore, the aims of this study were: (1) to understand if AT remains significant during a WL maintenance period, i.e., under a neutral energy balance (EB), comparing with a control group; and (2) if the degree of energy conservation is related with changes in body composition, weight-related hormones, or the percentage of energy restriction.

Methodology

This is a secondary analysis of the Champ4life project [21], a 1-year lifestyle intervention that consisted of a 4-month WL intervention and an 8-month WL maintenance period. All participants were former elite athletes, aged 18–65 years old, inactive (< 20 min/day of vigorous physical activity intensity for at least 3 days per week or < 30 min/day of moderate intensity physical activity for at least 5 days per week [22]) and with a body mass index (BMI) ≥ 24.9 kg/m². They also needed to be ready to modify their diet and physical activity habits and be available to attend the educational sessions at the study site. A detailed description of the protocol study (including inclusion and exclusion criteria) and its main results and are presented elsewhere [21, 23].

A total of 94 participants were included in this study (clinicaltrials.gov ID: NCT03031951) and were randomly assigned to one of the two groups: intervention (IG) or control group (CG). Randomization was performed according to an automated computer-generated randomization scheme managed by the principal investigator (A.M.S.). The study was single-blinded, as the research team who assessed all

outcomes were blinded to participant group assignment. Also, all outcome data were kept blinded until the final data entry for the entire study was completed.

The study was approved by the Ethics Committee of the Faculty of Human Kinetics, University of Lisbon (Lisbon, Portugal, CEFMH Approval Number: 16/2016) and was conducted in accordance with the Declaration of Helsinki for human studies from the World Medical Association [24]. Prior to participants' recruitment, the trial was registered at www.clinicaltrials.gov (clinicaltrials.gov ID: NCT03031951). Measures of body weight and composition, REE, and EB-related blood biomarkers were measured at baseline, post WL (4 months) and post WL maintenance (1 year).

The Champ4life intervention

The Champ4life was a 1-year intervention SDT-based [25], divided in 4 months of active WL and 8 months of follow-up (WL maintenance). For the active WL, participants from IG had a nutritional appointment with a registered dietitian to discuss their eating patterns and to induce a moderate caloric deficit (~ 300–500 kcal.d⁻¹). Additionally, the IG underwent 12 educational sessions (1 per week) aimed to promote behavioral changes possible to be integrated in participants' daily lives and contexts, including educational content and practical application in the areas of PA and exercise, diet and eating behavior as well as behavior modification [21]. Also, participants had their weight tracked weekly. After the active WL phase, participants underwent an 8-month weight maintenance period, aimed to understand if participants were able to maintain the reduced weight state at a long term. During this phase, the IG underwent nutritional appointments to adjust their caloric intake to create a neutral EB (maintenance calories). When needed, participants were able to contact with the project team throughout the follow-up period to clarify any doubts or to readjust their caloric intake. Participants from the CG were placed in a waiting list. After completing the 3 assessments (baseline, 4 months post-intervention, and after the follow-up period—1 year), they were provided with the Champ4Life intervention. A detailed description of the Champ4life program is provided elsewhere [21].

Body composition

Participants had their weight and height measured wearing a bathing suit and without shoes to the nearest 0.01 kg and 0.1 cm, respectively, with a scale and stadiometer (Seca, Hamburg, Germany). Body mass index was calculated using the formula [weight(kg)/height²(m²)]. Dual-energy X-ray absorptiometry (DXA) (Hologic Explorer-W, Waltham, USA) was used to assess total FM (kg and %), FFM (kg)

and sub-total lean soft tissue (LST) (kg) [26]. FM and LST were also presented for sub-regions, namely the trunk and appendicular (arms + legs) regions. When a participant did not fit within the active scan area (given the superior width dimensions), and to avoid overlapping of body parts, a partial scan was performed and the left arm was left outside the scan area [27]. Therefore, in 6 participants, this technique was considered for the body composition analysis.

Measured resting energy expenditure (m REE)

Assessment of REE was performed in the morning when fasted (8.00–10.00 a.m.). All measurements will be performed in the same room at an environmental temperature and humidity of approximately 22 °C and 40–50%, respectively. The MedGraphics CPX Ultima indirect calorimeter (MedGraphics Corporation, Breezeex Software, Italy) was used to measure breath-by-breath oxygen consumption (VO_2) and carbon dioxide production (VCO_2) using a face mask, for 30 min. Before the measurement, participants lay in a supine position for 15 min covered with a blanket. The first and the last 5 min of data collection were discarded and the mean VO_2 and VCO_2 of 5 min steady states was used in Weir equation [28] and the period with the lowest REE was considered for data analysis. Steady state was defined as a 5 min period with $\leq 10\%$ CV for VO_2 and VCO_2 [29]. Based on test–re-test of 7 participants, the technical error of measurement (TEM) for REE was 56.4 kcal. A more detailed description of the procedures is presented in the protocol paper [21].

Predicted resting energy expenditure (p REE)

To predict REE (p REE), a predictive equation using measured body composition values for FM and FFM for all participants as the independent predictors was created. The following prediction model was created:

$$p\text{REE} = 505.240 + 2.766\text{FM}_{(\text{kg})} + 17.531\text{FFM}_{(\text{kg})}$$

$$(r^2 = 0.570, p < 0.001)$$

The equation was used to predict p REE at baseline and after 4 (WL) and 12 months (WL maintenance) using the body composition values measured at each respective time point.

Physical activity energy expenditure (PAEE) and total daily energy expenditure (EE)

PAEE was objectively measured using a tri-axial accelerometer (ActiGraph GT3X+, Pensacola, FL) as described

elsewhere [23]. EE was estimated as the sum of REE, PAEE and thermic effect of food (TEF):

$$EE_{(\text{kcal}/\text{d})} = REE_{(\text{kcal}/\text{d})} + PAEE_{(\text{kcal}/\text{d})} + TEF_{(\text{kcal}/\text{d})}$$

The TEF component was assumed as 10% of TDEE [30].

Adaptive thermogenesis (AT)

AT was assessed after 4-month WL and 8-month follow-up based on the difference between predicted and measured REE, after accounting for baseline differences in these parameters:

After 4 months of WL:

$$AT(\text{kcal.d} - 1) = [((\frac{4\text{mo}}{12\text{mo}})REE - (\frac{4\text{mo}}{12\text{mo}})REE) - ((\frac{B}{m}\text{aseline})REE - (\frac{B}{p}\text{aseline})REE)];$$

After 8 months of follow-up:

$$AT(\text{kcal.d} - 1) = [((\frac{1}{2}\text{mo})REE - (\frac{1}{2}\text{mo})REE) - ((\frac{B}{m}\text{aseline})REE - (\frac{B}{p}\text{aseline})REE)]$$

Negative values indicate a lower-than-expected decrease in REE considering the changes in body composition (measured REE lower than predicted REE) and positive values represent a change in REE equal to or greater than the predicted REE (measured REE higher than predicted REE) [31].

Energy balance (EB)

To assure the EB state for each time point, the EB equation was applied to quantify the average rate of changed body energy store or lost in kilocalories per day.

The EB equation is denoted as follows:

$$EB (\text{kcal.d}^{-1}) = EI - EE$$

A negative EB is considered when the EE surpasses the EI, while EB is positive when EI is larger than EE. A neutral EB represents the average rate of energy deficit or surplus expressed in kilocalories per day. EB can be calculated from the changed body energy stores from the beginning to the end of the WL intervention. Hence, using the established energy densities for FM [32] and FFM [33], the following equation was applied:

$$EB (\text{kcal.d}^{-1}) = 1.0 \frac{\Delta\text{FFM}}{\Delta t} + 9.5 \frac{\Delta\text{FM}}{\Delta t}$$

where ΔFM and ΔFFM represent the change in grams of FM and FFM from the beginning to end of the intervention and Δt is the time length of the intervention in days.

Energy intake (EI)

EI was estimated by the “intake-balance method” [34]. This method has been previously validated [35, 36] and has been shown to provide valid estimation of EI through changes in body energy stores such FM and FFM (please check the EB section), together with EE. The following equation was used:

$$EI_{(kcal/d)} = EE_{(kcal/d)} + EB_{(kcal/d)},$$

where EE represents the total daily energy expenditure measured by accelerometry and the EB (calculated through changes in FM and FFM). For the baseline EI, as participants were weight-stable during at least 3 months (inclusion criteria), we considered an $EB=0$, and therefore $EI=EE$.

This equation was used not only to determine EI at each time point, but also to calculate the degree of energy restriction during the WL phase.

Adherence to the diet

In the Champ4life project, rather than having a fixed diet plan, participants were asked to change some of their eating patterns to induce a caloric restriction between 300 and 500 $kcal.d^{-1}$ (previously calculated by a registered dietitian). Therefore, the prescribed caloric restriction varied among participants and was calculated as:

$$CR_{prescribed(\%)} = 100 \times \left(1 - \frac{EI_{baseline} - C}{EI_{baseline}} \right)$$

where C represents the number of calories that were taken out from the initial EI (between 300 and 500 kcal).

Adherence was assessed through the following equation proposed by Racette et al. [36]:

$$Adherence_{(\%)} = 100 \times \left[\left(1 - \frac{EI_{4mo}}{EI_{baseline}} \right) \times \frac{100}{CR_{prescribed(\%)}} \right]^v$$

Blood samples

Blood samples were collected according to the standard procedures by venipuncture from the antecubital vein into ethylene-diamine-tetra-acetic acid tubes (EDTA) and dry tubes with accelerated for serum separation. Whole blood was used directly, or sample treatment was performed, including centrifugation at 500g at 4 °C for 15 min. Serum was frozen at -80 °C for posterior analyses.

The thyroid panel [including Thyroid-Stimulating Hormone (TSH) free tri-iodothyronine (FT3) and free thyroxine (FT4)] and insulin were assessed by immuno-quimio-luminescence in a different automated analyzer (Cobas e411, Roche Diagnostics, Portugal). Serum levels of leptin were assessed by ELISA (enzyme-linked immunosorbent assay) using commercial kits (DIAsource ImmunoAssays, Belgium).

Statistical analysis

Statistical analysis was performed using IBM SPSS statistics version 25.0 (IBM, Chicago, Illinois, USA). The Kolmogorov–Smirnov test was performed to examine whether variables followed a normal distribution. Baseline differences between the intervention and control groups were assessed by independent two sample *t* test. Changes in body composition and EB-related hormones were previously assessed through linear mixed models. To assess the effect of time, group and time–group interaction in AT, linear mixed models using group (intervention vs control group) and time (baseline vs 4 months and vs 12 months) as fixed effects were performed. The covariance matrix for repeated measures within subjects over time was modeled as compound symmetry.

The one-sample *t* test was performed to test the significance for AT (if it is different from zero). Pearson’s correlation was performed to examine the association between AT and body composition, blood samples and adherence to the diet. The analysis was intention-to-treat, as none of the participants were excluded whether they completed or not the 1-year intervention and missing data were treated through maximum likelihood (by linear mixed models). The typical error (TE) for AT was calculated from the SD of AT for the control group divided by $\sqrt{2}$, representing the technical error of measurement as well as the within-subject variability [37]. Statistical significance was set at a two-sided $p < 0.05$.

Results

Ninety-four participants [mean (SD): BMI = 31.1 (4.3) kg/m^2 , age = 43.0 (9.4)y, 34% females] were initially included in this study and randomized to either intervention [IG, $n=49$, mean (SD): BMI = 31.7 (3.9) kg/m^2 , age = 42.4 (7.3) y, 35% females] or control groups [CG, $n=45$, mean (SD): BMI = 30.5 (4.7) kg/m^2 , age = 43.6 (11.3)y, 33% females]. A detailed description of the results of the Champ4life intervention is presented elsewhere [23]. Values of body composition, blood biomarkers, and changes between time points are presented in (Table 1).

Table 1 Values of body composition and blood biomarkers*

		Control (n = 45)	Intervention (n = 49)	Changes†	95% CI	p-value
Body composition						
Weight (kg)	Baseline	91.2 (0.5)	91.1 (0.4)	Changes†	95% CI	p-value
	4 months	91.5 (0.5)	86.8 (0.5) [‡]	- 4.7	- 6.1, - 3.3	<0.001
	12 months	92.2 (0.5)	86.8 (0.5) [§]	- 5.3	- 6.9, - 3.8	<0.001
BMI (kg/m ²)	Baseline	31.0 (0.2)	31.0 (0.2)	Changes†	95% CI	p-value
	4 months	31.1 (0.2)	29.5 (0.2) [‡]	- 1.6	- 2.1, - 1.1	<0.001
	12 months	31.2 (0.2)	29.5 (0.2) [§]	- 1.7	- 2.2, - 1.2	<0.001
Fat mass (kg)	Baseline	29.7 (0.4)	29.6 (0.4)	Changes†	95% CI	p-value
	4 months	30.1 (0.4)	26.3 (0.4) [‡]	- 3.8	- 5.1, - 2.6	<0.001
	12 months	30.7 (0.4)	26.6 (0.4) [§]	- 4.1	- 5.4, - 2.8	<0.001
Fat mass (%)	Baseline	33.1 (0.3)	33.1 (0.3)	Changes†	95% CI	p-value
	4 months	33.3 (0.3)	30.7 (0.3) [‡]	- 2.6	- 3.6, - 1.7	<0.001
	12 months	33.9 (0.3)	30.9 (0.3) [§]	- 3.1	- 4.1, - 2.1	<0.001
Fat-free mass (kg)	Baseline	60.2 (0.2)	60.2 (0.2)	Changes†	95% CI	p-value
	4 months	59.9 (0.2)	59.3 (0.2) [‡]	- 0.7	- 1.5, 0.1	0.118
	12 months	59.7 (0.3)	59.1 (0.2) [§]	- 0.6	- 1.5, 0.2	0.099
Trunk FM (kg)	Baseline	14.9 (0.7)	16.9 (0.7)	Changes†	95% CI	p-value
	4 months	15.1 (0.7)	14.9 (0.7) [‡]	- 2.1	- 2.9, - 1.3	<0.001
	12 months	15.5 (0.7)	15.1 (0.7) [§]	- 2.4	- 3.2, - 1.5	<0.001
Trunk LST (kg)	Baseline	29.2 (0.6)	29.4 (0.6)	Changes†	95% CI	p-value
	4 months	29.0 (0.6)	29.0 (0.6)	- 0.2	- 0.8, 0.4	0.472
	12 months	28.9 (0.6)	28.8 (0.6) [§]	- 0.3	- 0.9, 0.3	0.274
Appendicular FM (kg)	Baseline	12.1 (0.5)	13.0 (0.5)	Changes†	95% CI	p-value
	4 months	12.2 (0.5)	11.6 (0.5) [‡]	- 1.5	- 2.0, - 0.9	<0.001
	12 months	12.5 (0.5)	11.7 (0.5) [§]	- 1.6	- 2.2, - 1.0	<0.001
Appendicular LST (kg)	Baseline	26.5 (0.6)	27.3 (0.6)	Changes†	95% CI	p-value
	4 months	26.6 (0.6)	26.8 (0.6) [‡]	- 0.6	- 1.1, - 0.1	0.029
	12 months	26.4 (0.6)	26.8 (0.6)	- 0.4	- 1.0, 0.2	0.169
Blood biomarkers						
Insulin (μU/mL)	Baseline	13.0 (0.7)	13.9 (0.7)	Changes†	95% CI	p-value
	4 months	11.1 (0.8)	9.2 (0.8) [‡]	- 2.9	- 5.8, 0.1	0.078
	12 months	14.1 (0.9)†	10.2 (0.9) [§]	- 4.9	- 8.0, - 1.8	0.006
TSH (μIU/mL)	Baseline	2.1 (0.1)	2.2 (0.1)	Changes	95% CI	p-value
	4 months	2.0 (0.1)	2.0 (0.1)	- 0.04	- 0.32, 0.25	0.802
	12 months	1.9 (0.1)	1.9 (0.1) [§]	- 0.07	- 0.37, 0.24	0.670
T3 (pg/mL)	Baseline	3.3 (0.05)	3.3 (0.05)	Changes	95% CI	p-value
	4 months	3.2 (0.05)	3.1 (0.05) [‡]	- 0.10	- 0.29, 0.10	0.328
	12 months	3.2 (0.06)	3.1 (0.06) [§]	- 0.08	- 0.29, 0.13	0.447
T4 (ng/dL)	Baseline	1.3 (0.02)	1.3 (0.02)	Changes	95% CI	p-value
	4 months	1.2 (0.02)	1.2 (0.02) [‡]	- 0.02	- 0.11, 0.06	0.563
	12 months	1.2 (0.02)	1.2 (0.02)	- 0.01	- 0.10, 0.08	0.847
Leptin (ng/mL)	Baseline	22.7 (0.6)	23.1 (0.6)	Changes	95% CI	p-value
	4 months	24.1 (0.6)	20.8 (0.6) [‡]	- 3.8	- 5.9, - 1.7	<0.001
	12 months	23.2 (0.7)	19.5 (0.7) [§]	- 4.2	- 6.5, - 2.0	<0.001

Data are presented as estimated means (SE) from linear mixed models

Changes: differences in change scores between control and intervention groups e.g.,

(4 months/12months_{intervention} - baseline_{intervention})-(4 months/12months_{control} - baseline_{control})

*All models were adjusted for baseline values and sex

[‡]Differences within group between baseline and 4 months, *p* < 0.05

[§]Differences within group between baseline and 12 months, *p* < 0.05

[†]Differences within group between 4 and 12 months, *p* < 0.05

Eleven participants (IG: 8; CG: 4) were lost to follow-up after 4 months and a further fourteen during the 8-month follow-up (IG: 6, CG: 8). The drop-out rate was ~27.7% and was similar between groups (28.6% and 26.7% for the IG and CG, respectively).

After 4 months, the IG showed significant decreases for weight, BMI, and FM (kg and %) ($p < 0.001$). These alterations remained significant at the end of the intervention ($p < 0.001$). The IG also showed a larger trunk and appendicular FM loss when compared with the CG at 4 months (trunk FM: ED = -2.1, [95% CI: -2.9 to -1.3], $p < 0.001$; appendicular FM: ED = -1.5, [95% CI: -2.0 to -0.9], $p < 0.001$) and 12 months (trunk FM: ED = -2.4, [95% CI: -3.2 to -1.5], $p < 0.001$; appendicular FM: ED = -1.6, [95% CI: -2.2 to -1.0], $p < 0.001$). For the blood biomarkers, insulin decreased for the IG after the 1-year intervention (Estimated difference (ED) = -4.9, [95% CI: -8.0 to -1.8], $p = 0.006$) when compared with the CG. Leptin levels decreased more in the IG than in the CG at 4 months (ED = -3.8, [95% CI: -5.9 to -1.7], $p < 0.001$) and 12-month (ED = -4.2, [95% CI: -6.5 to -2.0], $p < 0.001$) time points. No differences were found for the thyroid panel (TSH, T3 and T4).

Considering within group differences, the IG showed decreases in body composition variables (weight, BMI, FM, FFM, trunk FM and appendicular FM), insulin and leptin after 4- and 12-month time points (compared with baseline, $p < 0.05$). No differences were found between after 4 months

and after 12 months for the IG. The CG increased insulin from 4 months' time point to after 12 months ($p < 0.001$).

After the intervention (4 months), the IG underwent a negative EB (EB = -269.7 ± 289.1 kcal.d⁻¹, $p < 0.001$), while the CG was at a neutral EB (EB = 14.0 ± 129.4 kcal.d⁻¹, $p = 0.489$). At the end of the program, both groups were at a neutral EB (15.6 ± 72.3 kcal.d⁻¹, $p = 0.204$ for IG; 21.5 ± 98.7 kcal.d⁻¹, $p = 0.219$ for CG).

The values for REE and AT are presented in (Table 2).

A group-time interaction was found for mREE, pREE and AT estimated using both equations ($p < 0.05$). Participants from the IG decreased mREE and pREE estimated from both equations after 4 months and 1 year, when compared with the baseline values (within group, $p < 0.05$). After 1 year of intervention, the CG increased pREE using both equations (within group, $p < 0.05$).

A time-by-group interaction was found for AT assessment ($p = 0.012$). After 4 months, AT occurred for the IG (statistically different from zero, $p = 0.002$) and remained significant after 1 year ($p = 0.031$). On the other hand, the CG showed an energy dissipation (with a positive value for AT) after 1 year ($p = 0.047$).

No correlations (adjusted for group) were found between AT and WL (kg and %), Δ trunk (FM and LST), Δ appendicular (FM and LST) and blood biomarkers, except for AT and Δ trunk FM (%) at the end of the intervention (12 months) ($R = 0.294$, $p = 0.031$).

Table 2 Resting energy expenditure (measured and predicted) and adaptive thermogenesis

		Control (n=45)	95% CI	Intervention (n=49)	95% CI	Group*time p-value
mREE (kcal.d ⁻¹)	Baseline	1637 (39)	1560, 1713	1663 (37)	1590, 1737	<0.001
	4 months	1605 (40)	1525, 1684	1549 (39) [‡]	1472, 1625	
	12 months	1720 (42) [†]	1638, 1803	1546 (41) [§]	1466, 1627	
pREE (FM and FFM) pREE (kcal.d ⁻¹)	Baseline	1637 (24)	1590, 1684	1656 (23)	1611, 1702	0.105
	4 months	1635 (24)	1587, 1682	1631 (23) [‡]	1585, 1677	
	12 months	1624 (24)	1576, 1671	1629 (23) [§]	1583, 1675	
mREE - pREE (kcal.d ⁻¹)	Baseline	-3 (32)	-65, 59	5 (30)	-54, 65	0.001
	4 months	-32 (33)	-97, 34	-78 (33) [‡]	-142, -13	
	12 months	98 (35) [†]	29, 167	-66 (35)	-135, 2	
AT (kcal.d ⁻¹)	Baseline	NA	NA	NA	NA	0.012
	4 months	-26(29)	-87, 28	-85 (29) [*]	-143, -28	
	12 months	88 (31) ^{*†}	27, 149	-72 (31) [*]	-134, -10	

Data are presented as estimated means (SE) from linear mixed models, with all models adjusted for sex

mREE measured resting energy expenditure (indirect calorimetry), *pREE* predicted resting energy expenditure (predictive equation), *AT* adaptive thermogenesis

^{*}Statistically different from zero (*t*-test) (only for AT)

[‡]Differences within group between baseline and 4 months, $p < 0.05$

[§]Differences within group between baseline and 12 months, $p < 0.05$

[†]Differences within group between 4 and 12 months, $p < 0.05$

Changes in body composition stores (FM and FFM) and in REE (measured and predicted) are displayed in (Fig. 1).

Comparison between adherence and AT

Diet adherence was ~89% (95%IC: 40 to 137%), with a calculated CR of 13.6% (95%IC: 6.4 to 20.9%) compared with 17.5% (95%IC: 16.3 to 18.7%) prescribed. The calculated CR was negatively associated with AT (kcal/d and %), where participants with higher degrees of restriction were those who showed an increased energy conservation ($R = -0.325$, $p = 0.036$ and $R = -0.308$, $p = 0.047$, respectively). No associations were found between adherence (%) and AT.

AT variability: differences between thrifty and spendthrift individuals

A sub-analysis comparing changes in body composition and blood samples dividing the IG in those who showed an energy conservation (negative value for AT, thrifty) with those who dissipate energy (positive value for AT, spendthrift) is presented in (Table 3).

The TE for AT was 103 kcal/d and individuals with an energy conservation < -103 kcal/d were considered “thrifty” and those with positive values for AT as “spendthrift”.

Differences were found between groups for weight, BMI, FM (kg and %), trunk FM and appendicular FM ($p < 0.05$). The group with a higher energy conservation showed a lower WL and fat loss. These thrifty individuals showed a lower initial EI [mean difference = -396 (174) kcal/d, 95%IC (-754 , -39), $p = 0.031$] when compared to the spendthrift group. No differences were found between groups for the adherence (%) nor the measured CR (%) ($p > 0.05$).

Discussion

The main finding of this study was the presence of AT in REE after a moderate WL (~5%), which remained significant after an 8-month WL maintenance period in which body weight was maintained. These results indicated that energy is conserved via adaptive mechanisms both during active WL and in the weight-reduced state.

The existence of AT and its clinical relevance has been widely debated in the literature [6]. However, the findings are not consistent, as some studies suggest that AT exists and works as a barrier to WL and its maintenance [38], while others indicate that AT is not a predictor of weight regain [17, 39].

Recently, Martins et al. [39] found an AT of ~ -90 kcal. d^{-1} after a 9-week WL period, which halved to ~ -38 kcal. d^{-1} after a 4-week period of weight stabilization. It should also be noted that the used approach to calculate AT differed between studies, as AT was assessed by subtracting the pREE to the mREE, without taking into consideration the baseline residuals (baseline measured REE minus baseline predicted REE). However, despite decreasing its magnitude, AT was still significant even under a period of an “assumed” neutral EB. Nevertheless, despite participants being weight-stable during this period, the authors did not assess the “real” EB at each time point and, consequently, a true neutral EB cannot be assured. According to the authors, 4 weeks of weight stabilization may not be sufficient to return to a neutral EB, especially if participants underwent a very-low-calorie diet (~800 kcal. d^{-1}), which may explain why AT remained significant after this phase [17]. In our study, participants underwent a moderate caloric restriction (300 to 500 kcal/d of CR) and a longer WL maintenance period (~32 weeks). Nevertheless, AT remained significant at the end of the intervention. Moreover, although a neutral EB was calculated at the end of the program, it is

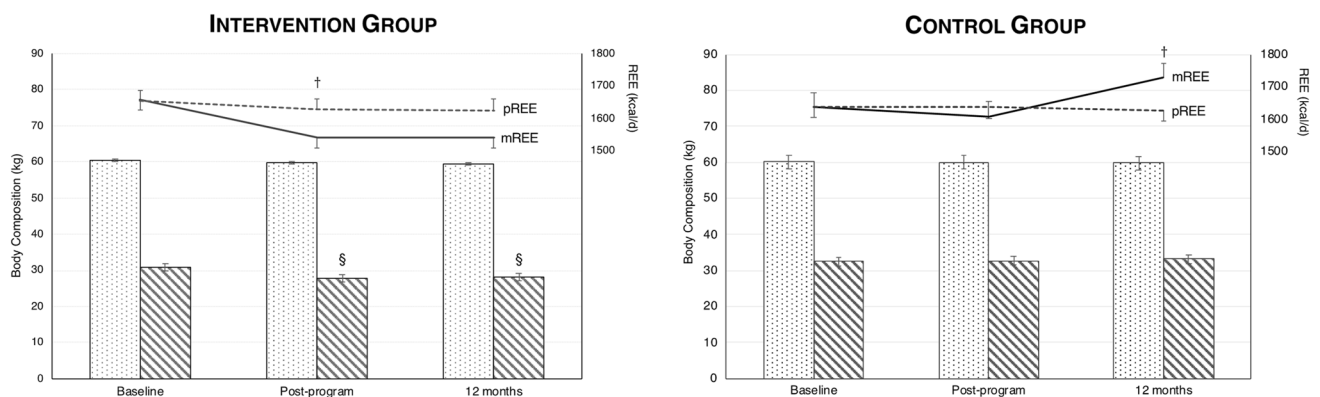


Fig. 1 Changes in body composition stores (FM and FFM) and Resting Energy Expenditure (mREE and pREE) from mixed model analysis (estimated means (SE), $n = 94$)

Table 3 Comparisons between thrifty and spendthrift individuals from the IG*

		Thrifty (n = 11)	Spendthrift (n = 25)	Changes†	95% CI	p-value
Body composition						
Weight (kg)	Baseline	92.0 (3.2)	91.7 (4.0)			
	4 months	88.5 (3.2) [‡]	85.3 (4.0) [‡]	- 2.8	- 5.4, - 0.3	0.032
	12 months	88.5 (3.2) [§]	84.9 (4.0) [§]	- 3.2	- 5.9, - 0.5	0.020
BMI (kg/m ²)	Baseline	31.0 (0.9)	31.9 (1.1)			
	4 months	29.8 (0.9) [‡]	29.7 (0.9) [‡]	- 1.0	- 1.9, - 0.2	0.019
	12 months	29.8 (0.9) [§]	29.5 (1.1) [§]	- 1.2	- 2.1, - 0.3	0.008
Fat mass (kg)	Baseline	28.4 (1.5)	31.7 (1.8)			
	4 months	25.9 (1.5) [‡]	26.5 (1.8) [‡]	- 2.8	- 4.9, - 0.6	0.012
	12 months	26.3 (1.5) [§]	26.4 (1.8) [§]	- 3.2	- 5.4, - 1.0	0.005
Fat mass (%)	Baseline	31.4 (1.0)	35.5 (1.2)			
	4 months	29.8 (1.0) [‡]	32.0 (1.2) [‡]	- 1.9	- 3.7, - 0.1	0.036
	12 months	30.0 (1.0) [§]	31.9 (1.2) [§]	- 2.2	- 4.0, - 0.4	0.020
Fat-free mass (kg)	Baseline	62.1 (2.1)	59.0 (2.6)			
	4 months	61.2 (2.1)	57.7 (2.6) [‡]	- 0.4	- 1.7, 0.8	0.475
	12 months	61.1 (2.1) [§]	57.4 (2.6) [§]	- 0.5	- 1.7, 0.8	0.456
Trunk FM (kg)	Baseline	15.7 (0.9)	17.1 (1.1)			
	4 months	14.2 (0.9) [‡]	14.2 (1.1) [‡]	- 1.4	- 2.8, <0.1	0.053
	12 months	14.5 (0.9) [§]	14.0 (1.1) [§]	- 1.8	- 3.3, - 0.4	0.013
Trunk LST (kg)	Baseline	30.1 (1.1)	28.4 (1.3)			
	4 months	29.6 (1.0)	28.0 (1.3) [‡]	0.2	- 0.7, 1.1	0.615
	12 months	29.7 (1.1)	27.4 (1.3) [§]	- 0.5	- 1.4, 0.5	0.322
Appendicular FM (kg)	Baseline	11.6 (0.7)	13.5 (0.8)			
	4 months	10.7 (0.7)	11.3 (0.8) [‡]	- 1.4	- 2.3, - 0.4	0.004
	12 months	10.8 (0.7)	11.3 (0.8) [§]	- 1.4	- 2.4, - 0.4	0.005
Appendicular LST (kg)	Baseline	27.9 (1.1)	26.5 (1.3)			
	4 months	27.6 (1.1) [‡]	25.6 (1.3) [‡]	- 0.6	- 1.5, -0.3	0.187
	12 months	27.4 (1.1) [§]	26.0 (1.3) [§]	- 0.1	- 1.0, 0.8	0.880
Blood samples						
Insulin (μU/mL)	Baseline	15.3 (1.6)	12.5 (2.2)			
	4 months	11.3 (1.6) [‡]	7.2 (2.2)	- 1.3	- 6.7, 4.1	0.624
	12 months	11.6 (1.7)	9.0 (2.3)	0.2	- 5.5, 5.9	0.943
TSH (μUI/mL)	Baseline	2.3 (0.2)	2.2 (0.3)			
	4 months	2.2 (0.2)	1.9 (0.3)	- 0.2	- 0.7, 0.3	0.410
	12 months	2.0 (0.2)	1.9 (0.3)	0.1	- 0.5, 0.6	0.771
T3 (pg/mL)	Baseline	3.3 (0.1)	3.3 (0.1)			
	4 months	3.1 (0.1) [‡]	3.1 (0.1)	0.5	- 0.2, 0.3	0.739
	12 months	3.1 (0.1)	3.2 (0.1)	0.1	- 0.2, 0.4	0.553
T4 (ng/dL)	Baseline	1.3 (0.1)	1.2 (0.1)			
	4 months	1.2 (0.1)	1.2 (0.1)	0.1	- 0.1, 0.3	0.289
	12 months	1.2 (0.1)	1.2 (0.1)	0.1	- 0.1, 0.3	0.473
Leptin (ng/mL)	Baseline	25.1 (2.0)	23.3 (2.5)			
	4 months	23.4 (2.0)	20.6 (2.5)	- 1.0	- 4.6, 2.3	0.595
	12 months	21.5 (2.0) [§]	18.9 (2.6) [§]	- 0.7	- 4.7, 3.3	0.719

Data are presented as estimated means (SE) from linear mixed models

Changes: differences in change scores between control and intervention groups e.g.,

(4 months/12months_{intervention} - baseline_{intervention})-(4 months/12months_{control} - baseline_{control})

*All models were adjusted for baseline values and sex

[‡]Differences within group between baseline and 4 months, $p < 0.05$

[§]Differences within group between baseline and 12 months, $p < 0.05$

important to consider that this calculation is integrated over several months, which may raise some concerns regarding the weight stabilization (i.e., if participants were able to maintain the WL steadily or suffered significant weight fluctuations marked by periods of WL followed by periods of weight regain). Though body weight was not tracked by our team, the last educational session lectured to the participants from the IG aimed at discussing strategies to foster weight loss maintenance and a healthy lifestyle [21], such as the regular self-weighting [40]. Moreover, participants were allowed to contact our team members if they were struggling to maintain their reduced weight state, to clarify any rising doubts, ask for advice and, if necessary, to readjust their maintenance diet. Lastly, before the measurements, participants were asked to provide some details regarding their WL maintenance period. Therefore, despite we did not track weight between month 4 and month 12, mean weight changes were below 3% of the weight loss observed in the IG [23].

Apart from the aforementioned recent manuscripts, few studies have assessed AT after WL and after a period of WL maintenance [10, 41–43]. Participants of The Biggest Loser competition [10], after a massive WL (~ 58 kg), showed an AT of ~ - 275 kcal.d⁻¹. Additionally, after 6 years of follow-up, AT's magnitude increased to ~ - 500 kcal.d⁻¹, with a huge variability among participants in terms of the regained weight and AT's magnitude. Nevertheless, as participants are considered a very specific group (TV show participants) and the sample size was small ($n = 14$), the results cannot be generalized to our study. Consistent with our data, Karl et al. [41] showed similar AT after 12 weeks of a diet intervention (~ - 54 kcal.d⁻¹). However, after 1 year of ad libitum diet (follow-up periods), some participants regained part of their weight and AT was attenuated [41]. In our study, participants were able to maintain the WL during 8 months of follow-up (with a neutral EB) and, thus, this may be the reason why AT remained significant.

In fact, the existence of a relationship between the degree of AT and the magnitude of weight loss has been postulated by some authors [11, 44]. However, some studies have reported contradictory results [17, 45]. Also, if a relationship between WL and AT exists, it would be expected that studies with higher WL (for example, bariatric surgery) would lead to a greater energy conservation. However, in our recent systematic review aimed to understand if AT occurs after WL (induced by different types of interventions) [6], considering the surgical interventions, only Tam et al. reported higher values for AT (> 300 kcal/d) [46]. Interestingly, despite their higher amount of WL (~ 20%), two studies did not report AT [47, 48].

Our study included the analysis of weight-related hormones. No differences were found for thyroid hormones but participants from the IG showed a decrease in leptin

throughout time. We could state that the lack of an association between AT and changes in leptin or thyroid hormones might be due to the moderate amount of WL (~ 5%); however, other authors also did not find any associations between these WL-related hormones and the degree of AT. Muller et al. [49], whose study included participants that presented a WL of ~ 8% after a lifestyle intervention, did not find any association between AT and hormones. Additionally, participants from the Johannsen et al. study [11] who showed a WL of ~ 10 and ~ 38% after 6 and 30 weeks, a significant larger WL when compared with our findings, did not observe associations between AT and changes in the aforementioned hormones. Moreover, Bettini et al. study [50] who studied participants that underwent a sleeve gastrectomy and lost ~ 30% of BW, did not find a relationship between AT and weight-related hormones. Therefore, our findings extend the results observed from the aforementioned studies [11, 49, 50].

Although no correlations were found between AT and WL, a sub-analysis comparing those who conserved energy versus those who dissipated energy (IG only) showed that the thrifty phenotype presented a lower WL and FM loss compared to the spendthrift phenotype ($p < 0.05$). As no differences were found regarding the %CR nor the %adherence, we may hypothesize that those who showed a higher energy conservation may struggle to remain in a weight-reduced state. Nevertheless, the role of metabolic adaptations in other EE components and behavioral compensations (decreases in physical activity) were not analyzed and may have also influenced the magnitude of WL. Therefore, more studies are needed to better address the observed large inter-individual variability in AT, including the use of accurate methodologies for assessing metabolic and behavioral compensations during WL and WL maintenance.

Although the reported AT values in the present paper were statistically significant, it is important to consider their clinical importance during WL and WL maintenance. Similar to Martins et al., the magnitude of AT values reported was small. Also, the reliability of the used instrument to assess REE must be taken into account. In our laboratory, the coefficient of variation (CV) and the technical error of measurement (TEM) for REE were 4% and ~ 60 kcal/day, respectively [51], where the TEM was similar to our AT values at the end of the intervention (~ 60–70 kcal/d). Therefore, the precision of the AT assessment may be affected by the reliability of the used instrument to assess REE (indirect calorimetry).

Though AT may play a role in WL and its maintenance, these findings suggest that AT is unlikely to be a major barrier for WL and its maintenance, especially due to its limited magnitude [17]. In fact, a recent systematic review showed that AT seems to be attenuated or non-existent after a period of weight stabilization/neutral EB [6].

Moreover, the role of behavioral compensations as possible barriers to WL is unquestionably more impactful than AT, whereas behavior is 100% of EI and 20–60% of EE [52]. During a lifestyle intervention, new healthy habits aimed to reduce weight are presented and expected to be adopted. However, only a small percentage of people adopt and maintain these new behaviors that promote a reduced body weight long-term [53] and thus, long-term success rates for WL maintenance are low, as participants often report weight regain [5]. In fact, a decrease in physical activity after a period of caloric restriction has already been showed by Redman et al. [43]. In our main paper regarding Champ4life's results, during the active WL phase (4 months), participants showed a slight tendency to decrease their sedentary behavior and to increase ~ 10 min/day of moderate-to-vigorous physical activity (MVPA), although this was not statistically significant (data not shown in this paper). However, at the end of the program (1 year), participants from the IG increased their sedentary time (compared with baseline) and returned to the baseline values of MVPA. Therefore, the lack of a successful WL and its maintenance may be mostly due to behavioral issues, such as increasing food intake and/or decreasing physical activity. Nevertheless, metabolic adaptations can also contribute to the difficulty in maintaining the reduced weight by increasing the "energy gap" [53]. Under a negative EB, this concept is characterized by a discordance between appetite (by increasing hunger) and energy requirements (by decreasing EE), resulting in a desire for more calories than are actually required [53]. This response, together with the behavioral compensations, may force an individual to re-establish a positive EB and to retake the body weight set point [53].

It should be mentioned that comparisons among studies should be interpreted carefully due to the discrepancy among methodologies to assess AT, also dependent on how REE and body composition are assessed. A recent systematic review showed that studies with stronger methodologies are those who observed lower or non-significant values for AT [6]. Moreover, when participants are measured during a neutral EB, the degree of AT is reduced or even non-significant [17, 49, 54]. Another methodological issue that should be addressed is the precision of the measurements involved in the calculation of AT, such as the REE, as these errors must be below changes between two longitudinal measurements to represent a "true" difference. Indeed, the technical error of measurement of our REE method is 56 kcal/day, a value that is way below the decrease in REE observed in the IG [estimated changes (SE)], that is – 115 (28) kcal/d and 117 (31) kcal/d after 4 and 12 months, respectively. Thus, we expect that changes in REE were "true" differences that could be biologically explained rather than artifacts resulting from the measurement error.

Additionally, the inclusion of a control group is also important to understand if AT occurs as a result of the WL intervention rather than other external factors. Moreover, the calculation of the typical error for AT, that takes into account the standard deviation for control group (where the outcomes of interest are not expected to change), will allow us to better clarify which AT values are likely to be meaningful in practice [55].

Taking into account the aforementioned methodological issues, there is a need to standardize the calculation of AT and to include precise and accurate methods for body composition and REE determination to fully understand whether a meaningful energy conservation in the REE occurs during and/or after WL when designing future studies [9]. Lastly, measurements of EE should be conducted in a neutral EB, not only to assure a similar condition to the baseline but also to eliminate the potential influence of an acute state of energy deficit.

One of the major strengths of this study was that it was conducted as a randomized controlled trial, with a CG who did not receive the lifestyle intervention. Also, we collected data not only after a period of WL (negative EB) but also after 8 months of WL maintenance in which (neutral EB). However, some limitations need to be addressed. First, our findings need to be interpreted carefully, as the Champ4life was a lifestyle intervention targeting former elite athletes with overweight/obesity and inactive. While a non-athletic population with obesity may have been sedentary all their life's, when it comes to athletes, they generally experienced a weight gain and a transition to a sedentary state throughout adulthood. Although former athletes tend to adopt healthier lifestyles after their retirement, if that is not carried throughout their lives, they do not seem to have health-related benefits when compared to a non-athletic population [56, 57]. In fact, a study that aimed to analyze 25-year trends in weight gain showed that after an athletic retirement the weight gain reported was of a similar magnitude to that observed in studies with non-athletic populations [58]. Also, the same study showed that former football athletes appear to have similar risk factors for developing cardiovascular disease when compared to the general U.S. population [58]. It may be expected that athletes gain weight with a different body composition, characterized by a higher percentage of lean muscle mass, in comparison to that seen in other cohorts [56, 59]. However, as we used not only BMI but also %FM to characterize this sample, we believe that the results are not strictly useful for this specific population, but also for non-athletic populations that were highly active in their youth and with similar levels of %FM. Nevertheless, most of the studies have been conducted in non-athletes. It is also important to mention that our intervention was not designed to prescribe a standardized diet or physical activity to each participant which may have contributed to

the large WL variability and, consequently AT. This large variability within subjects is widely reported in studies that determined changes in body composition stores (FM and FFM) [6]. Also, tracking changes in body composition by DXA does not assess the changes in FFM composition (i.e., molecular and anatomical composition) [60]. Therefore, possible changes in the FFM contribution to REE were not taken into account. Moreover, it is known that a particular limitation of the DXA equipment is the reduced width of the active scanning area, which compromises the measurement in individuals who surpass the scan width. In this study, 6 participants had their body composition measured with a technique called “Reflection scan”, where their left arm was placed outside the scan window and data from the right arm were “reflected” to the left upper limb, validated elsewhere [27]. Though a small impact was observed in whole-body bone measurement using this approach, no differences were found in assessing soft tissues [27]. Nevertheless, this technique affects the weight measured by DXA, as the left upper limb is not included. In the scan area and therefore it is not being correctly weighted which may have contributed to so a certain degree of discrepancy between weight measured by DXA vs scale. Regardless, a Pearson’s correlation was performed between weight measured by DXA vs scale and an almost perfect association was found between measurements ($R=0.999$, $p<0.001$). It is also important to address that we used method to assess EB did not account for the daily variations related to food intake. Lastly, AT was just calculated for the REE compartment. It is known that AT may occur in all EE components and it might be of a larger magnitude at the level of non-resting EE [4]. Therefore, it would be interesting to calculate AT in all EE components to better understand its magnitude.

To conclude, AT occurred after 4 months of a moderate WL and persisted during the 8-month WL maintenance. Nevertheless, researchers should be aware of the lack of standardization among the techniques and of a huge variability within-studies. Future studies on AT should consider not only changes in FM and FFM but also the FFM composition. Results from studies examining AT should be interpreted carefully according to the used methodology, avoiding overstatements and academic clickbait about its existence and/or influence of AT in WL and its maintenance.

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Declarations

Conflict of interest The authors reported no conflicts of interest.

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