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ORIGINAL CONTRIBUTION

Adaptive thermogenesis after moderate weight loss: magnitude and methodological issues

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Abstract

Purpose The aim of this study was (1) to assess AT through 13 different mathematical approaches and to compare their results; and (2) to understand if AT occurs after moderate WL.

Methods Ninety-four participants [mean (SD); BMI, 31.1 (4.3) kg/m^2; age, 43.0 (9.4) years; 34% females] underwent a 1-year lifestyle intervention (clinicaltrials.gov ID: NCT03031951) and were randomized to intervention (IG, $n=49$) or control groups (CG, $n=45$), and all measurements were made at baseline and after 4 months. Fat mass (FM) and fat-free mass (FFM) were measured by dual-energy X-ray absorptiometry and REE by indirect calorimetry. AT was assessed through 13 different approaches, varying in how REE was predicted and/or how AT was assessed.

Results IG underwent a mean negative energy balance (EB) of 270 (289) kcal/day, $p<0.001$), resulting in a WL of −4.8 (4.9)% and an FM loss of −11.3 (10.8)%. Regardless of approach, AT occurred in the IG, ranging from ~ −65 to ~ −230 kcal/day and three approaches showed significant AT in the CG.

Conclusions Regardless of approach, AT occurred after moderate WL in the IG. AT assessment should be standardized and comparisons among studies with different methodologies to assess AT must be avoided.

Keywords Metabolic adaptation · Metabolic slowing · Resting energy expenditure · Energy balance

Introduction

The prevalence of obesity is increasing worldwide and is considered a major global health problem. Since obesity is caused by an alteration in energy balance (EB), as a result of a prolonged excess energy intake (EI) that surpasses energy expenditure (EE), a strategy to achieve weight loss needs to affect one or both sides of the EB equation by increasing EE and/or decreasing EI. Although it seems simple, EB represents a complex and dynamic system in which its components vary over time [1] and change in response to perturbations in either side of the equation [2, 3].

Interventions aimed at losing weight are abundant in the current literature [4, 5]. However, difficulties in losing weight and maintaining it are common. The lack of adherence to dietary and physical activity (PA) recommendations has been pointed out as one of the major problems, especially if they are not adopted at a long-term basis [6]. Additionally, the existence of metabolic, behavioral, and psychological compensations that may occur during negative EB,

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including compensatory changes in EE [7], spontaneous PA [8], and increases in EI [9] have been studied.

Originally called "luxuskonsumption", evidence regarding the existence of adaptive thermogenesis (AT) was reported at the beginning of the last century [10, 11]. However, this "phenomenon" only became a matter of debate in the second half of the century, mainly due to the possible role of the brown adipose tissue as the main effector on AT [12, 13]. In 1995, Leibel et al. [14] brought an innovated perspective by showing that the measured decrease in metabolic rate induced by weight loss (WL) was greater than the change predicted by baseline values of fat mass (FM) and fat-free mass (FFM). Therefore, AT has been defined as the decrease in the EE components [resting energy expenditure (REE) and physical activity energy expenditure (PAEE)] beyond what could be predicted from the changes in FM and FFM in response to a negative EB [15, 16].

AT has been studied as a possible barrier to WL, as its existence has been reported not only after a period of WL but also in an early stage of a caloric restriction. In fact, Heinitz et al. [17] showed that the magnitude of AT in the early stage of caloric deficit predicts long-term changes in body composition. Therefore, similarly to the assessments used to categorize spendthrift versus thrifty phenotypes, the inclusion of AT as a predictor of WL may lead to a better understanding the reasons for a higher susceptibility to weight change and therefore difficulties in maintaining a reduced weight state [17]. However, AT's existence has been recently questioned, especially in the long-term weight management [18–24], whereas some authors showed that AT may difficult WL and promote weight regain in studies inducing massive WL [22, 25–27], others argued that the suppositions regarding AT are exaggerated [28, 29].

The lack of consistency among studies may be due to the lack of standardization of the methodologies to assess AT in REE. As a consequence, different methodologies have been used in the literature, varying on how REE and body composition were assessed [30]. To our knowledge, only Byrne et al. [31] assessed AT using more than one approach to calculate changes in REE, using three different equations to predict REE. As their goal was to compare two different approaches of caloric restriction (intermittent versus continuous), comparisons among methodologies were not addressed in detail. Therefore, the aim of this study was (1) to assess AT through 13 different mathematical approaches (differing in how AT is assessed and/or how REE is predicted) and (2) to understand if AT occurs after a lifestyle intervention.

Methodology

Participants and study design

This study is a part of a major randomized clinical trial performed among healthy former top-level athletes with overweight and obesity (clinicaltrials.gov ID: NCT03031951) [32]. A schematic description of the study phases is presented in Fig. 1.

A total of 94 healthy participants of both sexes were selected and randomly assigned to one of the two groups: intervention or control group. All of the participants were overweight/obese (BMI $\geq$ 24.9 kg/m^2), 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 [33]), aged 18–65 years, and ready to modify their diet to achieve a lower body weight. For a more detailed description of inclusion and exclusion criteria, see the study protocol [32]. In this study, we used measurements made at baseline (0 months) and after the intervention (4 months).

Lifestyle intervention

Nutritional appointments were given by a registered dietitian to each participant. This meeting was intended to provide a

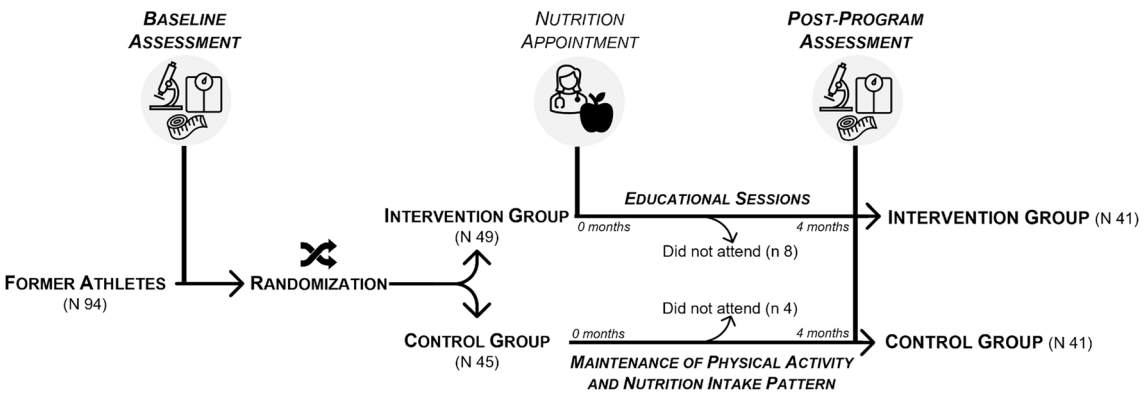

Fig. 1 Schematic description of the study phases

well-balanced personalized diet plan, calculated to create a moderate energy restriction from ~ 300 to 500 kcal/day according to each participant's energy requirements and preferences. Additional appointments were also realized to adjust caloric intake throughout the intervention. In addition, participants attended 12 educational sessions aimed to promote a healthy lifestyle, including educational content and practical application in the areas of PA and exercise, diet and eating behavior, as well as behavior modification.

Participants from the control group were placed on a waiting list to be offered the lifestyle intervention. Upon the completion of the study's assessments, they had the opportunity to receive the proper nutritional monitoring and the content taught during the educational sessions.

Anthropometry

Subjects 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)/height^2 (m^2)].

Dual-energy X-ray absorptiometry (DXA)

To estimate total and regional FM and FFM, dual-energy X-ray absorptiometry (DXA) (Hologic Explorer-W, Waltham, USA) was used. A whole-body scan was performed, and the attenuation of X-rays pulsed between 70 and 140 kV synchronously with the line frequency for each pixel of the scanned image will be measured. Total abdominal fat, which includes intra-abdominal fat plus subcutaneous fat, was distinguished using DXA by identifying a specific region of interest (ROI) within the analysis programme. Specific DXA ROI for abdominal regional fat was defined as follows: from the upper edge of the second lumbar vertebra (approximately 10 cm above the L4–L5) to above the iliac crest and laterally encompassing the entire breadth of the abdomen, and thus determining total abdominal FM. The calibration procedures were performed according to the manufacturer's instructions [34]. All the assessments (before and after the intervention) were performed by the same investigator.

Measured resting energy expenditure (REE)

Measured REE (mREE) was obtained in the morning when fasted (7.00–10.00 a.m.). All measurements were performed in the same room at an environmental temperature and humidity of approximately 22 ºC and 40–50%, respectively. The MedGraphics CPX Ultima indirect calorimeter (MedGraphics Corporation, Breezeex Software, Italy) was used to measure breath-by-breath oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) using a facial mask. The oxygen and carbon dioxide analyzers were calibrated in the morning before testing using known gas concentration. The flow and volume were measured using a pneumotachograph calibrated with a 3L-syringe (Hans Rudolph, Inc. TM). Before testing, participants were instructed about all the procedures and asked to relax, breathe normally, and not to sleep or talk during the evaluation.

Before the test, participants rested in supine position for 15 min covered with a blanket, and the calorimeter device was then attached to the mask and breath by breath. $\dot{V}O_2$ and $\dot{V}CO_2$ were measured for 30 min, performing a total test duration of 45 min. The first and the last 5 min of data collection were discarded. Steady-state intervals were defined as 5-min periods with ≤ 10% CV for $\dot{V}O_2$ and $\dot{V}CO_2$ and Respiratory Exchange Ratio between 0.7 and 1.0 [35]. The mean $\dot{V}O_2$ and $\dot{V}CO_2$ of 5 min steady states was used in Weir equation [36] and the period with the lowest REE was considered for data analysis.

Adaptive thermogenesis (AT)

To detect differences in REE beyond what we would expect from body composition alterations, AT was assessed through different approaches, varying in how predicted REE ($_p$REE) was calculated and/or how AT was assessed (Table 1).

To identify the four used approaches regarding the $_p$REE, numbers 1–4 were attributed, where pREE was assessed:

1. By creating a predictive equation using baseline FFM (kg) as an independent predictor;
2. By creating a predictive equation using baseline FM (kg) and FFM (kg) as independent predictors;
3. By creating a predictive equation using baseline FM (kg), FFM (kg), sex, and age as independent predictors;
4. According to the Hayes' model, i.e., through the sum of the energy production of tissue-organ components (brain, skeletal muscle, adipose tissue, bone, and residual mass) derived from DXA [37].

Regarding the assessment of AT, four approaches were used, identified from A to D, in which:

(A) mREE was adjusted for FM and FFM by linear regression and AT was assessed as the difference between an adjusted REE at baseline and after 4 months (for this approach, $_p$REE was not used) [31];
(B) AT was assessed simply by subtracting pREE (assessed through one of the four aforementioned equations) from mREE (indirect calorimetry), at the end of the intervention (4 months) [24, 31, 38];

Table 1 Methodologies to assess AT

Approach	Methodology			
	To assess AT		To predict REE	
A	A	$AT\ (kcal/day) = {}^{4mo}_{m}REE_{adjFM/FFM} - {}^{baseline}_{m}REE_{adjFM/FFM}$	NA	
B.1	B	$AT\ (kcal/day) = {}^{4mo}_{m}REE - {}^{4mo}_{p}REE$	1	${}_{p}REE\ (kcal/day) = 581.9 + 17.6 \times FFM_{(kg)}$ †
B.2			2	${}_{p}REE\ (kcal/day) = 505.2 + 2.8 \times FM_{(kg)} + 17.5 \times FFM_{(kg)}$ ‡
B.3			3	${}_{p}REE\ (kcal/day) = 604.6 + 17.6 \times sex_{(0=male,\ 1=female)} - 1.621 \times age + 2.902 \times FM_{(kg)} + 16.8 \times FFM_{(kg)}$ §
B.4			4	According to Hayes et al. [37]*
C.1	C	$AT(kcal/day) = [({}^{4mo}_{m}REE - {}^{4mo}_{p}REE) - ({}^{Baseline}_{m}REE - {}^{baseline}_{p}REE)];$	1	${}_{p}REE\ (kcal/day) = 581.9 + 17.6 \times FFM_{(kg)}$ †
C.2			2	${}_{p}REE\ (kcal/day) = 505.2 + 2.8 \times FM_{(kg)} + 17.5 \times FFM_{(kg)}$ ‡
C.3			3	${}_{p}REE\ (kcal.d^{-1}) = 604.6 + 17.6 \times sex_{(0=male,\ 1=female)} - 1.621 \times age + 2.902 \times FM_{(kg)} + 16.8 \times FFM_{(kg)}$ §
C.4			4	According to Hayes et al. [37]*
D.1	D	$\%AT = 100 \times \left(\frac{{}^{4mo}_{m}REE}{{}^{4mo}_{p}REE} - 1\right)$	1	${}_{p}REE\ (kcal/day) = 581.9 + 17.6 \times FFM_{(kg)}$ †
D.2		$AT\ (kcal/day) = \frac{\%AT}{100} \times {}^{baseline}_{m}REE$	2	${}_{p}REE\ (kcal/day) = 505.2 + 2.8 \times FM_{(kg)} + 17.5 \times FFM_{(kg)}$ ‡
D.3			3	${}_{p}REE\ (kcal/day) = 604.6 + 17.6 \times sex_{(0=male,\ 1=female)} - 1.621 \times age + 2.902 \times FM_{(kg)} + 16.8 \times FFM_{(kg)}$ §
D.4			4	According to Hayes et al. [37]*

*Through the sum of the energy production of tissue-organ components (brain, skeletal muscle, adipose tissue, bone, and residual mass) derived from DXA

†Predictive equation using baseline FFM (derived from DXA) as the independent predictor ($R^2 = 0.564$, $p < 0.001$)

‡Predictive equation using baseline FM and FFM (derived from DXA) as the independent predictors ($R^2 = 0.570$, $p < 0.001$)

§Predictive equation using baseline FM, FFM (derived from DXA), age, and sex as the independent predictors ($R^2 = 0.572$, $p < 0.001$)

(C) AT was calculated as: (a) subtracting pREE from mREE at 4 months; (b) subtracting pREE from mREE at baseline and therefore subtracting the result of (b) from the result of (a) [19, 39];

(D) %AT was calculated as 100 × [(mREE/pREE) – 1) after 4 months, and therefore, AT is assessed as (%AT/100) × mREE at baseline [40, 41].

To assess AT, approaches 1–4 (pREE) and A–D (AT) were combined, creating 13 methodologies (pREE is not required for approach A).

For all situations, negative values indicate a lower-than-expected decrease in REE considering the changes in body composition, i.e., the measured REE is lower-than-predicted REE, whereas positive values represent a change in REE equal to or greater than the predicted REE (measured REE higher than predicted REE) [7].

Calculation of energy balance (EB)

The EB equation is denoted as follows:

$$EB\ (kcal/day) = EI - EE.$$

When the EE surpasses the EI, EB is negative. On the other hand, EB is positive when EI is larger than EE. EB represents the average rate of energy deficit or surplus expressed in kilocalories per day and 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 and FFM, the follow equation will be applied to quantify the average rate of changed body energy store or lost in kilocalories per day

$$EB\ (kcal/d) = 1.0\frac{\Delta FFM}{\Delta t} + 9.5\frac{\Delta FM}{\Delta t},$$

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.

Statistical analysis

Statistical analysis was performed using IBM SPSS statistics version 25.0 (IBM, Chicago, Illinois, USA). To test the normality of the variables, the Kolmogorov–Smirnov test was performed. Baseline differences

between intervention and control group, and between the groups arbitrarily divide into those who lost at least 3% of body weight (which is likely to result in clinically meaningful health benefits [42]) *vs* those who did not (lost < 3% of body weight) were assessed by independent two sample *t* test.

Changes in body composition and were assessed by performing Linear Mixed Models, adjusted for randomized group and time as fixed effects and for sex and the baseline values as covariates, assessing the impact of treatment, time (baseline—0 months, post-intervention—4 months) and treatment-by-time interaction. 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.

Statistical significance was set at a two-sided $p < 0.05$.

Results

A total of 94 participants [BMI = 31.1 (4.3) kg/m^2, age = 43.0 (9.4) years, 34% females] were included. Changes in body composition and resting energy expenditure are presented in Table 2. A detailed description of the main results of the Champ4life project is presented elsewhere [43].

A time*group interaction was observed for weight and FM ($p < 0.05$). Weight, FM, and FFM decreased over time for intervention group (within group differences, $p < 0.05$).

Table 2 Estimated means and respective changes (diff-in-differences) after a 16-week weight-loss intervention*

		Control	Intervention			
Body composition						
Weight (kg)	Baseline	91.2 (0.5)	91.1 (0.4)	Changes†	95% CI	*p* value
	Post-programme	91.5 (0.5)	86.8 (0.5)‡	−4.7	−6.1, −3.3	< 0.001
Fat mass (kg)	Baseline	29.7 (0.4)	29.6 (0.4)	Changes†	95% CI	*p* value
	Post-programme	30.1 (0.4)	26.3 (0.4)‡	−3.8	−5.1, −2.6	< 0.001
Fat mass (%)	Baseline	33.1 (0.3)	33.1 (0.3)	Changes†	95% CI	*p* value
	Post-programme	33.3 (0.3)	30.7 (0.3)‡	−2.6	−3.6, −1.7	< 0.001
Fat-free mass (kg)	Baseline	60.2 (0.2)	60.2 (0.2)	Changes†	95% CI	*p* value
	Post-programme	59.9 (0.2)	59.3 (0.2)‡	−0.7	−1.5, 0.1	0.085
Resting energy expenditure						
$_m$REE (kcal/day)	Baseline	1643 (15)	1645 (15)	Changes†	95% CI	*p* value
	Post-programme	1622 (17)	1526 (17)‡	−97	−161, −33	0.003
$_p$REE (kcal/day)						
Equation 1	Baseline	1644 (3)	1644 (3)	Changes†	95% CI	*p* value
	Post-programme	1637 (4)	1626 (4)	−12	−26, 2	0.089
Equation 2	Baseline	1643 (4)	1643 (3)	Changes†	95% CI	*p* value
	Post-programme	1639 (4)	1617 (4)	−23	−37, −8	0.002
Equation 3	Baseline	1643 (3)	1643 (3)	Changes†	95% CI	*p* value
	Post-programme	1641 (4)	1619 (4)‡	−23	−37, −9	0.002
Equation 4	Baseline	1787 (6)	1787 (6)	Changes†	95% CI	*p* value
	Post-programme	1783 (7)	1774 (7)	−9	−35, 16	0.464

Data are presented as estimated mean (SE)

SD standard deviation, *CI* confidence interval

*All models were adjusted for baseline values and sex

Equation 1: $_p\text{REE (kcal/day)} = 581.9 + 17.6 \times \text{FFM}_{(kg)}$

Equation 2: $_p\text{REE (kcal/day)} = 505.2 + 2.8 \times \text{FM}_{(kg)} + 17.5 \times \text{FFM}_{(kg)}$

Equation 3: $_p\text{REE (kcal/day)} = 604.6 + 17.6 \times \text{sex}_{(0=\text{male},\ 1=\text{female})} - 1.621 \times \text{age} + 2.902 \times \text{FM}_{(kg)} + 16.8 \times \text{FFM}_{(kg)}$

Equation 4: According to Hayes et al. [37]

‡Differences within group between baseline and post-programme, $p < 0.05$

†Difference in differences estimated changes

$(\text{Post-programme}_{\text{intervention}} - \text{baseline}_{\text{intervention}}) - (\text{post-programme}_{\text{control}} - \text{baseline}_{\text{control}})$

Energy balance calculation

A mean negative EB of 270 (289) kcal/d was observed for the intervention group (different from zero, ($p < 0.001$), which resulted in a WL of − 4.8 (4.9)% and an FM loss of − 11.3 (10.8)%. The control group presented an EB of 14 (129) kcal/day (not different from zero, $p = 0.489$), as no significant WL or changes in body composition stores were observed.

Adaptive thermogenesis' assessment: comparison among approaches

The results for AT are presented in Table 3.

The intervention group showed a significant AT for all four approaches, while the control group presented it for approach A, B.4, and D.4. Differences between groups were found for approach A and C.1 ($p < 0.05$).

A large variability was found for every approach for both intervention and control group. Approach A was the only with smaller variability (− 179 to 176 and − 205 to 103 for control and intervention group, respectively). When comparing the remaining approaches, approaches C.1.–C.4. were the ones that showed a lower variability.

Relation between the variability in AT and the magnitude of WL

The variability in AT (in relative values, %) according to the amount of WL (in relative values, %) for approaches that differed between groups ($p < 0.05$) is illustrated in Fig. 2 for the IG and CG. The variability in AT according to the amount of WL for all the approaches is presented as a supplementary file (Supplementary file 1).

Implications of adaptive thermogenesis' calculations according to a specific weight-loss cut-off

A sub-analysis comparing AT values arbitrarily dividing the sample in those who lost at least 3% of their initial weight (WL ≥ 3%) with those who did not (WL < 3%) is presented in Table 4. From the intervention group, 27 participants (66%) lost at least 3% of their initial weight, being included in the WL group. The WL group was composed of 30 participants [37% female, age: 44.6 (6.0) year] with a mean weight of 90.8 (14.4) kg and 33.6 (8.3)% of FM.

Fifty-two participants were included in the other group (WL < 3%) [33% females, age: 43.4 (10.5) year], with 91.4 (17.9) g and 32.8 (7.7)% for FM. No differences were found between groups for the baseline values.

A mean EB of − 324 (276) and of 132 (84) kcal/day was found for the WL ≥ 3% and the WL < 3% group, respectively (both different from zero, $p < 0.001$). AT values ranged from ~ − 70 to ~ − 220 kcal for those who lost weight and all the approaches were statistically significant ($p < 0.05$), except for D.2. For the WL ≥ 3% group, AT was not found in any approach ($p > 0.05$). Differences between groups were found for approach A, C.1, C.2, C.3, and C.4 ($p < 0.05$).

Table 3 Values for adaptive thermogenesis for control and intervention group

Approach	Control	Range	Intervention	Range	*p* value between groups
A	− 65 (71)*	− 179, 176	− 107 (62)*	− 205, 103	0.007
B					
B.1	− 40 (238)	− 620, 604	− 86 (193)*	− 513, 351	NS
B.2	− 39 (228)	− 597, 575	− 76 (190)*	− 479, 382	NS
B.3	− 38 (228)	− 573, 568	− 77 (191)*	− 502, 375	NS
B.4	− 191 (291)*	− 870, 449	− 229 (217)*	− 655, 251	NS
C					
C.1	− 14 (149)	− 356, 290	− 93 (156)*	− 407, 180	0.033
C.2	− 16 (146)	− 347, 283	− 84 (154)*	− 403, 186	NS
C.3	− 16 (147)	− 350, 284	− 87 (154)*	− 408, 182	NS
C.4	− 20 (152)	− 605, 301	− 93 (172)*	− 403, 216	NS
D					
D.1	− 23 (225)	− 403, 716	− 75 (195)*	− 486, 409	NS
D.2	− 24 (214)	− 405, 671	− 66 (197)	− 464, 454	NS
D.3	− 23 (215)	− 391, 660	− 67 (197)*	− 479, 444	NS
D.4	− 144 (237)*	− 531, 492	− 200 (194)*	− 559, 276	NS

Values are presented as mean (SD)

NS non-significant

*One-sample *t* test, significantly different from zero, $p < 0.05$

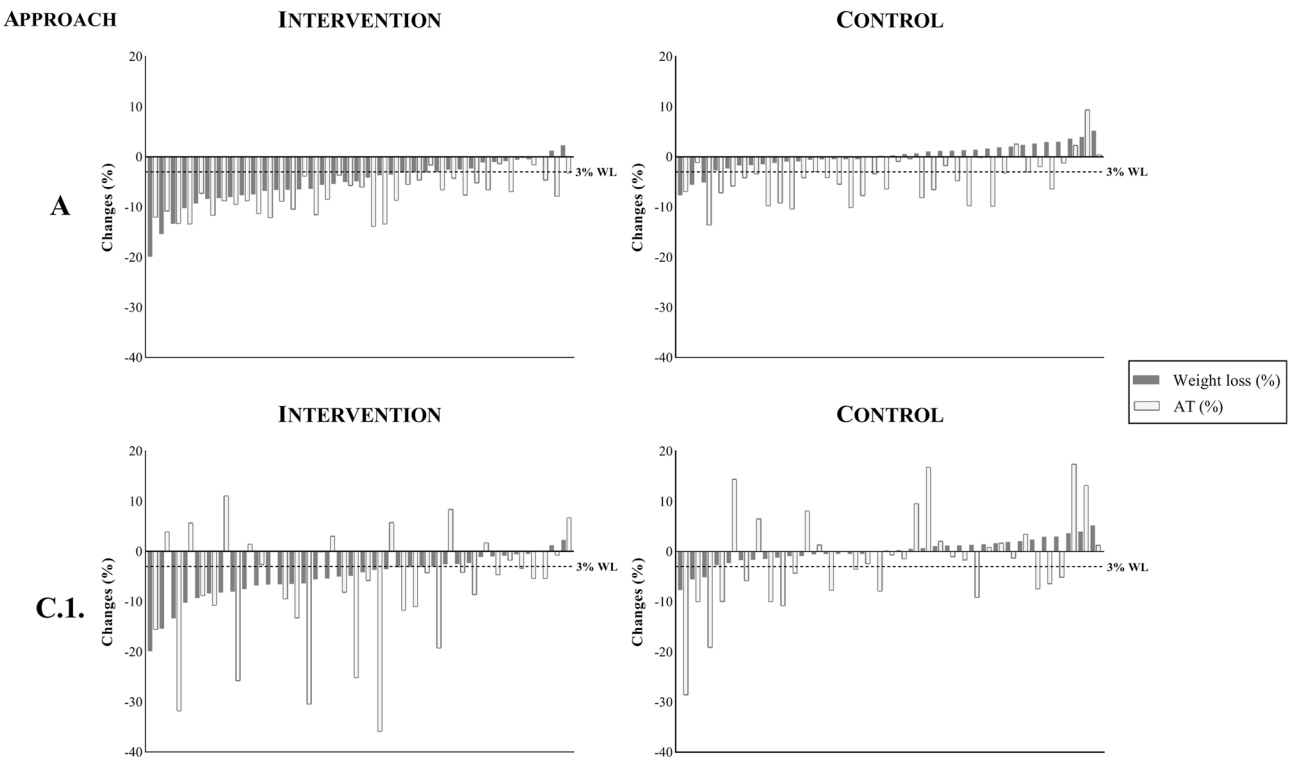

Fig. 2 Variability of AT (presented as a percentage related to post-programme REE) and %WL for approach A and C.1 for intervention and control groups

Discussion

The major finding of this paper is the clear discrepancy among the methodologies used to assess AT, with values ranging from ~ − 70 to − 220 kcal/day for the intervention group.

An effect of the intervention on AT was observed only for approach A and C.1, while no significant differences between the IG and the CG were found for the remaining methodologies used to assess AT. The IG presented a lower-than-predicted REE when using all the approaches, whereas the CG showed a lower-than-expected decrease on REE using approaches A, B.4, and D.4, though no significant changes in energy stores were observed. In the current literature, AT can be calculated through several mathematical approaches, varying in how REE is predicted and/or how AT is assessed. The most common approach is to assess AT as the difference between measured and predicted REE (calculated through a predictive equation using population's baseline outcomes) [18, 23, 38]. Other studies performed a similar approach but considering the baseline residuals (measured minus predicted REE at baseline) [19, 39]. Other methodologies were performed, such as the difference between an adjusted measured REE (for FM and/or FFM) before and after a weight-loss intervention (without predicting REE) [31] or as described in Thomas et al. [7, 40]. Therefore, the discrepant findings regarding AT among studies can be in part due to differences in their methodologies.

The mechanisms underlying AT are not well understood, but it has been speculated to involve decreases in circulating leptin, thyroid hormones [15, 44], and blunted activity of the sympathetic nervous system [15]. A leptin reduction is usually associated with an increase in hunger and consequently increased EI [45, 46], leading to a neutral or even positive EB, jeopardizing WL. Moreover, Tremblay et al. [47], showed that changes in circulating organic pollutants (organochlorines), known for their anti-thermogenic properties, were the main predictors of AT, explaining about 50% of its variance. More specifically, increases in organochlorines after WL may exert influence on metabolism, as these compounds play a role on mitochondrial activity [48] and they seem to be an independent predictor of the REE [49]. In our study, AT seems to be subtle, highly variable between individuals, and possibly affected by the high variability seen in body weight responses to the intervention [2]. Also, when comparing people who lost at least 3% of their initial weight with those who did not, only approach A and C (C.1–C.4) showed differences between groups ($p < 0.05$). Nevertheless, all approaches showed significant values for AT for those who had a WL ≥ 3%. Also, AT seems to be irrelevant for the other group, as only three approaches significant AT values.

Table 4 Values for adaptive thermogenesis for those who lost at least 3% of their weight (WL ≥ 3%) *vs* those who did not (WL < 3%)

	WL ≥ 3%	Range	WL < 3%	Range	*p* value between groups
A	− 127 (50)*	− 205, − 16	− 61 (69)*	− 177, 176	< 0.001
B					
B.1	− 107 (213)*	− 513, 351	− 21 (198)	− 558, 604	NS
B.2	− 95 (209)*	− 479, 382	− 20 (191)	− 566, 575	NS
B.3	− 95 (211)*	− 502, 375	− 19 (191)	− 538, 568	NS
B.4	− 231 (221)*	− 633, 251	− 180 (258)*	− 843, 449	NS
C					
C.1	− 139 (166)*	− 407, 180	2 (124)	− 181, 290	< 0.001
C.2	− 128 (166)*	− 403, 186	< 1 (122)	− 185, 283	0.001
C.3	− 130 (166)*	− 408, 182	1 (122)	− 191, 284	0.001
C.4	− 129 (186)*	− 403, 216	− 8 (134)	− 253, 333	0.005
D					
D.1	− 98 (218)*	− 486, 409	− 9 (195)	− 401, 716	NS
D.2	− 87 (220)*	− 464, 454	− 9 (185)	− 405, 671	NS
D.3	− 87 (221)*	− 479, 444	− 9 (186)	− 391, 660	NS
D.4	− 209 (205)*	− 559, 276	− 140 (218)*	− 531, 492	NS

Values are presented as mean (SD)

NS non-significant

*One-sample *t* test, significantly different from zero, $p < 0.05$

As a consequence of the high variability among AT approaches, some important methodological questions emerge, specifically: (i) should studies regarding AT be compared independently of their methodology to assess AT? (ii) which approach to assess AT should be used as a standard approach?

Since there are several plausible mathematical approaches to determine AT, it is possible that each study may present the approach that better reflects the existence of AT, which can explain the inconsistent findings that have been questioned for long-term weight management [18–22, 50–52]. Also, the EB status of the participants when measurements are taken were not always considered, as most studies did not assure a neutral EB when assessing AT. Therefore, the variability in the degree of energy conservation among studies may be partially explained by the EB status at the time of the measurements. Therefore, studies with different methodologies to assess AT should not be compared. Also, the discrepancy among methodologies underscores the importance of standardizing the mathematical approach to assess AT. Predicting REE from organ/tissue masses tied to their specific metabolic rates seems to be the most accurate method [53]. However, only a few studies used this method due to the considerable time and cost associated [54–56]. Hayes et al. [37] suggested an alternative approach that extends the DXA method to a tissue-organ level, predicting REE through the sum of the energy production of tissue-organ components derived from DXA. However, so far, no paper regarding AT used this approach to predict REE. In our study, using this solution to predict REE led to higher REE values when compared with the other approaches (predictive equations based on our sample's characteristics). Consequently, approaches that predicted REE through the DXA-REE solution revealed the highest AT values. Therefore, it seems that this methodology may not be suitable as an alternative to determine AT, as it may exacerbate the degree of energy conservation.

Alternatively, predicting REE through a predictive equation using the baseline outcomes from the studied population is widely used due to its simplicity [18, 23, 38, 50, 57]. Nevertheless, there are also several ways to compare measured and predicted REE (using equations) among studies (such as approaches B, C and D). However, it should be noted that approach C (AT (kcal/day) = [($^{4mo}_{m}$REE − $^{4mo}_{p}$REE) − ($^{Baseline}_{m}$REE − $^{baseline}_{p}$REE)]) reduces the large discrepancy between data treatment regarding pREE (approaches 1–4). Thus, it seems that it can be considered the strongest approach regarding methodologies to assess AT. Also, it is known that the FFM's impact on the REE differs after WL [58, 59]. It is recognized that after WL, anatomical and molecular changes on FFM occur. Recently, Müller et al. [60] studied the impact of these changes in FFM composition on AT. As a result, adjusting changes in REE for these

anatomical and molecular changes in FFM lead to a decrease on the magnitude of AT [60]. Therefore, along with mathematical issues, AT should also be accounted for functional body components when assessing energy conservation.

Considering mathematical approaches, some recommendations to standardize AT assessment models have been recently addressed [61]. First, the created predictive equation should provide a good fit for the observations and use the baseline participants' characteristics to derive the models. The use of equations developed for other populations should be avoided. Also, variables such as sex and age should be included when creating the equation as they have been shown to influence REE [62]. More important, residuals (i.e., differences between measured and predicted REE) should be calculated not only after WL but also at baseline and should be considered when assessing AT (approach C). If residuals are statistically different from zero at baseline, it means that participants have already a predicted REE different from the measured value that should be accounted when assessing AT.

Despite the limitations of each methodology, the magnitude of AT in our study was smaller than that observed from studies who reported higher WL (by diet-only or combined diet and exercise intervention) [63, 64]. Though, people who lost more weight were not necessarily those who had a larger degree of AT. In fact, changes in REE as a response to a caloric restriction are widely variable between-subjects [65], as some individuals lost weight and did not show a significant decrease in REE (spendthrift phenotype), while others showed greater decreases in REE (thrifty phenotype) [66]. Thus, the existence of these two different phenotypes may be the reason why some people were able to lose weight without any considerable decreases in any of the EE components. However, more studies should be conducted to understand why some people lose moderate weight and do not show a lower-than-expected decrease in REE.

Our AT values are consistent with those presented in other similar studies with smaller energy deficit [23, 39, 50, 54, 56, 67]. Thus, it is possible that AT appears not only after an aggressive energy restriction but also under a moderate energy deficit. Although AT values were statistically significant, its clinical significance needs to be taken into consideration. It is known that behavioral and metabolic compensations are interconnected, and AT may affect our eating behavior, and hence WL [53].

Although the current study reveals clear discrepancies between methods to assess AT some limitations should be addressed. First, it should be noted that there is no clear definition nor a criterion method for AT. Therefore, we cannot assure that a certain methodology is accurate as we do not have a "reference value" of AT to use when comparing methods of assessing AT. Also, we cannot assure that both at baseline and post-programme assessments of our participants occurred under an equal EB. As they were measured right after the intervention, they could still be attempting to lose weight and, consequently, be under a negative EB. Some studies that conducted a follow-up period after WL (where participants were weight stable) reported that AT disappeared over time [23, 50]. Thus, a weight maintenance period to maintain a stable weight would have strengthened the results. It is known that studies that follow up massive WL ("Biggest Loser" contestants) [68] showed that AT not only remains significant but also increased regardless of a substantial weight regain over time. However, in addition to methodological limitations, such as changes in instruments over the study timeline and the lack of control in diet and exercise prior to the final REE measurement [29], it is important to underscore that this type of intervention (intensive diet and exercise intervention to promote a massive WL) does not reflect the impact of moderate WL on AT. Therefore, their findings should not be extrapolated to other WL studies that assessed AT.

In conclusion, after a moderate WL, AT was present and differed between groups only for 2 out of the 13 used approaches. Therefore, the lack of standardization among methodologies leads to an uncertainty regarding AT's existence. Moreover, the magnitude of AT differed significantly among methodologies to predict REE and to assess AT. Therefore, there is a need to standardize the AT assessment and comparison among studies with different methods should be carefully interpreted.

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Declarations

Conflict of interest The authors reported no conflicts of interest.

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