UNIVERSIDADE DE LISBOA

FACULDADE DE MOTRICIDADE HUMANA

THE ROLE OF METABOLIC AND BEHAVIORAL COMPENSATIONS IN WEIGHT MANAGEMENT

CATARINA TERESA LUCAS NUNES

Orientador: Professora Doutora Analiza Mónica Lopes de Almeida Silva

Coorientador: Professora Doutora Anja Bosy-Westphal

Tese elaborada com vista à obtenção do grau de Doutor em ***Motricidade Humana*** *na especialidade de* ***Atividade Física e Saúde***

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Júri:

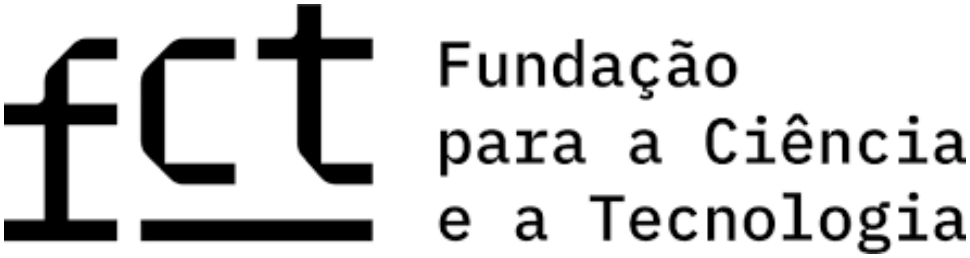
Presidente:

Doutora Maria Celeste Rocha Simões
Professora Associada com Agregação
Faculdade de Motricidade Humana da Universidade de Lisboa

Vogais:

Doutor Pedro Jorge do Amaral de Melo Teixeira
Professor Catedrático
Faculdade de Motricidade Humana da Universidade de Lisboa
Doutor Mark Evan Hopkins
Lecturer in Nutritional Physiology
School of Food Science & Nutrition, University of Leeds (Reino Unido)
Doutora Maria Isabel Caldas Januário Fragoso
Professora Associada com Agregação
Faculdade de Motricidade Humana da Universidade de Lisboa
Doutora Analiza Mónica Lopes Almeida Silva
Professora Associada com Agregação
Faculdade de Motricidade Humana da Universidade de Lisboa
Doutora Marta Filipa Paulino Silvestre
Professora Auxiliar
NOVA Medical School, Faculdade de Ciências Médicas da Universidade NOVA de Lisboa

2023



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ABBREVIATIONS

24hEE	24h Energy Expenditure
AgRP	Agouti-related protein
ANS	Autonomic nervous system
ARC	Arcuate nucleus
AT	Adaptive thermogenesis
ATP	Adenosine triphosphate
BDNF	Brain-derived neurotrophic factor
BF	Body fat
BFCC	Body-food choice congruence
BMI	Body mass index
BP	Blood pressure
BW	Body weight
CARDIA	Coronary Artery Risk Development in Young Adults
CART	Cocaine- and amphetamine-regulated transcript
CCK	Cholecystokinin
CDR	Cognitive dietary restraint
CEFMH	Ethics Committee of the Faculty of Human Kinetics
CER	Continuous energy restriction
CG	Control group
CHO	Carbohydrates
CI	Confidence intervals
CNS	Central nervous system
COX	Cytochrome *c* oxidase
CR	Caloric restriction
DiD	Differences-in-differences
DLW	Doubly labelled water

DXA	Dual energy X-ray absorptiometry
EAT	Exercise activity thermogenesis
EB	Energy balance
ED	Estimated difference
EDTA	Ethylenediaminetetraacetic acid tubes
EE	Energy expenditure
EI	Energy Intake
EiEE	Exercise-induced Energy Expenditure
EL	Explicit liking
EPR	Eating for physical rather than emotional reasons
ER	Energy restriction
ES	Energy stores
EW	Explicit wanting
FFM	Fat-free mass
FM	Fat mass
FT3	Free triiodothyronine
FT4	Free thyroxine
FTO	Fat mass and Obesity Associated Gene
GB	Gastric banding
GIP	Gastric inhibitory polypeptide/ glucose-dependent insulinotropic polypeptide
GLP-1	Glucagon-like peptide-1
HbA1c	Glycated hemoglobin
HDL	High-density lipoprotein
HOMA	Homeostatic model assessment
IER	Intermittent energy restriction
IES-2	Intuitive eating scale - 2
IG	Intervention group

INSIG2	Insulin-induced gene 2
IW	Implicit wanting
LCD	Low-calorie diet
LDL	Low density lopoprotein
LEP	Leptin
LEPR	Leptin receptor
LFPQ	Leeds food preference questionnaire
LST	Lean soft tissue
MA	Metabolic adaptation
MC4R	Melanocortin 4 receptor
MET	metabolic equivalent of task
MHCs	Myosin heavy chains
mREE	Measured resting energy expenditure
MSH	Melanocyste-stimulating hormones
MVPA	Moderate to vigorous physical activity
NA	Not applicable
NAcc	Nucleus accumbens
NEAT	Non-exercise activity thermogenesis
NEPA	Non-exercise physical activity
NHANES	National Health and Nutrition Examination Survey
NPY	Neuropeptide Y
NRT	Non-randomized trial
NS	Non-significant
NTRK2	Neurotrophic tyrosine kinase receptor type 2
PA	Physical activity
PAEE	Physical activity energy expenditure
PCr	Phosphocreatine

PCSK1	Proprotein convertase subtilisin/kexin type 1
PFC	Propective food consumption
PFK	Phosphofructokinase
Pi	Phosphate
PNS	Parasympathetic nervous system
PO	Prospective observational study
POMC	Proopiomelanocortin
PP	Pancreatic polypeptide
pREE	Predicted resting energy expenditure
PRO	Protein
PYY	Peptide YY
RCT	Randomized controlled trial
REE	Resting energy expenditure
RHSC	Reliance on hunger and satiety cues
RO	Retrospective observational study
ROI	Region of interest
RT	Randomized trial
RYGB	Roux-em-Y Gastric Bypass
SD	Standard deviation
Sdir	Standard deviation of individual response
SDT	Self-Determination theory
SE	Standard error
SEE	Sleeping energy expenditure
SERCA	Sarcoendoplasmic reticulum calcium ATPase
SG	Sleeve Gastrectomy
SNS	Sympathetic nervous system
SWC	Smallest worthwhile change

T3	Triiodothyronine
T4	Thyroxine
TDEE	Total daily energy expenditure
TE	Typical error
TEF	Thermic effect of feeding / thermic effect of food
TSH	Thyroid stimulating hormone
UPE	Unconditional permission to eat
VAS	Visual analogue scale
VCO2	Carbon dioxide production
VLDL	Very low calorie diet
VO2	Oxigen consumption
VTA	Ventral tegmental area
WHO	World Health Organization
WL	Weight loss
WM	Weight maintenance

ABSTRACT

The lack of efficacy of weight loss (WL) interventions can be mostly attributed to low adherence to dietary/physical activity (PA) recommendations. However, metabolic and behavioral compensations are expected to occur as a response to WL. These include decreases in energy expenditure (EE) components, reductions in PA and increases in energy intake (EI). Adaptive thermogenesis (AT), defined as a higher-than-expected decrease in any EE component that is not explained by changes in body composition stores (fat mass and fat-free mass) has been considered a possible barrier to WL and its maintenance. Regardless, evidence is still scarce about the presence and the assessment of these compensatory responses after a moderate WL, as well as some methodological limitations when assessing AT. Therefore, this dissertation presents 6 research papers that results from the Champ4life project, a randomized clinical trial involving a lifestyle intervention aimed to promote a moderate WL targeting former elite athletes who developed overweight/obesity and became inactive.

The first study consisted in a systematic review regarding the existence of AT in resting EE (REE), sleeping EE (SEE) and total daily EE as a response to an WL intervention. The results pointed out for some fragilities that needed to be studied further, such as the large variability between and within studies and the lack of consistency among methodologies to predict REE and/or to assess AT. Therefore, the second investigation aimed to compare 13 different methodologies varying in how REE was predicted and/or how AT was calculated. The findings of this study emphasized the substantial impact of the used methodological approach, as AT values varied among participants. The third manuscript aimed to understand if AT occurs after a moderate WL (<10%) and if it is still persists after a period of weight stabilization (8 months). AT occurred after 4 months of WL and remained significant after a successful WL maintenance. Study 4 aimed to understand if AT occurs in other EE components, namely in non-exercise activity thermogenesis (NEAT). Study 5 comprised behavioral compensations, aimed to

evaluate the interindividual variability in EI and EE after WL and to understand how changes in EI are associated with changes in PA duration and PAEE. For studies 4 and 5, neither an energy conservation in NEAT nor the existence of behavioral compensations after WL were found. Still, the large variability among participants were considered in both studies, emphasizing the need of analyzing not only the mean values but also the individual WL responses. The last study aimed to explore the impact of WL on intuitive eating and food reward outcomes. The findings revealed that food reward decreased after a moderate WL, as well as a decrease in willingness to allow themselves to eat whatever food is desired when hungry and an increase in better food choices (in terms of matching one's physical needs).

This dissertation contributes substantially to the available literature considering metabolic and behavioral compensations and the large individual variability observed that may occur as a response to WL, emphasizing the challenges that researchers and practitioners might face in WL management. Understanding these compensatory responses is crucial to better implement WL interventions that will lead to a successful WL and maintenance of a reduced weight state.

Key-words: energy balance, adaptive thermogenesis, energy expenditure, weight loss, body composition.

RESUMO

Embora a baixa eficácia das intervenções para perda de peso seja normalmente justificada pela baixa adesão às recomendações dietéticas/atividade física, a existência de compensações metabólicas e comportamentais têm sido sugeridas, incluindo reduções nos componentes do dispêndio energético (DE), reduções na atividade física e o aumento da ingestão energética (IE). A adaptação metabólica (AM), definida como uma diminuição maior do que o esperado em qualquer componente do DE face às alterações da composição corporal (massa gorda e massa isenta de gordura), tem sido considerada uma possível barreira para a perda de peso e a sua manutenção a longo prazo. Porém, juntamente com algumas questões metodológicas relativamente à avaliação da AM, a existência dessas respostas compensatórias após uma perda de peso moderada não é clara.

Assim, esta dissertação contém 6 artigos cujos resultados provêm do projeto Champ4life, um ensaio clínico randomizado com uma intervenção do estilo de vida para atletas em fase pós carreira que viviam com excesso de peso/obesidade e que eram considerados inativos, estando o projeto dividido numa fase de perda de peso ativa (4 meses) seguida de uma fase de manutenção do peso perdido (8 meses).

O primeiro estudo consistiu numa revisão sistemática relativamente à existência de AM no metabolismo de repouso, DE a dormir e no DE total como resposta a uma intervenção para perda de peso. Os resultados enfatizaram algumas fragilidades que devem ser analisadas com detalhe, como a grande variabilidade entre estudos e entre participantes, tal como a falta de consistência em relação às metodologias utilizadas para predizer o metabolismo de repouso e/ou para calcular a AM. Assim, o segundo estudo teve como objetivo comparar 13 metodologias que diferiam em como o metabolismo de repouso era predito e/ou como a AM era calculada. Os resultados deste estudo enfatizaram o impacto substancial da metodologia escolhida, pois os valores de AM variaram significativamente entre os métodos estudados. O terceiro artigo teve

como objetivo perceber se a AM ocorre após uma perda de peso moderada (<10%) e se continua relevante após um período de manutenção de peso. A AM não só ocorreu após 4 meses de perda de peso, como também se manteve significativa após o período de manutenção. O estudo 4 estudou a existência de AM noutros componentes do DE, nomeadamente a AM na atividade física que não é considerada exercício. O 5º artigo estudou a existência de compensações comportamentais, com o objetivo de analisar a variabilidade interindividual na IE e no DE após perda de peso e também em perceber como é que alterações na IE estão associadas com alterações na duração e a energia despendida em atividade física. Apesar de não terem sido encontradas nem uma conservação de energia nesse componente do DE nem compensações comportamentais, a grande variabilidade entre participantes foi considerada nos dois estudos, enfatizando a necessidade de analisar não apenas as médias como também as respostas individuais quando observamos variáveis de perda de peso. O último estudo teve como objetivo explorar o impacto da perda de peso em variáveis de alimentação intuitiva e de recompensa alimentar, observando ainda a relação entre alterações nestes componentes e a composição corporal. Após uma perda moderada de peso, os valores de recompensa alimentar diminuíram, tal como a permissão para comer alimentos desejados quando se está com fome, e ainda um aumento da realização de melhores escolhas alimentares (considerando as necessidades físicas individuais).

Esta dissertação contribui substancialmente para a evidência atualmente existente sobre as compensações metabólicas e comportamentais que ocorrem como resposta a uma perda de peso. O entendimento destas respostas compensatórias é importante para implementar intervenções adequadas, que levem a uma perda de peso bem-sucedida, bem como a sua manutenção a longo prazo.

Palavras-chave: balanço energético, adaptação termogénica, dispêndio energético, perda de peso, composição corporal.

CHAPTER 1

INTRODUCTION TO THE DISSERTATION

1. INTRODUCTION TO THE DISSERTATION

1.1. Dissertation structure

The present dissertation, entitled "The role of metabolic and behavioral compensations in weight management", incorporates a compilation of **6** research articles where 5 are already published and 1 is submitted for publication in peer-review journals with an established ISI Impact Factor.

This work is organized as follows:

CHAPTER 2 comprises a literature review, including an initial overview about the energy balance equation and its components. A detailed discussion regarding the systems that are involved in this regulation (homeostatic, environmental, and hedonic system) is included, as well as the description of some proposed models of body weight regulation (static/set-point, settling-point and dual intervention.

Secondly, the metabolic and behavioral compensatory responses that may occur as a response to a disturbance on the energy balance equation (i.e. weight loss) are addressed, where each compensation is presented, with a special focus on the adaptive thermogenesis on resting energy expenditure.

Lastly, the issues concerning adaptive thermogenesis assessment were underscored, pointing out some fragilities that need to be studied further. This chapter finishes with the presentation of the main goals of this work.

Although a methodology section with a general description of the methods is presented in each included manuscript, the **CHAPTER 3** comprises a detailed description of the methodology used through all the included studies.

CHAPTERS 4 - 9 correspond to the included studies that were performed to achieve the research aims that were stated in chapter 2.

A general discussion is present in **CHAPTER 10**, providing a summary and integrated discussion of the main findings that were obtained in the 6 included studies of this work. In this chapter, practical applications and limitations were also included.

1.2. List of articles and conference abstracts

Articles related to the dissertation (first author)

- **Nunes C.L.,** Rosa G, Jesus F, Francisco R, Bosy-Westphal, A, Heymsfield S.B., Minderico C.S., Martins P, Sardinha L.B., Silva A.M.; Interindividual variability in energy intake and expenditure during a weight loss intervention *(under review at International Journal of Obesity);*
- **Nunes, C. L.,** Carraca, E. V., Jesus, F., Finlayson, G., Francisco, R., Silva, M. N., Santos, I., Bosy-Westphal, A., Martins, P., Minderico, C., Sardinha, L. B., & Silva, A. M. (2022, May). Changes in food reward and intuitive eating after weight loss and maintenance in former athletes with overweight or obesity. Obesity (Silver Spring), 30(5), 1004-1014. https://doi.org/10.1002/oby.23407;
- **Nunes, C. L.,** Casanova, N., Francisco, R., Bosy-Westphal, A., Hopkins, M., Sardinha, L. B., & Silva, A. M. (2022, Feb 14). Does adaptive thermogenesis occur after weight loss in adults? A systematic review. Br J Nutr, 127(3), 451-469. https://doi.org/10.1017/S0007114521001094;
- **Nunes, C. L.,** Jesus, F., Francisco, R., Hopkins, M., Sardinha, L. B., Martins, P., Minderico, C. S., & Silva, A. M. (2022, Dec). 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. Eur J Nutr, 61(8), 4121-4133. https://doi.org/10.1007/s00394-022-02951-7;

- **Nunes, C. L.,** Jesus, F., Francisco, R., Matias, C. N., Heo, M., Heymsfield, S. B., Bosy-Westphal, A., Sardinha, L. B., Martins, P., Minderico, C. S., & Silva, A. M. (2022, Apr). Adaptive thermogenesis after moderate weight loss: magnitude and methodological issues. Eur J Nutr, 61(3), 1405-1416. https://doi.org/10.1007/s00394-021-02742-6;
- **Nunes, C. L.,** Rosa, G. B., Jesus, F., Heymsfield, S. B., Minderico, C. S., Martins, P., Sardinha, L. B., & Silva, A. M. (2022, Nov 28). Interindividual variability in metabolic adaptation of non-exercise activity thermogenesis after a 1-year weight loss intervention in former elite athletes. Eur J Sport Sci, 1-10. https://doi.org/10.1080/17461391.2022.2147020.

Abstracts related to the dissertation (first author)

- Poster "A large variability in metabolic adaptation in non-exercise activity thermogenesis is observed after moderate weight loss in former elite athletes" Recent Advances & Controversies in the Measurement of Energy Metabolism (RACMEM), **2022**;
- Poster "Interindividual variability in metabolic adaptation of non-exercise activity thermogenesis after a 1-year weight loss intervention in former elite athletes" Jornadas Científicas ULisboa, **2022**;
- Oral communication "Assessing adaptive thermogenesis using a marker of adiposity limits an energy conservation effect on weight loss maintenance". VIII Congresso Brasileiro de Metabolismo, Nutrição e Exercício (CONBRAMENE), **2021**;
- Poster "Metabolic adaptation in former athletes with overweight/obesity maintaining a weight reduced state after the Champ4Life lifestyle intervention program" Sports Sciences Congress FMH-UL, **2021**;

- Poster “Characterization of body composition and health outcomes in former athletes with overweight/obesity” European and International Congress on Obesity (EASO), **2020**.

Other peer-reviewed articles (not related to the dissertation)

First author

- **Nunes C.L.,** Jesus F, Oliveira M., Heymsfield S.B., Sardinha L.B., Martins P., Minderico C.S., Silva A.M.; The impact of body composition on the degree of misreporting of food diaries *(submitted at European Journal of Sport Nutrition)*;
- **Nunes, C. L**., Matias, C. N., Santos, D. A., Morgado, J. P., Monteiro, C. P., Sousa, M., Minderico, C. S., Rocha, P. M., St-Onge, M. P., Sardinha, L. B., & Silva, A. M. (2018, May 30). Characterization and Comparison of Nutritional Intake between Preparatory and Competitive Phase of Highly Trained Athletes. Medicina (Kaunas), 54(3). https://doi.org/10.3390/medicina54030041.

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impedance devices. Eur J Clin Nutr, 73(7), 1077-1083. https://doi.org/10.1038/s41430-018-0355-z.

1.3. Awards

- Medicina 2020 Best Paper Award – “Characterization and Comparison of Nutritional Intake between Preparatory and Competitive Phase of Highly Trained Athletes”

CHAPTER 2

LITERATURE REVIEW

2. LITERATURE REVIEW

2.1. OVERVIEW

It is common knowledge that losing weight is not a simple matter of "move more and eat less". Although the energy balance (EB) equation appears simplistic, where the energy stores (ES) are determined by a balance between energy intake (EI) and energy expenditure (EE), it is in fact a complex and dynamic system, where a complex integration between biological, environmental, and behavioral factors is involved.

Obesity's prevalence is increasing worldwide, being the result of a prolonged positive EB, i.e. EI surpasses the EE. Despite the homeostatic system attempts to correct this positive EB, by decreasing appetite and hunger (through the action of appetite-related hormones), this system can be easily overridden by the current obesogenic environment. Moreover, the existence of hedonic pathways based upon the reward value of the food, together with the high abundance of highly palatable foods, may increase the desire to eat, independently of our energy stores.

Even though literature is full of weight loss (WL) interventions, the rate of success of losing weight and maintaining it throughout time is low (J. G. Thomas et al., 2014), with high levels of recidivism and weight regain (Greaves et al., 2017; Wadden et al., 2011). Together with a decreasing adherence to diet and physical activity (PA) recommendations throughout time (Heymsfield et al., 2007), the existence of metabolic and behavioral compensations that occur as a response to a negative EB has been proposed. These compensatory responses include decreases in EE components (Leibel et al., 1995), decreases in PA (Racette et al., 1995; Weigle, 1988) and increases in EI as a response to an increase in orexigenic drive (Doucet & Cameron, 2007), which work as a barrier to WL.

The regulation of body weight, as well as the compensatory responses that occur as a response to a negative EB are presented at **figure 2.1.**

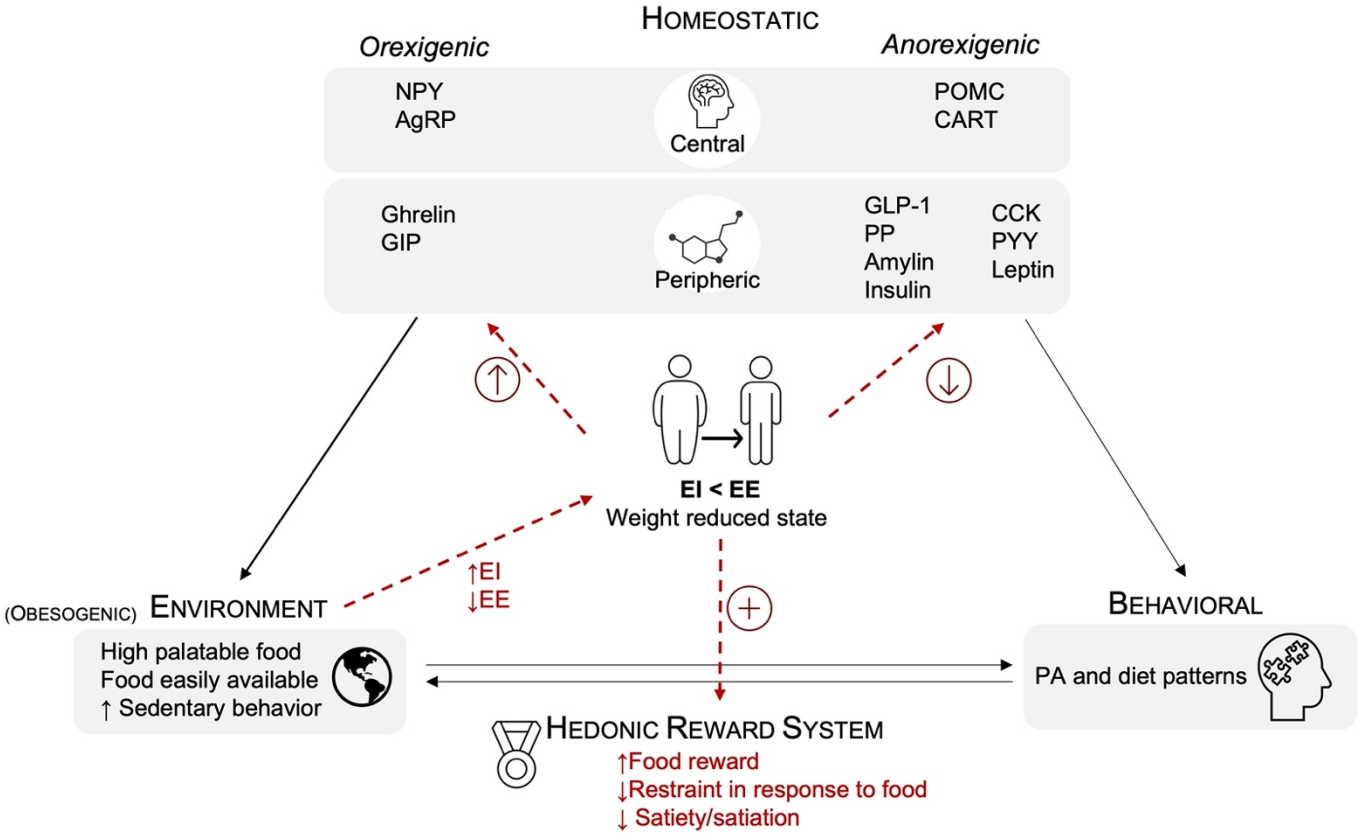

Figure 2.1. Regulation of body weight (in black) and metabolic and behavioral compensations that drive weight regain after weight loss (in red) [adapted from (Greenway, 2015)].

Legend: NPY – Neuropeptide Y, AgRP – Agouti-related protein, POMC – Proopiomelanocortin, CART - Cocaine- and amphetamine-regulated transcript, GIP - Gastric inhibitory polypeptide, GLP-1 - Glucagon-like peptide-1, PP - Pancreatic polypeptide, CCK – Cholecystokinin, PYY – Peptide YY, PA – Physical activity, EE – Energy expenditure, REE – Resting energy expenditure, PAEE – Physical activity energy expenditure, TEF – Thermic effect of feeding

Therefore, this chapter is divided in 2 main topics: 1) **Body weight regulation**, where the concept of energy balance regulation is defined, describing the systems that are included in this regulation (homeostatic, environmental and hedonic system), as well as some proposed models of body weight regulation (static/set-point, settling-point and dual intervention), and 2) **What happens when we lose weight**, comprising all the metabolic

and behavioral compensatory responses that occur as a response to a negative EB and comparing them between the active WL and WL maintenance phase.

2.2. BODY WEIGHT REGULATION

2.2.1. Energy Balance Equation

The maintenance of body weight is a major determinant of the survival of humans and other mammals (Jéquier & Tappy, 1999). According to the first law of thermodynamics, in a system of constant mass, energy cannot be created or destroyed, but only be converted from one to another (gained, lost, or stored) (Zohuri, 2018). The EB equation complies with this law, where the physiological mechanisms that control EB aim to ensure that adequate energy is available for cellular processes required for survival and reproduction (Faulconbridge & Hayes, 2011).

The EB equation states that the rate of ES is equal to the rate of EI minus the rate of EE (Hill et al., 2012), defined as:

$$ES_{(kcal/d)} = EI_{(kcal/d)} - EE_{(kcal/d)}$$

Where the EI comprises the energy yielded by the macronutrients (carbohydrates, protein and fat), as well as alcohol, and EE refers to the energy expended by the body. Total daily EE (TDEE) can be divided into 3 components (**figure 2.2.**):

1) Resting Energy Expenditure (REE), i.e., the metabolic cost of maintaining vital body functions;

2) Thermic Effect of Feeding (TEF), i.e., the energy required in the post-prandial period (digestion, absorption, transport and storage of dietary nutrients) (Westerterp, 2004);

3) Physical Activity Energy Expenditure (PAEE), i.e., the energy expended mainly in the form of physical activity (PA) (Leibel et al., 1995).

PAEE can be divided in two different components: 1) Exercise-induced Energy Expenditure (EiEE) – also known as exercise activity thermogenesis -, the energy expended during exercise/sports practice (a planned and structured PA with a specific aim regarding physical fitness), and 2) Non-Exercise Activity Thermogenesis (NEAT), the energy expended in daily life activities, such as fidgeting, posture maintenance and non-specific ambulatory activities, which is considered non-exercise PA (NEPA) (Levine et al., 1999).

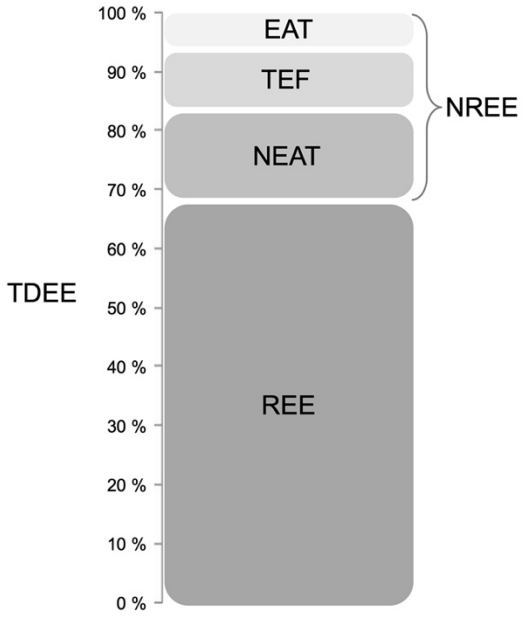

Figure 2.2. EE components and its contribution to total EE [adapted from (MacLean et al., 2011)]

Legend: TDEE – total daily energy expenditure, EAT – Exercise activity thermogenesis, NEAT – Non-exercise activity thermogenesis, TEF – Thermic effect of feeding, PAEE – Physical activity energy expenditure, REE – Resting energy expenditure.

The REE is the most significant contributor for total EE, contributing approximately 60-70% of total EE (Hall et al., 2012). Following REE, the energy expended in both exercise and non-exercise physical activity (PA) is also an important contributor for total EE, being the component that varies the most among individuals (Westerterp, 2013).

How to measure the components of the EB equation?

Energy stores (ES)

An accurate assessment of both EI and EE is paramount to better implement nutritional and/or PA interventions aimed to WL and/or to prevent weight (re)gain. Given this dynamic relation between EI and EE, it is possible to calculate one term of the EB equation (usually EI) if the other two terms were accurately measured. When the body weight is stable (ΔES = 0), EI closely approximates from EE. However, when changes in body weight occur, although EI is not equal to EE, it can be approximated by using the EB equation (Schoeller, 2009), through the assessment of total EE and ΔES.

Changes in ES (kcal/d) can be calculated from the changes in body energy stores, namely changes in fat-mass (ΔFM) and fat-free mass (ΔFFM), by multiplying these changes by the established energy densities of each tissue, namely 9.5 kcal/g for FM (Merril; & Watt.) and 1.1 kcal/g for FFM (Dulloo & Jacquet, 1999), divided by the number of days (Δt):

$$ES = 9500\frac{\Delta FM}{\Delta t} + 1020\frac{\Delta FFM}{\Delta t},$$

Therefore, if FM and FFM are known over a time interval, then ES can be directly calculated and summed with EE to objectively estimate EI (Ravelli & Schoeller, 2021).

Although this equation can be useful to estimate the other terms of the EB equation, especially EI, there are a few assumptions that should be considered. First, short periods of time could compromise the accuracy of these measurements, where a period of at least 28 days was suggested to reduce this inaccuracy (Hall & Chow, 2011). Moreover, these equations assume a constant energy density for both FM and FFM during all the entire WL process, which is not necessarily true, especially during short periods of WL, where there are unaccounted alterations in body fluids.

Energy expenditure (EE)

The doubly labelled water (DLW) method is considered the gold standard for measuring total EE (Speakman et al., 2021; Westerterp, 2017). This methodology involves augmenting the body water of a subject with hydrogen and oxygen isotopes, and then observing the washout kinetics of both isotopes as they gradually decline to their natural abundance levels in an exponential manner. Therefore, despite its accuracy, DLW is time and cost consuming, requiring specialized technicians, making it unfeasible for widespread application (Poslusna et al., 2009).

As an alternative, total EE can be calculated through the assessment of the 3 main EE components – REE, TEF and PAEE - specifically:

$$\text{Total EE(kcal/d)} = \text{REE(kcal/d)} + \text{TEF(kcal/d)} + \text{PAEE(kcal/d)}$$

The gold standard to measure REE is the indirect calorimetry (Delsoglio et al., 2019). This methodology measures the oxygen consumption (VO_2) and the carbon dioxide production (VCO_2), with the advantage of providing information on the subtract utilization (carbohydrates, fat and protein). Considering PAEE, accelerometry-based wearable motion devices provide detailed, continuous, and objective measurements (Pisanu et al., 2020; Poslusna et al., 2009), being more accurate and reliable than self-reported tools and less time and cost consuming than DLW (Ndahimana & Kim, 2017). Moreover, unlike DLW, this methodology has the advantage of providing objective information on the amount, intensity, frequency, and duration of PA, assessing PA in exercise and non-exercise contexts. To measure TEF, some methodologies were proposed, such as computing the difference in EE between the fed and fasting states (Tataranni et al., 1995), or the difference between the postabsorptive REE and the EE at 0 activity (estimated from the intercept of the linear regression between EE and PA in the

postprandial state) (Schutz et al., 1984). A modified version involves subtracting the sleeping EE (SEE) rather than REE (Westerterp et al., 1999). Nevertheless, their accuracy has been questioned, as sometimes it leads to negative TEF values (Ravussin et al., 1986; Westerterp et al., 1999). Despite recent strategies has been proposed (Ogata et al., 2016), currently, most studies do not measure TEF, assuming that it is static and accounts to 10% of total EE (TEF = 0.1 total EE) (Melanson, 2017), which simplifies the previous equation to:

$$\text{total EE(kcal/d)} = \frac{REE\text{(kcal/d)} + PAEE\text{(kcal/d)}}{0.9}$$

Energy intake (EI)

Measuring EI is a difficult task for researchers, as it can only be measured accurately and precisely in the inpatient setting or when food is provided in the outpatient condition (Burrows et al., 2019; Ravelli & Schoeller, 2021). Self-reported tools, such as food diaries, are known to be inaccurate, presenting a higher degree of misreporting (usually underreporting) (Burrows et al., 2019; Ravelli & Schoeller, 2020). Several studies reported a certain degree of misreporting (Bawadi et al., 2021; Dahle et al., 2021; Dhurandhar et al., 2015; Maurer et al., 2006; Speakman et al., 2021), which can be explain by the conscious or sub-conscious exclusion of foods that were consumed, as well as the lack of literacy regarding portion size.

Under a neutral EB, i.e. EE equals EI, EI can also be indirectly assessed by DLW (de Jonge et al., 2007). Also, given the relation between EI and EE in the EB equation, if two terms of the equation are known (ES and EE), it is possible to calculate the third one (EI), the so-called “intake-balance method” (Ravelli & Schoeller, 2021), which provides a more accurate and objective assessment of EI when compared to self-reported instruments (Gilmore et al., 2014).

Therefore, the EB reflects the dynamic relationship between EI and EE, where the stabilization of body weight at a long-term implies that the EI, i.e., all the foods that are ingested, equals the energy that is expended throughout the day – EE (Hill et al., 2013). On the other hand, any energy imbalance that occurs in at least one of the two components of the EB equation (and EI is no longer equal to EE), leads to changes in body weight (Hill & Commerford, 1996). Despite apparently simple, EB represents a complex and dynamic system in which its components (EI and EE) fluctuate over time (Edholm et al., 1970). Also, any change that leads to a perturbation in either side of the equation will instigate compensatory events to counteract the created perturbation.

Obesity – Result of an imbalance between EI and EE

According to the World Health Organization (WHO), overweight and obesity are defined as an "abnormal or excessive fat accumulation, which presents a risk to health" (World Health Organization, 2021). **The prevalence of obesity is increasing worldwide**, with 52.7% of the European Union population presenting overweight or obesity (FFMS, 2019) (regional trends presented in **figure 2.3.).** If this trend continues, global obesity prevalence will reach 18% in men and surpass 21% in women by the year of 2025 (NCD Risk Factor Collaboration, 2016).

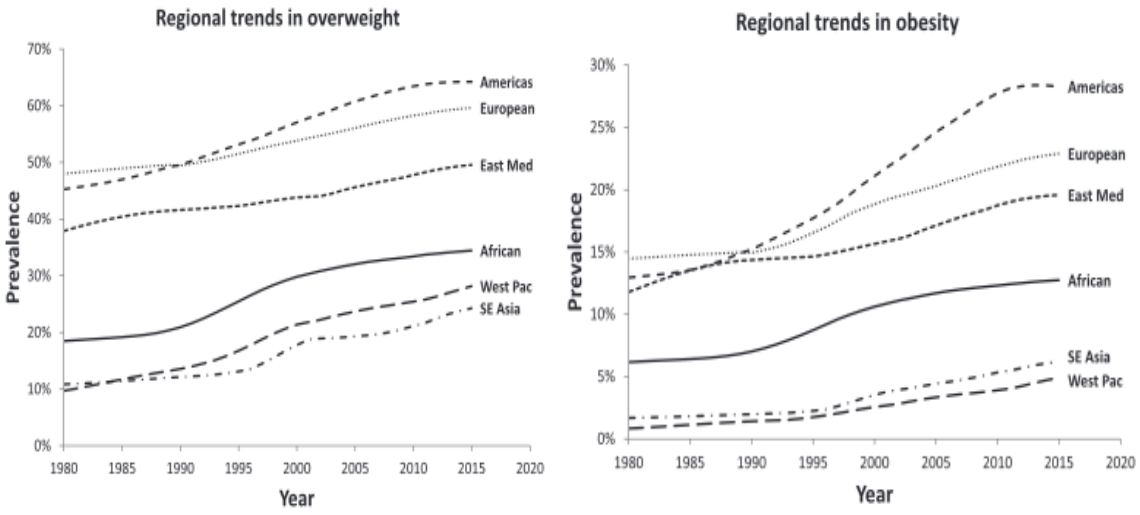

Figure 2.3. Regional trends in overweight and obesity (Chooi et al., 2019)

Then, obesity is considered a major public health issue, where an **excess of adiposity raises the risk of developing several diseases** like diabetes mellitus, cardiovascular disease, non-alcoholic fatty liver disease, endocrine problems and certain forms of cancer, leading to an increased overall mortality (Gurevich-Panigrahi et al., 2009). Therefore, effective interventions to counteract this problematic tendency are needed, not only aimed to weight loss and to avoid weight regain for people who have excessive body weight/fat but also to prevent weight gain in people who are not living with overweight or obesity. Surprisingly, alongside with increasing obesity rates, the number of scientific manuscripts comprising weight loss strategies is also increasing year by year. It would be expected that the increasing number of strategies to treat obesity led to a decrease in the obesity rates, which is not what is happening currently. Thus, we are facing a different problem: Despite knowledge regarding weight loss management is increasing, there is a lack of truly effective strategies that will decrease the obesity prevalence. Then, it is crucial to find the best approach to treat obesity not only for a short period of time but also at a long-term, avoiding weight regain.

Therefore, it is logical to state that **obesity is the result of a prolonged state of a positive EB, where the EI surpasses the EE.** When this happens, the surplus energy

tends to be stored in one's body, and, if this positive EB is sustained over time, weight gain occurs (Hall & Guo, 2017).

Given the fact that people living with obesity are in a positive EB, a plausible solution to treat this problematic and reduce obesity rate would comprise a combination of changes in EI and/or EE to achieve a negative EB and sustained it throughout time in order to lose weight. In fact, Hill et al, by analyzing the population from National Health and Nutrition Examination Survey (NHANES) and from Coronary Artery Risk Development in Young Adults (CARDIA) study (Dutton et al., 2016), showed that the median weight gain over the past 2 decades has been ~0.45 to 0.91 kg/year (1 to 2 lb/year) (Hill et al., 2003). Considering a very conservative analysis of the distribution of weight gain over time, this can be explained by a positive EB of only ~15kcal/d, with 90% of the population presenting a surplus of 50 or fewer kcal/d. Therefore, weight gain could be prevented for most people by implementing small behavioral changes, such as walking an extra mile or slightly reducing portion size. However, as stated before, the balance between EI and EE is influenced by several factors, not only physiological but also external ones, such as the environment and one's behavior.

2.2.2. Body Weight Homeostasis

Although the stabilization of body weight appears to be simple according to the EB equation (where the EI must equals the EE), maintaining a steady body weight involves different factors (Greenway, 2015). The mechanisms underlying the regulation of body weight are not clear, yet the current evidence suggests that there is complex integration between biological, environmental and behavioral factors (Hill et al., 2012), where all of these systems seem to be influenced by genetics (MacLean et al., 2011).

The Homeostatic system

In humans, both EI and EE are tightly co-regulated by conserved neuronal and endocrine circuits (Leng, 2014). The homeostatic regulation of body weight and adiposity involves a neural regulator that senses fuel availability in the internal milieu and generates the appropriate signals to the neural circuits in order to control food intake and also energy expenditure, and therefore to maintain a neutral EB (Lenard & Berthoud, 2008).

Together with the central regulation, peripheral signals that convey information about short- (nutrient availability) and long-term food intake (energy stores) also play an important role in this homeostatic system, with a feedback loop created between the brain and the periphery (Greenway, 2015). More specifically, peripheral organs such as adipose tissue, muscle, pancreas, liver and all the gastrointestinal tract are intimately connected with the brain, sending neural connections provided by the autonomic nervous system (ANS), or hormonal signals through the release of appetite-related hormones to regulate EI and EE (Faulconbridge & Hayes, 2011). Considering the central nervous system (CNS), the most important areas regarding the regulation of EB are the caudal brainstem, the hypothalamus and parts of the cortex and limbic system, although other brain areas are also involved (Lenard & Berthoud, 2008).

The hypothalamus is the region of the brain that controls food intake and body weight (Roh & Kim, 2016), acting as the control center for hunger and satiety. This brain area integrates nutritionally relevant information received by all peripherical organs, mediated through circulating hormones and metabolites and/or neural pathways from the brainstem (Lenard & Berthoud, 2008). The arcuate nucleus in the hypothalamus (ARC) comprises 2 distinctive neuronal populations with opposing effects: orexigenic neurons – Neuropeptide Y (NPY) and Agouti-related peptide (AgRP) -, which stimulates the food intake, and anorexigenic neurons – proopiomelanocortin (POMC) and cocaine and amphetamine regulated transcript (CART), that suppresses food intake (Abdalla, 2017).

Appetite-related hormones

There are circulating hormones that interact with specific regions in the hypothalamus to produce sensations of appetite and satiety, which consequently leads to increase or decrease food intake, respectively (Yeung & Tadi, 2022). More specifically, the ingestion of a meal triggers the secretion of anorexigenic hormones that act in the anorexigenic neurons, resulting in a decrease in appetite. On the other hand, fasting will lead to a liberation of orexigenic hormones, which act in the orexigenic neurons to increase hunger and appetite. The **table 2.1.** comprises all the appetite-related hormones and its characteristics.

Ghrelin is an orexigenic hormone primarily released from the stomach as a response to a negative EB state (Sovetkina et al., 2020). Together with its well-known role in body weight regulation, by stimulating appetite (short-term) and changing body weight (long-term) (Al Massadi et al., 2017), this hormone also contribute to blood glucose regulation, by regulating insulin and glucagon secretion (Mihalache et al., 2016).
The role of GIP remains inconclusive, as earlier work had considered this incretin as an "obesity" hormone (Marks et al., 1988), but recent animal studies suggested that GIP might exert weight-reducing effects (Mroz et al., 2019; Norregaard et al., 2018; Zhang et al., 2021). Nevertheless, as there is a lack of recent human studies regarding the role of GIP in body weight regulation, this incretin will be classified as orexigenic in this dissertation due to its role on increasing adipose tissue blood flow and triglyceride uptake, which promotes lipid storage (Asmar et al., 2017).

Considering anorexigenic hormones, there are many peripheral peptides that are associated with satiety, being secreted by several organs, such as the gastrointestinal tract, pancreas, and the adipose tissue (Austin & Marks, 2009).

Leptin is one of the most important hormones to body weight regulation, by suppressing food intake (Austin & Marks, 2009). This hormone is secreted by the white adipose tissue and enter the brain through the bloodstream. More specifically, leptin binds in the hypothalamus via ObRb-receptor, activating a complex neural circuit comprising anorexigenic and orexigenic neuropeptides to control food intake (Klok et al., 2007). Leptin activates anorexigenic neurons that synthesize POMC and CART, and inhibits orexigenic neurons that synthesize AgRP and NPY (Varela & Horvath, 2012).

Insulin is secreted by the pancreatic β-cells, being dependent on the blood glucose level (short-term) and on the level of adiposity (long-term), exerting a strong anorexigenic effect (Woods et al., 2006). Similar to leptin, insulin acts in the POMC and AgRP neurons in the hypothalamus, regulating food intake, body weight and glucose homeostasis (Varela & Horvath, 2012). However, despite reducing food intake centrally, insulin may cause weight gain when used peripherally to treat diabetes (Russell-Jones & Khan, 2007). Moreover, both insulin and leptin are known as “adiposity signals”, as a change in circulating levels of these hormones indicates a state of altered energy homeostasis and adiposity (Hillebrand & Geary, 2010). Thus, in order to regulate adiposity levels, the brain adjusts food intake. There is evidence showing that leptin and insulin may exert a role in CCK, by enhancing the satiety action of this anorexigenic hormone, causing meals to be terminated earlier and reducing food intake (Baskin et al., 1999).

The role of gut hormones on the body weight regulation also needs to be addressed. CCK is produced in the small intestine and released in response to food ingestion (Little et al., 2005). This hormone plays an important role in digestion and appetite regulation by stimulating the release of digestive enzymes from the pancreas and the contraction of the gallbladder, slowing gastric emptying (Little et al., 2005). Similarly, GLP-1 is produced in the L-cells of the intestine, being released in response to food intake (Holst, 2007). This hormone exerts an influence in glucose homeostasis by regulating blood sugar levels. More specifically, GLP-1 stimulates the insulin release as a response to an increase in blood glucose levels and inhibits the glucagon release, helping lowering

blood sugar levels. Other hormones such as PP and PYY are also produced in the gut and are released following a meal, regulating postprandial satiety (De Silva & Bloom, 2012). All of these anorexigenic gut hormones also work as satiety signals, acting on the hypothalamus and reducing feelings of hunger and increasing satiety (Little et al., 2005). Amylin is an anorexigenic hormone secreted by pancreatic B-cells with a significant role in regulating nutrient fluxes by decreasing food intake, delaying gastric emptying, and reducing glucagon secretion after meals (Lutz, 2012; Woods et al., 2006).

Most studies attempting to explain the increasing obesity prevalence were focused on possible flaws on the homeostatic system. However, although few individuals might be more prone to develop obesity due to homeostatic system impairments (Hellström et al., 2004), for most people, the homeostatic system works properly within their biological potency, which suggests the existence of other systems that may exert a significant influence and possibly override the role of the homeostatic system on body weight regulation (Berthoud, 2004). For instance, it is known that the environment where we are living plays an important role on body weight regulation, exerting an influence on the homeostatic system (Greenway, 2015). Since the environment suffered some changes throughout time, which originated the current modern world, this system might override the homeostatic one, as it is not powerful enough to cope with these alternations.

Table 2.1. Orexigenic and anorexigenic hormones

	Site of synthesis	Acts	Stimulus	Mediation of action	Action (EI-related)
Orexigenic					
Ghrelin	Stomach	Hypothalamus	Fasting Circadian rhythm	GIP Receptor, GHS-R1a	↑ GH release ↑ Food intake ↑ gastric mobility
Glucose-dependent insulinotropic polypeptide (GIP)	Stomach, duodenum, jejunum	Pancreatic β-cells, CNS	Food intake	GIP Receptor	↑ insulin secretion ↓ Food intake (results from animal studies, not conclusive for humans) ↑ lipid storage
Anorexigenic					
Leptin	Adipose tissue	Hypothalamus	Food ingestion	ObRb-receptor	↑ Satiety
Insulin	Pancreatic β-cells	Hypothalamus	Food ingestion	Insulin receptor	↓ Food intake ↑ Leptin and CCK secretion
Amylin	Pancreatic β-cells	Hypothalamus	Food ingestion (co-secreted with insulin)	Amylin receptor	↓ Food intake ↓ Rate of gastric emptying
Cholecystokinin (CCK)	Duodenum, proximal jejunum	Hypothalamus, small intestine	Food ingestion, fat intake	CCK A/1 CCKB/2	↓ Rate of gastric emptying ↓ Food intake ↑ Satiety
Glucagon-like peptide-1 (GLP-1)	Ileum, colon	Several organs, Hypothalamus	Food ingestion	GLP-1 Receptor	↓ Glucagon release ↓ Food intake ↓ Gastric emptying
Peptide YY (PYY)	Ileum, colon, rectum	Hypothalamus	Food ingestion, fat intake	Y2	↓ Food intake ↓ Gastric emptying
Pancreatic polypeptide (PP)	Pancreas, colon, rectum	Hypothalamus	Food intake	Y4, Y5	↓ Appetite ↓ Food intake ↓ Gastric expression of ghrelin ↓ Gastric emptying

Environment

The involving environment can be defined as all aspects of one's surroundings which are human-made or modified, such as buildings, parks, facilities and infrastructure (Lam et al., 2021). In this sense, the environment can influence body weight regulation through behavior, including PA and diet patterns, and through direct exposure, including biological responses (e.g. relation between weight regulation and air pollution) (Frank et al., 2019; Sallis & Glanz, 2009).

The evolution of modern industrialized societies changed the environment to what is known today. The increasing availability of food and portion sizes, as well as the severe marketing of energy-dense foods, lead to a higher consumption of large portions of high-fat and/or high-sugary foods (Ledikwe et al., 2005). Moreover, there is a strong pressure to increase the time spent in sedentary behavior, with modern jobs requiring spending a considerable number of hours sitting in front of a desk and the decline in the promotion of PA in schools (Church et al., 2011; Weedon et al., 2022). Therefore, the current so-called "obesogenic" environment has been pointed out as a potential driver of obesogenic behaviors, as it can affect negatively both sides of the EB equation. Consequently, this leads to a higher difficulty for individuals to maintain a healthy body weight and fat even when undergoing an energy restriction and/or adequate levels of PA (Greenway, 2015).

A perfect illustration of the role and impact of the environment on body weight regulation can be observed by analyzing the economic embargo that Cuba was subjected in the nineties. During this period, sustained shortages in the food rationing system, which culminated in a decreased food availability, led to reductions in EI (from 2,899 kcal in 1988 to 1,863 kcal in 1993) (Rodriguez-Ojea et al., 2002). More specifically, the percentage of dietary fat decreased, while the contribution of carbohydrates, specially rice and refined cereals, increased from 64 to 79% (Rodriguez-Ojea et al., 2002). Dietary intake of essential amino acids and fatty acids decreased, as animal protein and edible

oils were not easily available. Similarly, the lack of public transportation resulted in an increase in PA, as people needed to walk or use bicycles as means of transportation, which led to an increase in EE. Indeed, the percentage of the population that were considered physically active arose from 30% (1987) to almost 70% (1991-1995). In the subsequent years, obesity's prevalence halved, while the prevalence of people who had a "healthy" weight increased, as well as the overweight status (which can be explained by a shift from the obesity to overweight level). Moreover, rates of mortality dropped 51, 35 and 18% for type 2 diabetes, coronary heart diseases and all causes mortality, respectively (Franco et al., 2007). Nevertheless, when the economy started to rise, the prevalence of obesity resurged. In what concerns EI, alongside with the increases in food supplies, EI increased, being ~16% higher than in 1993 (2335kcal/day in 1996), together with the ~20% increase in fat intake (Rodriguez-Ojea et al., 2002). Surprisingly, PA did not decrease significantly, as 67% were considered physically active. Therefore, mostly due to increases in EI, a relapse in the population's body weight occurred and the prevalence of obesity increased after the crisis.

More recently, a similar situation is currently undergoing in Venezuela. According to the Venezuela's Living Conditions Survey, ~64% of the population lost an average of 11kg in 2017 due to the economic crisis (Landaeta-Jiménez et al., 2016). Similarly to Cuba, food and medicine are not easily available, being in a short supply, with a highly-cost or even unavailable. According to a questionnaire, the major contribution to the dietary intake is from carbohydrates, as most people replaced animal protein with vegetables and tubers. Nevertheless, the real impact of the Venezuela's crisis is yet to be known, as no papers were published regarding its impact on body composition and overall mortality.

As illustrated by the previous examples, changes in the environmental can have a powerful impact on the regulation of EB and body weight. Nevertheless, its important role is also well documented in conditions other than economic, political and/or social crisis. Indeed, there are several environmental factors that may interact with other

components (e.g. genetics), and consequently impacting body weight. The impact of the environment on one's body weight begins during pregnancy, with the intrauterine environment playing an important role in programming metabolism and behavior throughout life (Gluckman & Hanson, 2004). Later, the relationship between the child and their parents (specially the mother), as well as the parents' behavior will exert a strong influence in one's body weight regulation in adulthood. For instance, children who were exposed to poor maternal care are in a higher risk of developing obesity in their adolescence (Anderson et al., 2012) and eating high-energy dense food in their adulthood (Faber & Dubé, 2015). When it comes to parents body weight and feeding-related behaviors, children whose parents are living with obesity (specially the mother's weight status (Andriani et al., 2015; Whitaker et al., 2010)) are more likely to develop obesity during their childhood (Fuemmeler et al., 2013). In fact, a study showed that children from families with obesity are more susceptible to obesogenic behaviors, having a higher preference for fatty foods, a lower liking for vegetables and a higher tendency to spend more time in sedentary activities (Wardle et al., 2001).

Apart from family influences, the accessibility to food is also important. In fact, the easy access to fast-food chains is associated with obesity (Larson et al., 2009; Ni Mhurchu et al., 2013), while neighborhoods with an increased access to supermarkets and grocery stores usually have lower prevalence of obesity. In fact, high neighborhood walkability, which can be characterized as the proximity to recreational facilities, access do sidewalks and paths, access to parks, which is considered a facilitator of PA (Salvo et al., 2018), has been associated with a lower prevalence of obesity (Creatore et al., 2016). It is reasonable to think that food accessibility is tightly connected with the social economic status, as well as with the built infrastructures. For instance, people with lower socioeconomical status are more prone to develop obesity due to the lack of quality of their diet (Darmon & Drewnowski, 2008). The economic status of the country will also influence this relation, as in wealthy countries, the prevalence of obesity is higher in

people with lower incomes, where the opposite occurs in poor countries (Templin et al., 2019). When it comes to educational level, which is closely related to socioeconomic status, higher educational levels can lead to a better knowledge regarding healthy food and better food choices (Bhurosy & Jeewon, 2014), being correlated with a lower body mass index (BMI) (Kim, 2016).

In sum, the involving environment can strongly influence body weight regulation specially through changes in EI and/or EE. Moreover, it is becoming clearer that the interaction between the individual and the environment goes beyond a single event, encompassing their whole life, starting in gestation. The current obesogenic environment fosters weight gain by decreasing PA and increasing sedentary behavior, as well as increasing EI. Despite this component was addressed independently, the interaction between gene and environment must be considered as it can increase the susceptibility to develop obesity.

Genetics

Despite this non-favorable environment in what regards to maintain an adequate body weight/fat, some individuals are able to maintain a healthy body weight/fat throughout their life, as not every people are living with overweight or obesity. Likewise, it has been suggested that the genetic predisposition to obesity exerts a significant influence in body weight regulation.

For instance, studies involving Pima Indians emphasize the role of genetics on the etiology of obesity. This population have one of the higher obesity (Knowler et al., 1991) and non-insulin dependent diabetes mellitus prevalence (Knowler et al., 1978), with a higher risk of gaining weight and a relatively low REE (Ravussin et al., 1988). In 1990, 75% of this population lived with obesity and the prevalence of diabetes surpassed 45% (Ravussin & Bogardus, 1990). The evidence suggests that Pima Indians have a genetic predisposition to store the excess energy as fat, which was considered a survival

advantage when food was scarce. However, when under an obesogenic environment, this genetic trait might lead to obesity and other related health issues.

Moreover, some studies involving twins, families and/or adoption pointed to the fact that body weight regulation have a strongly genetic component that might overcome environmental factors (Silventoinen et al., 2010). Bouchard et al found that ~40% of the variance in REE, TEF and the energy cost of low to moderate intensity exercise is explained by inherited characteristics, emphasizing that changes in EE components as a response to a disturbance in the EB equation can be partially determined by one's genotype (Bouchard et al., 1993; Bouchard & Tremblay, 1990). Moreover, a study involving twins that were reared apart showed the significant genetic effects on the BMI, presenting a coefficient of intrapair correlation (twin 1 vs twin 2) of 0.70 for men and 0.66 for women (Stunkard et al., 1990). Additional research aimed to compare the degree of obesity in adopted individuals with their biological relatives and adoptive family, supported the idea that there is a significant genetic impact on obesity that surpasses the influence of the environment where they were raised (Maes et al., 1997). Therefore, although some individuals are more susceptible to weight gain than others due to genetic variances, people who share the same genotype, such as monozygotic twins, will respond similarly to the same disturbance in the EB equation, emphasizing the influence of the genotype on body weight regulation.

Thus, although the obesogenic environment is considered an important factor for body weight regulation, the genetic predisposition to obesity must also be considered (Speakman, 2004). The current literature characterizes obesity as an oligogenic disease, modulated by an interaction between polygenic modifier genes with environmental factors, such as EI and PA patterns, and smoking (R. J. F. Loos & G. S. H. Yeo, 2022). Nevertheless, despite being rare, some genetic forms of obesity have a little or no environmental influence, where individuals usually develop a severe and early-onset obesity (Huvenne et al., 2016).

Genetics forms of obesity can be classified into syndromic and non-syndromic, considering the existence of congenital defects and developmental delay (Mahmoud et al., 2022). Syndromes such as Prader-Willi, and Bardet-Biedl are examples of syndromic obesity that are linked with an early onset obesity but also with other characteristics, such as dysmorphic features, congenital anomalies, and neurodevelopmental deficits such as developmental delay (Kaur et al., 2017). Non-syndromic obesity can also be divided in 1) monogenic obesity, an early-onset, severe and typically rare and 2) polygenic obesity, also known as “common” obesity, a result of some polymorphisms that exert a small effect *per se* in the body weight regulation (R. J. F. Loos & G. S. H. Yeo, 2022).

When it comes to monogenic obesity, large chromosomal deletions or single-gene defects are usually involved. Moreover, these mutations occur essentially in genes involved in the leptin-melanocortin axis, a pathway that is responsible for appetite, satiety, and body weight regulation (Yeo et al., 2021). Shortly, after being produced and secreted by adipose tissue, leptin acts at the leptin receptor in the arcuate nucleus of the hypothalamus, activating the production of POMC in POMC neurons. This will be processed to melanocyste-stimulating hormones (MSH) by proprotein convertase subtilisin/kexin type 1 (PCSK1). MSH acts at the melanocortin receptor, which includes the melanocortin 4 receptor (MC4R), leading to a reduction in EI and an increase in EE (**figure 2.4.**).

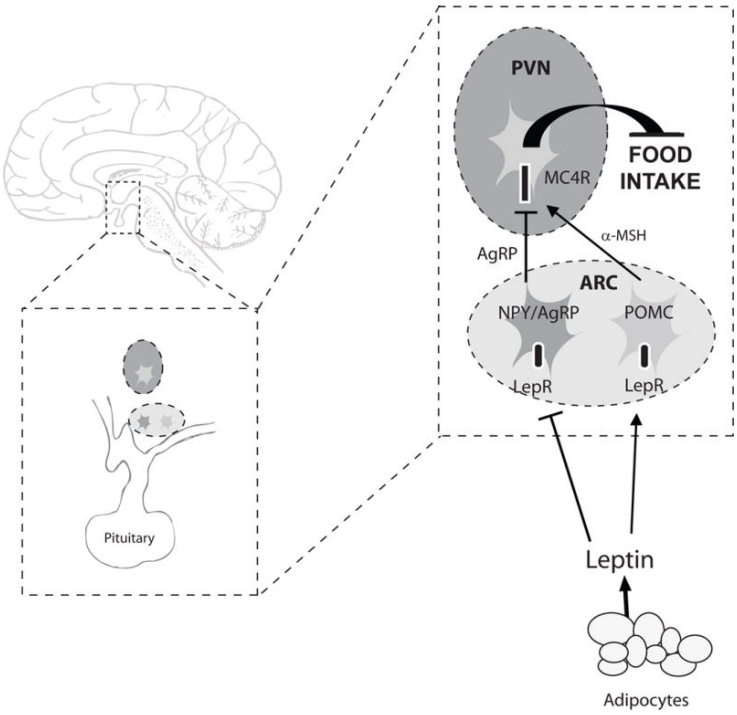

Figure 2.4. Illustration of the leptin-melanocortin axis (Yeo et al., 2021).

Legend: MC4R – Melanocortin 4 receptor, AgRP – Agouti-related protein, MSH – Melanocyste-stimulating hormone, ARC – Arcuate nucleus, NPY – Neuropeptide Y, LepR – Leptin receptor.

From over 500 genes that were found to be associated with obesity, the vast majority of single-gene mutations that cause a severe early-onset obesity comprises changes in leptin (LEP), leptin receptor (LEPR), proopiomelanocortin (POMC), prohormone convertase 1(PCSK1) and melanocortin 4 receptor (MC4R). These mutations exert a powerful effect on body weight regulation without any influence of environmental or other factors (Rankinen et al., 2006), leading to a severe hyperphagia and a profound, childhood-onset obesity. Although these mutations are rare, valuable insights are provided regarding the identification of genes that are crucial for a normal body weight regulation.

The study of monogenic obesity and the identification of genes that are linked to this type of obesity relied strongly on mouse genetic studies. Initially, the *ob* mutation, characterized as a single-base deletion which results in a premature stop codon in a

gene that was later found to encode leptin (Zhang et al., 1994), is associated with hyperphagia and hyperglycemia (together with other neuroendocrine abnormalities), leading to morbid obesity (Coleman & Hummel, 1973). Then, a mutation in the LEP gene leads to a leptin deficiency, causing severe obesity in mouse. After this discovery, mutations in LEP were also found in humans, more specifically in consanguineous relatives (Mazen et al., 2009; Montague et al., 1997). In fact, as monogenic obesity often exhibits a recessive inheritance pattern, consanguineous families have further chances of homozygosity of deleterious mutations (Saeed et al., 2018). Individuals with this deficiency have their circulating leptin levels almost nondetectable, where the symptoms include severe hyperphagia and an early onset obesity (for both heterozygous and homozygous mutations), but also can include hypogonadotropic hypogonadism and hypothyroidism (only homozygous state) (Wasim et al., 2016). Later, mutations LEPR were also found (Clement et al., 1998), with a similar phenotype comparing to mutations in LEP (early-onset morbid obesity, hyperphagia and reduced EE), but with high serum levels of leptin and loss of sensitivity of its receptor (Kleinendorst et al., 2020). Likewise, these rare mutations were found specially in consanguineous families (Farooqi et al., 2007).

These findings were followed by discoveries in mutations in other genes that are involved in the leptin-melanocortin pathway, such as PCSK1, MC4R and POMC. Although all of them lead to an early-onset obesity, other symptoms can be present, such as hypogonadism, hypercortisolism and small-intestinal absorptive dysfunction for PCSK1 (Stijnen et al., 2016); adrenal insufficiency and specific pigmentary characteristics such as pale skin or red hair for POMC (R. J. F. Loos & G. S. H. Yeo, 2022); or hyperphagia, severe hyperinsulinemia and an increased lean body mass for MC4R (Styne et al., 2017).

Currently, mutations in MC4R are the most common form of human monogenic obesity, impacting up to 4% of individuals living with morbid obesity (Hainer et al., 2020). Nevertheless, mutations in MC4R are mostly heterozygous and with variable

penetrance, as not every individual with these alterations develop obesity (Farooqi et al., 2003). On the other hand, homozygous mutations are associated to a fully penetrant early-onset severe obesity (Yazdi et al., 2015). Likewise, novel mutations in other genes such as single-minded homolog 1 (SIM1), brain-derived neurotrophic factor (BDNF), and the neurotrophic tyrosine kinase receptor type 2 gene (NTRK2) have also been described in the literature, all of which leading to hyperphagia and early obesity (Mahmoud et al., 2022; Manco et al., 2023). Nevertheless, additional studies are needed to understand the impact of these mutations in the pathogenesis of obesity.

Worth mentioning, despite initial genetic discoveries focusing on a single gene, for most individuals, the genetic predisposition to obesity has a polygenic basis encompassing the interactions between various genes. Also, evidence shows that the expression of mutations responsible to monogenic obesity can be at least partially influence by the individual's polygenic susceptibility to obesity (Chami et al., 2020). For instance, together with MC4R, other two gene variants were identified, namely 1) Fat mass and Obesity Associated Gene (FTO), and 2) insulin-induced gene 2 (*INSIG2*), which may exert a small but replicable effect on body weight regulation. In fact, FTO polymorphisms have been strongly related with an increased risk of obesity, being associated with several poor eating behaviors, such as higher hunger, episodes of overeating, higher fat intake and refined starches (Harbron et al., 2014; Tanofsky-Kraff et al., 2009). Considering INSIG2, the results are inconsistent, as some authors found an association between this mutation and obesity (Chu et al., 2008; Lazzaro et al., 2008; Malzahn et al., 2014), but others did not (Boes et al., 2008; Bressler et al., 2009; Kumar et al., 2007). A meta-analysis showed that polymorphisms in INSIG2 were associated with an increased obesity risk for general population studies (Heid et al., 2009). However, considering studies involving "healthy population", defined as studies including subjects from working populations or studies excluding subjects with a specific disease, a decreased obesity risk was found. Nevertheless, there is no evidence strong enough to prove an overall

association between the INSIG2 polymorphisms and an increased risk of obesity. Even though an association with an extreme degree of obesity was found, the heterogeneity can be (at least partially) explained by different study designs.

While the environment exert little or no influence on the monogenic obesity (i.e., the mutations are so severe that can cause morbid obesity in almost any environment), when it comes to polygenic obesity, the interaction between the environment (nurture) and the genes (nature) must be considered as it may affect the predisposition to develop obesity (Flores-Dorantes et al., 2020). For instance, adhering to an adequate diet and PA patterns can modulate the risk of developing obesity that are conferred by polymorphisms in some specific genes (Corella et al., 2012; Huang et al., 2014; Zhang et al., 2012). Therefore, even if some polymorphisms can confer susceptibility to develop obesity, it is possible to adapt the environment to reduce the risk. Nevertheless, more research is needed comprising the role of genes in developing obesity in the presence of a specific environment that enhances or impair the trait.

To sum up, there is little or no environmental influence on monogenic obesity, characterized by a single mutation in one gene, with a large genetic effect. On the contrary, when it comes to polygenic obesity, where there are hundreds of variants in or near many genes (susceptibility genes), although the effects are considered minimal, they can be strengthen by the involving environment (Ruth J. F. Loos & Giles S. H. Yeo, 2022). Then, the obesogenic environment interacts with individual genetic predisposition, where the so-called “common obesity” results as an interaction of the current environment with a polygenetic obesity predisposition (Berthoud et al., 2020).

Cognitive/behavioral

Despite the existent gene-environment interaction, not every individual is equally susceptible to these pressures. To illustrate, two individuals with the same genetic predisposition to obesity, in the same environment, may drastically differ in terms of food

intake (amount of fast food, portion size, number of meals, etc.) and energy expenditure (exercise and non-exercise physical activity) (Speakman, 2004). Therefore, it is plausible to think that there are individual differences on the ability to regulate body weight and protect against weight gain, even under a non-favorable environment and/or genetic. These dispositional tendencies that lead an individual to respond in a certain way in a specific scenario can be defined as our personality (American Psychological Association, 2008).

To lose weight, it is necessary to change dietary and PA patterns and, more important, these adjustments need to be maintained throughout time. In fact, a study showed that participants who were able to maintain their weight-reduced state where those that showed frequent self-monitoring of body weight and of food intake, higher tendency to choose non energy-dense foods and planned meals in advance (Milsom et al., 2011). Therefore, these personality traits can explain why some people are able to maintain these behaviors throughout time, while others abandoned them and faced weight regain. Indeed, there has been growing research interest in the impact of individual traits/personality on weight management and the effectiveness of a WL intervention (Dalle Grave et al., 2018).

According to a recent systematic review (Brindal & Golley, 2021), most studies covering personality traits were based on the Five-Factor model (or “The big 5”)(Costa & McCrae, 1992) or the three-dimensional psychobiological model of Cloninger (Cloninger, 1987).

The Five-Factor model theory assumes that personality can be divided in 5 domains: **extraversion, conscientiousness, openness to experience, neuroticism and agreeableness** (Goldberg, 1990). Of the five traits, conscientiousness is the domain that was most consistently associated with adiposity (Magee & Heaven, 2011; Sutin et al., 2011). This domain have also been associated with adequate eating habits (Brummett et al., 2006; Lunn et al., 2014; Sullivan et al., 2007; Terracciano et al., 2009), as individuals with higher scores of conscientiousness are more likely to adopt a healthy

lifestyle and to undergo several healthy-eating behaviors. This can be explained by the fact that people with higher scores for self-discipline and order, both facets of conscientiousness, are more organized and have more willing to stick to their diet plan and/or meal schedule (Terracciano et al., 2009). In fact, low levels of conscientiousness were reported in people living with overweight/obesity (Magee & Heaven, 2011).

Together with conscientiousness, a review comprising 9 studies suggested that openness to experience is also associated with healthier eating behaviors (Lunn et al., 2014). For instance, Mõttus et al. found that higher scores on "openness to experience" were associated with better food choices, such as following the Mediterranean diet pattern, with an adequate consumption of fruit, vegetables, fish and beans (Mõttus et al., 2012). This association can be explained by the fact that individuals with higher values for openness to experience are more willing to try new foods and not necessarily by a desire to be healthy (Mõttus et al., 2012). When it comes to neuroticism, a peculiar association between this domain and body weight has been reported. For instance, higher scores of "impulsivity" - a facet of the neuroticism – have been presented in people with obesity (Mobbs et al., 2010; Terracciano et al., 2009). Nevertheless, other studies showed that people with overweight/obesity had lower scores of neuroticism, reporting a negative association (Gerlach et al., 2015). It seems that this domain is associated with both extremities of BMI, suggesting a curvilinear relation between weight and neuroticism, with both ends (underweight and overweight/obesity) having higher values of this domain (Sutin et al., 2011).

The relationship between the other dimensions with dietary habits and weight management needs more evidence (Munro et al., 2011; Sutin et al., 2011), as some authors showed that people living with obesity/overweight scored lower on extraversion (Kakizaki et al., 2008) and agreeableness, but others found the opposite (Brummett et al., 2006; Terracciano et al., 2009).

According to the psychobiological model of Cloninger, personality is the combination of two interconnected domains: temperament and character (Cloninger, 1987). While the

temperament is an emotional facet of personality, reflecting the human tendency to respond to a certain stimulus (novelty, danger, punishment), character is more sociocognitive and referred to self-concept, goals and values, being both partially inherited and partially experience-influenced (Cloninger et al., 1994). Temperament consists of three dimensions, where although they are genetically independent, they interact among them in terms of the basic stimulus-response characteristics, named **novelty seeking** (heritable tendency toward exploratory activity, excitement in response to a novel stimuli, cues for potential rewards, and potential relief of punishment), **harm avoidance** (heritable tendency to respond intensely to signals of aversive stimuli, avoiding punishment, which is linked with high serotonergic activity) and **reward dependence** (heritable tendency to respond intensely to signals of reward) (Cloninger, 1987). Later, **persistence** (ability of being perseverance in one's intentions and actions) emerged as the fourth dimension (Cloninger et al., 1993). Considering character traits, three dimensions were proposed: **Self-Directedness** (ability to adjust their behavior according to the selected goals and values)**, Cooperativeness** (ability to accept and identify with other individuals), and **Self-Transcendence** (the individual interest to search for something beyond their individual existence, such as ethics, art and culture) (Lu et al., 2012).

Although some personality traits have been associated with body weight and other related outcomes, these results are not consistent, possibly due to the different methodologies to assess personality traits and the population's characteristics (Gerlach et al., 2015). Sullivan et al. showed that people with obesity presented higher values of novelty seeking as well as lower persistence and self-directedness when compared with people with a BMI<25kg/m^2 (Sullivan et al., 2007). Similarly, Dalle Grave et al. showed that higher levels of novelty seeking, harm avoidance and low levels of self-directedness are associated with higher scores of the Binge Eating Scale (Dalle Grave et al., 2013). Moreover, when submitted to a WL intervention, people with obesity scored higher for

reward dependence and cooperativeness than people who were not trying to lose weight (for the same BMI range) (Sullivan et al., 2007). Plus, those who were able to lose ≥10% of their initial weight reported lower scores for novelty seeking than those who had a WL<5%. Also, another study showed that higher scores of novelty seeking (for both sexes) and lower scores of reward dependence (women only) are considered predictors of a higher BMI (Hintsanen et al., 2012). The results from harm avoidance are also discrepant, as some authors showed that people with obesity scored higher for this trait when compared with people with a BMI<25kg/m^2 (López-Pantoja et al., 2012; Sarisoy et al., 2014), while others failed to find this association (Hintsanen et al., 2012; Sullivan et al., 2007). When it comes to self-directedness, some authors found that people with obesity have lower scores for this trait when compared to individuals who are not living with this condition (Dalle Grave et al., 2013; Fassino et al., 2002). Moreover, a study found that higher scores of self-directedness can exert a protective effect on weight gain in men (Hintsanen et al., 2012). When it comes to reward dependence, Sullivan et al. showed that people with obesity that were enrolled in a WL intervention scored higher for this trait when compared to people with the same BMI range but without undergoing any intervention (Sullivan et al., 2007). Overall, as people with high reward dependence tend to be dedicated and sociable, they are more likely to commit to a WL intervention. Nevertheless, no differences were found between people with obesity and individuals who did not live with this condition. Lastly, most authors did not find any association between persistence and body weight or the success of a WL intervention (Hintsanen et al., 2012; Sullivan et al., 2007).

Hence, some personality traits can be associated with body weight regulation by influencing certain behaviors such as engaging certain PA and eating patterns, manipulating our ability to maintain an adequate weight/fat mass, independently of the genetic predisposition or the living environment. Despite results not being consistent for some personality traits, it seems that people living with obesity have different personality

traits when compared to those who are not living with this condition, which can partially explain their difficulties on maintaining an adequate body weight and avoiding weight gain.

Hedonic reward system

Eating behavior is not only influenced by metabolic but also by hedonic drives (Berthoud, 2011). Although food intake is regulated according to the need to maintain energy homeostasis, the high abundance of highly palatable food can also influence our EI independently of our normal or even excessive energy stores (Egecioglu et al., 2011). In fact, in our modern world, where an obesogenic environment is present, people no longer eat only when they are hungry. Moreover, appetite-related hormones play a role in the hedonic system (Berthoud, 2011), where the control of food intake and body weight is guided by a "cognitive and emotional brain", based upon the reward value of the food (Yu et al., 2015) **(figure 2.4.).**

Dopamine is the neurotransmitter of primary importance for incentive motivation, playing an important role in feeding and satiety (Berridge, 2007). Dopaminergic pathways associated with reward and motivational behaviors involves a pathway from the ventral tegmental area (VTA) of the midbrain to the nucleus accumbens (NAcc) – mesolimbic dopamine pathway – and also a neuronal network that includes VTA projections to the prefrontal cortex, amygdala and hypothalamus – mesocortical dopamine pathway (Egecioglu et al., 2011).

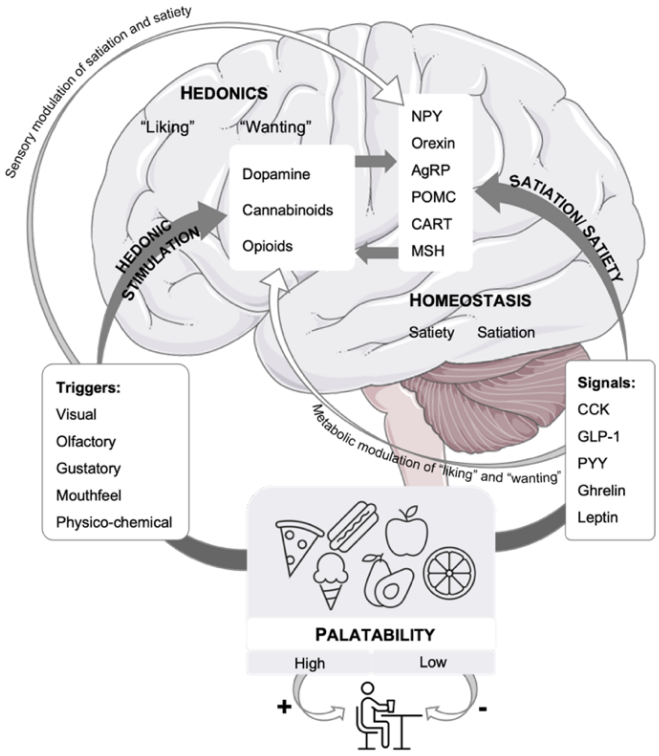

Figure 2.5. Relation between homeostatic and hedonic systems (Adapted from (Gibbons & Blundell, 2015)

Legend: NPY – Neuropeptide Y, AgRP – Agouti-related protein, POMC – Proopiomelanocortin, CART - Cocaine- and amphetamine-regulated transcript, MSH – Melanocyste-stimulating hormone, CCK – Cholecystokinin, GLP-1 - Glucagon-like peptide-1, PYY – Peptide YY.

Food reward can be defined as a process that contributes to the pleasure and motivation/drive to obtain food (Cameron et al., 2014), where two distinct neurobiological components are recognized: “liking” (immediate experience or anticipation of pleasure derived from oro-sensory stimulation of food) and “wanting” (reward seeking, the motivation to engage in eating) (Mela, 2006). While implicit “wanting” is primarily determined in the mesolimbic dopaminergic neurons that project from VTA to NAcc, neural networks responsible for the “liking” component include pathways involved in taste processing in the brainstem, pons, NAcc, ventral pallidum, amygdala and prefrontal cortex (Pecina & Berridge, 2000).

The mu-opioid system emerges as a key target for the hedonic experience of feeding, being associated with “liking” orofacial responses (Peciña & Berridge, 2005). Also, mu-opioid receptor stimulates the NAcc, which has been shown to increase the intake and the preference for highly sweet and fat foods (Zhang et al., 1998; Zhang & Kelley, 2002). Therefore, the high abundance of highly palatable food, typical in the current obesogenic environment, leads to an over-consumption of palatable/rewarding foods, activating the brain reward circuits (Monteleone et al., 2012). This might result in an imbalance between hedonic and homeostatic signals, where the hedonic overrides the homoeostatic pathway. As a consequence, a larger demand on the cognitive, less intuitive, regulation of eating behavior will be expected (Espel-Huynh et al., 2018), influencing an individual’s food choices and consumption.

The rewarding value attributed to a specific food is highly variable among individuals, as it is not only influenced by food palatability but also by individual genetic/trait/psychosocial differences (Egecioglu et al., 2011). It has been suggested that individuals living with obesity might attribute inappropriate rewarding values to foods, as a response to allostatic changes in the hedonic set point (Egecioglu et al., 2011). This leads to a problematic over-consumption which reflects an amplified responsiveness of the reward circuits to rewarding foods and that overcomes the homeostatic signals to maintain homeostasis (Davis et al., 2004).

Hence, the distinction between metabolic and hedonic obesity needs to be considered, as weight gain is explained by different mechanisms. Considering that there is a body weight set point (described in the next section) (Kennedy, 1953), metabolic obesity exists when this set point is abnormally high. Consequently, this set point will be metabolically defended by the homeostatic system. On the other hand, in hedonic obesity, although the set point is not elevated, a frequent overconsumption occurs due to impairments in the reward regulation system, even when the metabolic signals indicating an energy surplus are present (Yu, 2017; Yu et al., 2015). As this sustained weight gain is

maintained above the metabolic set point, an increase in EE occurs as an attempt to restore the previous body weight set point (Yu, 2017).

2.2.3. **Models of body weight regulation**

Set point

The set point regulation model (also entitled “lipostatic” model) was based on the simple concept of negative-feedback system linking the adipose tissue (stored energy) to intake and expenditure (Kennedy, 1953). According to the author, this model suggests that each individual has a specific body weight /fat set-point, and differences between the target and the actual signal will generate changes in EI (by increasing or decreasing appetite) and/or EE (reducing all EE components), until the actual level equals the target body fat and therefore maintain the homeostasis. Then, for that to happen, the adipose tissue will produce a specific signal that is recognized by the brain, and it will be compared with a specific target level of body fat (the set point). Therefore, periods of voluntary energy restriction or overfeeding will perturb the system, and if these changes are maintained throughout time, it will lead to changes in body weight (weight loss or weight gain, respectively) (Leibel et al., 1995; Luke & Schoeller, 1992). However, during this period, changes in EE should occur to counteract the alterations in EI and hence prevent the changes in body weight (Rosenbaum et al., 2008; Rosenbaum & Leibel, 2010; Rosenbaum et al., 2003).

This model is strongly supported by the fact that when this dieting period ceases, people return to their original state, approximating their original fat mass, usually at a faster rate than they lose/gain weight voluntary (MacLean et al., 2011; Melby et al., 2017). Nevertheless, under this lipostatic mechanism, one’s individual body weight should be maintained at a relatively constant level only with slightly fluctuations around the body weight “set point”. However, with the obesity’s rates increasing worldwide, it seems that the body weight is regulated not only by a homeostatic system, but also by other

components, such as the environment and hedonic factors (Ghanemi et al., 2018). Plus, specially nowadays, these two components not only play a role in the body weight regulation but also can overcome the homeostatic system (Greenway, 2015). Therefore, the set point fails to consider the influence of the environment and social influences on food intake, physical activity and consequently, on obesity.

The nature of this set point has yet to be found, but it is believed to have a major genetic component, together with environmental influences (Levin, 2007). Nonetheless, the idea of having a fixed set-point can be easily questioned, as a shift in the set point may occur in some situations, such as in some diseases (infectious diseases) and disorders (anorexia nervosa, depression), leading to changes in body weight (Speakman et al., 2011). Then, it seems that the set point can be substantially perturbed rather than being static.

Settling point

With all the flaws that were pointed out to the set point model, an alternative was proposed by some authors (Payne & Dugdale, 1977a, 1977b; Wirtshafter & Davis, 1977), defending that multiple “body weight steady states” are considered rather than a fixed set-point. More specifically, an imbalance between EI and EE will lead to changes in body weight and, consequently, the maintenance of energy requirements will also change, stabilizing the original imbalance and creating a new equilibrium (Speakman et al., 2011). For instance, if someone is under a neutral EB (where EI equals the EE) and starts dieting, this will lead to a decrease in body mass, which is often accompanied by a decrease in EE (Leibel et al., 1995). Therefore, this decrease will meet the current EI, attenuating the initial created imbalance and achieving a new neutral EB. Thus, it seems that the fat stores’ equilibrium is determined by the EI, which is subsequently matched by the EE.

As this model considers the role of the environment and one's behavior on weight management (Speakman et al., 2011), the increasing prevalence of obesity can be (at least partially) explained by the obesogenic environment, characterized by an elevated availability/exposure of food, together with a decrease on PA levels (Greenway, 2015). Nevertheless, despite this model seems to be more adequate when compared to the set point model, there are some concerns that must be stated. The well-known semi-starvation Minnesota Experiment study (Keys et al., 1950) is probably one of the best examples, where participants lost ~25% of their weight (under a very low energy diet) but regained it partially after a period of an ad-libitum follow-up period. The weight loss period was supported the settling point model, as a plateau was achieved at some point of their process. However, when the restriction phase ceased, participants did not return to their old habits and gradually return to their initial body weight. Instead, they underwent a period of overfeeding, increasing their fat mass and body weight rapidly. This response can be considered a form of active regulation, working as an attempt to drive up their body mass or adiposity.

Also, this model still not explains why some individuals, under the same (obesogenic) environment, do not gain weight while others develop obesity. Therefore, it seems that there are some individual's characteristics that make people more susceptible to gain weight under a non-favorable environment.

Dual intervention point

The two models that were described previously differs in how the obesity problematic is conceptualized. While the set point model comprises mostly the physiological and genetic domains, the settling point evolves the effects of social, nutritional, and environmental factors (Speakman et al., 2011). However, no model considers the possible "gene-by-environment" interactions nor metabolic adaptations. In fact, it is known that the environment has effects that vary according to the genotype, and the genotypes only work in the context of an environment (Li et al., 2010). Then,

understanding the interaction between genes and the environment is important to reach to a better understanding of the obesity problematic.

Speakman and colleagues proposed the most recent model, named “Dual intervention model”, combining the set point (with a feedback control of body weight at the two boundaries only) with the settling point (flexible weight changes between the boundaries) (Speakman et al., 2011). With this model, the concept of a single set point is not incorporated, but rather some “intervention points” (upper and lower), where body weight can change as a response to environmental factors within those intervention points (boundaries) that are biologically determined (Müller et al., 2018). Then, the lowest intervention point reflects risk of starvation, survival, or some diseases, where the upper limit, although being a matter of debate, is regulated by the risk of predation (in some animals) (Speakman et al., 2011).

The regulation of these two points (lower and upper) are yet to be well understood. Despite some authors proposing that those boundaries are linked together (Higginson et al., 2016), it is more plausible that the two points are regulated separately, as they may differ according to their meaning (Speakman, 2018). Indeed, while the lower body may reflect the resistance to weight loss, the upper point may explain why some individuals are able to resist weight gain even under an obesogenic environment (Speakman et al., 2011). Then, this model explains the inter-individual susceptibility to gain or lose weight in a specific environment, as both intervention points vary among individuals and are influenced by genetics.

2.3. WHY IS IT SO DIFFICULT TO LOSE WEIGHT?

2.3.1. Weight Loss Prediction Models

Predicting WL is important to improve our understanding of body weight regulation and to design accurate and effective WL interventions. Therefore, several mathematical

models were proposed, where WL was predicted as a function of time, varying in how changes in ES and EE are classified (Thomas et al., 2019).

In 1958, Wishnofsky suggested a simple regression model, where an energy deficit of 3500 kcal leads to the loss of 1 pound (~454 grams) (Wishnofsky, 1958). However, the '3500 kcal per pound' model assumes that WL occurs at a constant rate, considering that losing weight has no effect on the energy expended during an energy restriction (i.e., our EE will remain the same even after undergoing considerable WL). Also, it assumes that WL composition would be mostly body fat and, based on the assumption that the energy value of 1 gram of fat is 9 kcal and adipocytes are composed of 85-90% of triglyceride, it was reasoned that 1 pound of adipose tissue as an energy content of 3750 kcal (Wishnofsky, 1958). Later, this simplistic approach was proven to overestimate WL (Hall et al., 2011). Additionally, this static model has been proven incorrect by Thomas et al (D. M. Thomas et al., 2014), as it assumes that weight change follows a linear regression and, considering an extended period with a constant negative EB, leads to a constant weight loss.

In 1970, Forbes developed a second-order linear differential equation, where a non-linear relation between FM and FFM is assumed and changes in one will instigate changes on the other in the same direction. More specifically, the FFM proportion of a weight change [ΔFFM/ΔBody weight (BW)] varies as a function of the initial FM, i.e., an increased initial FM was associated with a smaller contribution of FFM to WL (lower (ΔFFM/ΔBW) (Forbes, 1987). Therefore, the composition of WL will be different for someone who is living with obesity vs someone who do not have this condition.

Also, with this model, two distinct phases were defined when losing weight: 1) Rapid WL phase, characterized by a rapid WL which can last days/weeks, followed by a 2) Slower WL phase, lasting up to 2 years (Heymsfield et al., 2012; Heymsfield et al., 2011). The first phase is characterized by a relatively rapid loss in body weight, consisting of a small carbohydrate (glycogen) pool, protein, and to a less extent fat as sources of energy. During this period, there is a negative water balance due to the release of water

associated with the oxidation of carbohydrates and protein, and the fluid balance is subsequently regulated by adjustments in dietary sodium intake. The second phase lasts from months to years and the main energy source during this period are adipose tissue triglycerides, with the WL rate slower compared to the first phase. Therefore, the energy content of weight change cannot be constant, being less than 7700kcal/g in the early rapid WL (due to the substantial contribution of body water changes in the initial phase, which decreases the energy density of WL) and reaching or surpassing 7700kcal/g during the second phase.

Later, Hall et all (Hall, 2007) extended the Forbes equation to account for the magnitude and direction of macroscopic body weight changes. With this model, as higher values of FM were associated with a lower ΔFFM/ΔBW, larger WL will result in a greater predicted contribution from FFM loss. Then, the composition of weight change depends on both the direction and magnitude of weight change in addition to the initial FM. This new model was also re-expressed in terms of an alternative representation of body composition change defined by energy partitioning parameters, called the P-ratio, as described:

$$\frac{\Delta \mathrm{FFM}}{\Delta \mathrm{t}} = \mathrm{P}(\mathrm{EI} - \mathrm{EE})$$

$$\frac{\Delta \mathrm{FM}}{\Delta \mathrm{t}} = (1 - \mathrm{P})(\mathrm{EI} - \mathrm{EE})$$

And consequently:

$$\text{P-ratio} = \frac{\Delta \mathrm{FFM}}{\Delta \mathrm{FFM} + 9.05 \times \Delta \mathrm{FM}}.$$

Based on these models, any energy imbalance is divided between energy stored in FM and FFM. The P corresponds to the energy partition ratio and describes the energy imbalance fraction to/from FFM and to/from FM and the values range between 0 and 1. The extent to which the contributors of FM and FFM during weight loss and maintenance affects the main EE components (REE and PAEE) is still unclear.

Nevertheless, these statistical-based models were substituted by thermodynamic models, which considers the physiological properties of body composition stores that are altered during WL (Thomas et al., 2019). They derived from the EB equation according to the first law of thermodynamics, varying in time scale and how ES (FM and FFM) and EE are compartmentalized.

Antonetti was the first developing a thermodynamic model, by correcting the 3500kcal/lb rule to include time varying changes in BW during weight change (Antonetti, 1973). Nevertheless, this simple model does not describe changes in body composition, as there was no compartmentalization of energy stores. Later, other models were created (Chow & Hall, 2008; Christiansen & Garby, 2002; Flatt, 2004; Hall, 2010; Kozusko, 2001; Speakman & Westerterp, 2013; Thomas et al., 2011; Westerterp et al., 1995), each one with different ES and/or EE divisions, providing different insights regarding WL prediction and its composition. These models are currently implemented in several web-based and smart phone applications, used to predict weight change, to quantify adherence to a WL intervention by comparing the actual vs expected WL and to understand the physiology behind the mechanisms of weight change (Thomas et al., 2019).

2.3.2. What happens when we lose weight?

A combination of strategies aimed to decrease EI and/or increase EE to achieve a negative EB is necessary to lose weight. The literature is full of interventions aimed to induce WL, varying in the intervention's type (pharmacological, surgical, diet and/or exercise interventions) (Felix & West, 2013; Ma et al., 2017; Mameli et al., 2017). Although a clinically meaningful WL is usually achieved in most WL interventions, levels of recidivism and weight regain are high (Greaves et al., 2017; Wadden et al., 2011). In fact, according to a recent systematic review, only around one third of people who lost weight were able to maintain it after 2 years (LeBlanc et al., 2018), suggesting that only a small number of people are well-succeeded at maintaining a reduced weight state at a long-term. Therefore, when implementing a WL intervention, it is important to consider

not only the **active WL phase**, where a negative EB is created in order to lose weight, but also the **maintenance of the reduced weight state**, where the aim is not to lose but to maintain the body weight (under a neutral EB).

Whilst active WL has a finite duration (lasting from weeks to years), the maintenance of the new body weight requires an ongoing attention as it should be sustained throughout life. Also, while during WL people can be motivated by external rewards such as the body weight going down, wearing a smaller size of clothing and/or improving some health outcomes (e.g. cholesterol, glycemia, HbA1c), WL maintenance lacks of these type of motivations, which can compromise the WL success (Hall & Kahan, 2018). As a consequence, people tend to abandon the dietary and PA recommendations that were implemented during the active WL phase, which has been suggested as one of the reasons for these high levels of weight regain (Del Corral et al., 2011).

The variability observed in weight and body composition changes – namely the rate of changes in FM and FFM - during WL and its maintenance is highly dependent on the approach used to generate the energy imbalance. For instance, diet-only interventions are expected to promote an energy deficit through decreases in EI but without increasing PAEE – low energy flux, whereas exercise only or combined exercise and diet intervention promote a negative EB (or neutral if at the maintenance phase) through a high energy flux, where EI is also restricted but not as much as the low energy flux due to the higher EE (Melby et al., 2017). Moreover, it seems that the body weight regulation (in this case the WL maintenance) is more effective when a high energy flux occurs, i.e., high EI and EE, by inducing metabolic changes that are more protective against weight gain (Hume et al., 2016). Furthermore, together with a different impact on WL composition (changes in FM and FFM), the ability of maintaining WL at a long term is also different when using a low vs high energy flux (Hume et al., 2016), but information is still scarce.

Even though the lack of adherence of dietary and PA recommendations is considered the main explanation for these high levels of weight regain (Heymsfield et al., 2007), there is evidence showing that metabolic, behavioral, and psychological compensations occur as a response to a prolonged negative EB, which may counteract the initial attempts to lose weight. In fact, during WL, changes in biological pathways that affect the complex neuro-hormonal system occur, perturbing the levels of circulating hormones involved in appetite regulation, energy utilization and storage, as well as alterations in nutrient metabolism and subjective appetite (Greenway, 2015). There are also changes in neuronal signaling that influences EI, affecting satiety/satiation and also food reward, as well as a decrease in sympathetic activity (Aronne et al., 2021). Alongside with this, changes in EE components, mostly characterized by a lower REE (Doucet et al., 2001; Leibel et al., 1995) and a lower energy cost of weight-bearing activities (muscular efficiency) (Levine et al., 2000; Schoeller & Jefford, 2002) also occur (**table 2.2.**). Therefore, by leading towards energy conservation, all of these compensations create the “perfect scenario” for weight regain.

The existence of these adaptive responses, as well as their impact on the EB regulation, are not the same in both phases, as some of these changes are attenuated or even disappear when people achieve a neutral EB (maintenance of the weight reduced state) (Sumithran et al., 2011) (**table 2.3.**). Nevertheless, some of them remain at a long term, linking this phase to a weight regain favorable state, where there is an increased hunger, metabolic efficiency and a reduced EE, compromising the maintenance of WL (Greenway, 2015). Therefore, these compensations may act as “barriers” for weight loss and its maintenance, showing that body tends to retake the “set point”, counteracting the initially created energy deficit (Major et al., 2007).

Table 2.2. Compensatory changes that occur in homeostatic systems and energy balance components as a response to WL.

ENERGY HOMEOSTATIC SYSTEM	ENERGY BALANCE COMPONENTS
Autonomic NS	**Energy Expenditure**
↑ PNS	↓ REE
↓SNS	↓ PAEE
	↑ Muscle contraction efficiency
Circulating hormones	**Energy Intake**
↓ T3, T4 and TSH	↓ Satiation
↓ Leptin/FM	↑ Hunger
	↑ Food reward
	↑ Impulsivity to food

PNS – parasympathetic nervous system, SNS – Sympathetic nervous system, REE – resting energy expenditure, PAEE – Physical activity energy expenditure, T3 – Triiodothyronine, T4 – thyroxine, TSH – thyroid stimulating hormone, FM – Fat Mass.

Table 2.3. Compensatory responses that occur in weight loss, divided in active weight loss and maintenance of reduced weight. adapted from (Aronne et al., 2021)

	Active WL	WL maintenance
Circulating hormones	↓↓ T3, T4 and TSH ↓↓ Leptin/FM ↑ Cortisol	↓ T3, T4 and TSH ↓ Leptin/FM
Autonomic NS	↑↑ PNS and ↓↓SNS	↑ PNS and ↓SNS
EI	↓↓↓ Satiation ↑↑ Hunger	↓↓ Satiation ↑ Hunger
EE components	↓↓ REE ↓ PAEE ↑ Muscle contraction efficiency	↓ REE ↓ PAEE ↑ Muscle contraction efficiency

WL – Weight loss, FM – Fat mass, ANS – Autonomic nervous system, PNS – parasympathetic nervous system, SNS – Sympathetic nervous system, EI – Energy intake, EE – energy expenditure, REE – resting energy expenditure, PAEE – Physical activity energy expenditure.

Changes in Energy Homeostatic systems

Circulating hormones

Changes in appetite-related hormones as a response to weight loss has been documented in the literature (Greenway, 2015; Sumithran et al., 2011). Decreases in anorexigenic hormones, as well as increases in orexigenic hormones as a response to a prolonged negative EB have been studied (Greenway, 2015), leading towards increases in hunger and energy storage promotion (Sumithran et al., 2011), which compromises WL and its maintenance.

Sumithran et al found that leptin levels decreased after 10 weeks of a very-low-energy diet and remained lower than the baseline levels after 1 year (Sumithran et al., 2011). Changes in other hormones, namely decreases in insulin, CCK, PP, GLP-1 and PYY and increases in ghrelin were also found. Similarly, Crujeiras et al showed that, after 8 weeks of energy restriction, participants lost ~5% of their initial weight and the levels of leptin and insulin decreased (Crujeiras et al., 2010). Also, a relation between the degree of WL and changes in anorexigenic hormones was found, with decreases in leptin and insulin greater in participants who showed a WL superior to 5%. Moreover, subjects who were able to maintain a reduced weight state showed lower leptin levels and higher ghrelin levels when compared to those who regained at least 10% of their lost weight (Crujeiras et al., 2010). Other study showed that leptin levels decreased after WL in both males and females but started to increase throughout the study (Kempf et al., 2022). Furthermore, the leptin reduction after 1 month was considered a predictor for weight and fat loss over 1 year (Kempf et al., 2022).

When it comes to ghrelin, the results are discrepant, as some authors found increases in this orexigenic hormone as a response to a negative EB (Garcia et al., 2006; Rejeski et al., 2021; Soni et al., 2011; Sumithran et al., 2011), but others did not (Crujeiras et al., 2010; Sumithran et al., 2011). Nevertheless, even when ghrelin increased during WL, it

seems that these changes are transient, being (at least partially) converted during the WL maintenance. Indeed, a study where ghrelin concentration increased during WL, found that these values returned to baseline during WL maintenance (Garcia et al., 2006). This decrease after the active WL phase also occurred in other studies, however, mean levels remained higher than baseline (Rejeski et al., 2021; Sumithran et al., 2011). Also, most of the evidence revealed that increases in ghrelin are not considered a predictor for weight regain, as according to a literature review, most studies failed to find an association between increases in ghrelin during WL and the ability of maintaining the reduced weight state (Strohacker et al., 2014). Nevertheless, Thom et al showed that the rise in ghrelin was a predictor of weight regain, as concentrations remained higher over time (G. Thom et al., 2020).

The impact of WL on thyroid hormones has been considered in some studies. Similarly to ghrelin, the results are not consistent, as some authors found a decrease in thyroid hormones (specially T3) even after a moderate WL (Agnihothri et al., 2014; Fontana et al., 2006; Marzullo et al., 2018), but others failed to find a significant decrease in thyroid hormone levels (Kouidrat et al., 2019). Moreover, while moderate WL (5-10%) led to decreases in T3 (Agnihothri et al., 2014), >10% WL were related not only to decreases in T3, but also in TSH and T4 (Marzullo et al., 2018).

Decreases in other appetite-related hormones, such as insulin, CCK , GIP, PP, GLP-1 and PYY, were also found (Chearskul et al., 2008; Edwards et al., 2022; Essah et al., 2010; Pourhassan et al., 2017; Sumithran et al., 2011). It is unknown whether these changes are considered transient or permanent compensatory responses to a negative EB.

In sum, although some findings are not consistent, as it seems that WL leads to compensatory changes in appetite-related hormones towards increasing hunger and decreasing satiety. Conducting high-quality studies are crucial to understand the impact

that WL can have in appetite-related hormones, and consequently, if changes in these hormones can undermine the ability of maintaining a weight reduced state.

Autonomic nervous system (ANS)

The ANS plays a central role in both short- and long-term regulation of body weight (Guarino et al., 2017), being involved in the control of eating behavior (Messina et al., 2013). The main mediators of short-term regulation of body weight are gastric distension and gut hormones release, which are influenced by nutrients' ingestion and the sensation of satiety (Guarino et al., 2017). Although not entirely clear, it seems that ANS also plays a role in the EE and storage, through long-acting signals such as insulin - which plays a role in energy storage in the white adipose tissue -, and leptin - through increases in EE by acting on brown adipose tissue or on the cardiovascular system (Guarino et al., 2017). More specifically, the sympathetic nervous system (SNS) plays an important role in regulating EB under both basal and stimulated conditions (e.g., exercise, food intake), by influencing REE, facultative thermogenesis (i.e., heat generation to maintain body temperature in response to cold or diet (Himms-Hagen, 1989)) and glucose and fat metabolism (Guarino et al., 2017; Straznicky et al., 2011).

It is known that obesity is associated to an autonomic dysfunction, with an increased sympathetic and decreased parasympathetic activity (Monda et al., 2016; Triggiani et al., 2017). This sympathetic over activity contributes to the development of metabolic syndrome and hypertension, as it outflows to organs such as the heart, kidneys and blood vessels (Guarino et al., 2017).

As abdominal FM is a strong determinant of ANS activity (Grassi et al., 2005), decreases in this component as a response to a negative WL will lead to changes in ANS activity, namely the reduction in the sympathetic tone and an increase in the parasympathetic tone. A systematic review including 27 studies showed that WL was associated with decreases in ANS activity, such as heart rate variability, indicating a sympathetic inhibition and parasympathetic activation (Costa et al., 2019). Though, there is a large

variability among methodologies, participants' characteristics and techniques to measure ANS activity among the included studies, leading to inconsistent findings regarding this topic.

Furthermore, when it comes to the WL maintenance phase, there is a scarcity of data with respect to the changes in ANS. Nevertheless, it seems that maintaining a weight reduced state is associated to a partial rebound of some ANS parameters that may occur during the active WL phase. Laaksonen et al. showed that the increase in cardiac parasympathetic tone and spontaneous baroreflex sensitivity and the reduction in ambulatory blood pressure that were found during active WL were significantly attenuated after 4 months of WL maintenance (Laaksonen et al., 2003). Straznicky et al also showed that after 4 months of WL maintenance, some parameters of ANS activity rebounded, (Straznicky et al., 2011).

Despite the well-known role of the ANS on the body weight regulation, the findings are still inconsistent, which can be explained by differences in participants' characteristics and/or the methodologies to estimate ANS activity. Nevertheless, the evidence suggests that, as a response to a negative EB, a decrease in sympathetic and an increase in parasympathetic activity occurs, influencing the EE towards energy conservation.

Changes in Energy Balance components

Metabolic and behavioral compensatory responses

As stated before, WL is usually accompanied by decreases in all EE components, mainly due to a reduction of body stores (FM and FFM). However, it seems that these decreases are higher than expected and cannot be totally explained by changes in FM and FFM. Adaptive thermogenesis (AT) (also known as metabolic adaptation (MA)) is considered the decrease in the EE components [resting energy expenditure (REE), PA energy

expenditure (PAEE) and thermic effect of food (TEF)] beyond what could be predicted from the changes in FM and FFM in response to a negative EB (Dulloo et al., 2012; Major et al., 2007). These compensatory responses emphasize the ability to conserve energy when a negative EB is induced, which undermines WL success. Then, as AT is directed towards energy sparing, to continue to lose weight, the effort needs to be increased, by decreasing food intake and/or increase PA levels. Despite the mechanisms underlying AT are not clear, it has been speculated that involve decreases in circulating leptin and thyroid hormones, known to influence appetite by increasing (MacLean et al., 2011; Major et al., 2007). Also, other factors that may potentially contribute to AT have been suggested, such as changes in sympathetic nervous system activity and concentrations of insulin and catecholamines after WL (Müller et al., 2015), but more research is needed.

Together with AT, the existence of behavioral adaptations, i.e., any compensation that occur as a response to a negative EB through behavior changes – changes in EI and/or in PA - has also been documented in the literature (King et al., 2007; Melanson et al., 2013). Although both terms of the EB equation are regulated by our behavior, its influence is not the same for EI and EE (in terms of magnitude). While EI is mostly regulated by our behavior, when it comes to EE components, our behavior will impact mostly PAEE, through changes in PA. Behavioral adaptations to a negative EB are mostly increases in EI to tackle an increase in PA/exercise and changes in PA (usually NEPA) as a response to a decrease in EI.

Although more attention was given to metabolic compensations (specially in REE), behavioral compensations will have a higher contribution when it comes to attenuating the negative EB than any metabolic response, as the magnitude of a behavioral compensation is higher than a decrease in some EE components. For instance, the impact of eating a higher energy-dense snack on the EB will be of a higher magnitude than the one caused by a decrease in REE. Then, comparing to metabolic responses, behavioral compensations may seriously jeopardize the WL success. Moreover, while

metabolic compensations are inevitable, i.e., they are obligatory responses programmed to counteract a negative EB, when it comes to behavioral responses, they are usually associated to a “choice” and can be (at least partially) controlled. Nevertheless, even if a compensatory response is behavioral-based, it does not mean that it is performed deliberately (King et al., 2007). In fact, some behavioral responses could be passive (e.g., slightly increase in meal size), while others are volitional (e.g. food as a reward after an exercise session) (King et al., 2007; Melanson et al., 2013).

In sum, despite more information is needed, both metabolic and behavioral compensations that occur as a response to a negative EB could influence the ability of losing weight and should be considered when implementing a WL intervention. Understanding the effect of these compensatory responses would lead to a better comprehension on why some people cannot lose weight and why is it so difficult to maintain a reduced weight state. Thus, the effectiveness of WL interventions can be improved, increasing the success and quality of WL.

Compensatory responses in energy intake

As it was stated previously, WL is associated with decreases in SNS activity, leptin and insulin (Costa et al., 2019; Greenway, 2015). As all of them are associated to food intake, decreases in these 3 components lead to an increased food consumption (Doucet et al., 2000). Food intake can be divided into hunger, satiation, and satiety. Satiety is the process that inhibits eating in the postprandial period (inter-meal satiety), while satiation is the process that leads an eating episode to an end (intra-meal satiety) (Blundell et al., 2010). Hunger is defined as the drive to eat or a conscious sensation reflecting a mental urge to eat (Blundell et al., 2010). These three concepts are influenced by both homeostatic and hedonic systems (Campos et al., 2022). In fact, as eating stimulates the brain centers involved in pleasure and reward, the motivation to consume food may

override the need to maintain energy homeostasis and body weight (Egecioglu et al., 2011).

Subjective appetite can be assessed by using a visual analogue scale (VAS), measuring desire to eat, hunger and prospective food consumption (PFC) (Parker et al., 2004). Some studies showed that WL is associated with an increase in hunger (Coutinho, With, et al., 2018; Nymo et al., 2017; Sumithran et al., 2011), possibly due to changes in some hormones such as ghrelin, leptin or cortisol (Greenway, 2015). Heini et al showed that during a negative EB, decreases in leptin were accompanied by increases in hunger-satiety ratings (Keim et al., 1998). Also, Doucet et al showed that an increase in appetite scores, namely desire to eat, hunger and prospective food consumption were observed in fasting state after a considerable WL (Doucet et al., 2000). Moreover, the inter-subject variability in VAS variables changes should be considered, which were partly explained by changes in cortisol. Also, losing weight is associated with an improvement in glycemic control, reflected by a decrease in fasting glucose, which can lead to an increase on feeding episodes (Yoon & Diano, 2021).

Furthermore, the impact of food restriction on food cravings has been questioned, as dieting/restrained eating usually increases the likelihood of food cravings at a short-term (Hill, 2007) but does the opposite at a long term (Anton et al., 2012). Indeed, a study showed that self-reported measures of restrained eating were positively correlated with self-report measured of food craving. That is, restrained eaters (which it is not the same as staying under an energy deficit) seem to experience more intensely often food cravings than those who are not restrictive (Meule et al., 2012).

Additionally, there is a speculation that exercising (which is usually encouraged in WL interventions) drives up hunger and therefore increases food intake (Dorling et al., 2018). Plus, physical exercise can change macronutrients preferences and food choices (Blundell et al., 2003), which leads to an increase in snacks' consumption throughout the day, meal size and also the energy density. Indeed, behavioral compensations as a response to an increase in exercise have been pointed out as the main reason for the

lower-than-expected (or even lack of) WL when undergoing an exercise-only intervention (King et al., 2007; Ross & Janssen, 2001). More specifically, it has been proposed that people who are not able to lose weight during an exercise-only intervention might be compensating their increase in exercise with an increase in EI (Myers et al., 2019; Stubbs et al., 2002).

Evidence also suggests that the hedonic value of food can be altered by exercise, as some people can seek for food as a reward after undergoing an exercise session (Blundell et al., 2003). In fact, a study showed that after exercise, the hedonic ratings about pleasure alters, as women showed an increase in these ratings for a range of foods after exercise (Lluch et al., 1998). Then, the degree of pleasure may power the action to induce reward, which may compromise the negative EB created by exercise. Looking at previous literature, when considering short term compensations, i.e., immediately after an exercise session, most studies showed that no behavioral compensations occurred after exercising (King et al., 1994; King et al., 1997; King et al., 1996; Kissileff et al., 1990; Thompson et al., 1988). On the other hand, Stubbs et al showed that a slightly compensation increase in EI was found in women but the magnitude was inferior to the negative EB created by the exercise session (Stubbs et al., 2002). Additionally, Whybrow et al observed that compensations in EI does not offset EE immediately after exercise but in the following days (Whybrow et al., 2008). More recently, a systematic review observed that an exercise intervention does not lead to changes in EI or appetite in people living with overweight/obesity (Beaulieu et al., 2021). Nevertheless, most studies assessed EI by self-reported tools, which are known to be inaccurate due to its higher degree of misreporting (Burrows et al., 2019; Ravelli & Schoeller, 2020). Therefore, these results need to be interpreted carefully.

Under WL maintenance, the findings are less clear. Nymo et al showed that, after 13 weeks of WL, participants showed an increase in hunger, postprandial feelings of fullness and satiety quotient for hunger and a decrease in PFC (Nymo, Coutinho, Eknes,

et al., 2018). After 1 year (WL maintenance), fasting hunger, satiety quotient hunger and postprandial fulness ratings were still increased and PFC reduced (Nymo, Coutinho, Eknes, et al., 2018).

Therefore, as a response to a negative EB, several mechanisms occur to counteract this imbalance, potentiating an increase in EI. Decreases in sympathetic and increases in parasympathetic activity, as well as decreases in anorexigenic hormones lead to increases in hunger and decreases in satiety, which consequently increases EI. An energy deficit is also associated to an increase in food cravings, as well as the pleasure associated to food. Also, changes in our PA patterns, such as increasing the time spent exercise and/or exercise intensity, which is often advocated in WL interventions, is associated to changes in the hedonic value of food, which also contributes to a higher EI. All these mechanisms towards increasing EI undermine the ability of losing weight, as well the WL maintenance. As EI is mostly controlled by our behavior, understanding these mechanisms is paramount to develop better WL strategies to mitigate hunger and increase satiety, avoiding compensatory increases in EI.

Compensatory responses in energy expenditure

It has already been stated that WL is usually accompanied by decreases in all EE components, mainly due to a reduction of body stores (FM and FFM). Understanding the mechanisms underlying this decrease in EE, especially the energy expended to maintain vital physiological functions, as a response to WL is still unclear. Recently, it has been hypothesized that mitochondrial proton leak, as well as adenosine triphosphate (ATP)-dependent futile cycles can contribute to this decrease in EE (Brownstein et al., 2022). It is known that cellular reactions that contribute to REE included ATP-demanding processes (Rolfe & Brown, 1997). ATP is the primary energy source for those important biological functions, being mostly produced in mitochondria. In fact, mitochondria is the

main site of energy production, providing over 90% of a cell's ATP (Javadov et al., 2020). Also, a proportion of the generated energy is dissipated through proton leakage, which decreases the efficiency of ATP synthesis (Harper et al., 2008) and contributes to whole body EE (Thrush et al., 2013). The amount of oxygen needed to produce ATP and therefore run cellular activities can be defined as mitochondrial efficiency (Brand, 2005), measured as ATP generated per molecule of O_2 utilized (P/O). Therefore, it is plausible to think that variations in mitochondrial activity influence EE. Indeed, Thrush et al revealed that people who lost weight showed an increase in mitochondrial efficiency and a reduced proton leak (Thrush et al., 2013). The same study also revealed that people with higher rate of muscle mitochondrial proton leak lose weight in a faster rate than the others as they expended more energy. Similarly, 6 months of energy restriction led to an increase in the mitochondria efficiency, increasing mitochondrial biogenesis and content (Civitarese et al., 2007). Nevertheless, more research is needed to understand the contribution of mitochondrial efficiency to body weight management and EE.

Similar to mitochondrial proton leak, energy can also be dissipated through other futile cycles that are ATP-dependent, i.e., a set of biochemical reactions that concurrently run in opposite directions, consuming ATP in one direction, while the other is energetically spontaneous, which leads to a net decrease in ATP (Brownstein et al., 2022). These cycles involve mostly the creatine/phosphocreatine substrate cycling, sarcoendoplasmic reticulum calcium ATPase (SERCA)-mediated calcium (Ca^{2+}) cycling and lipid/fatty acid cycling, but other futile cycles are known (Brownstein et al., 2022). Then, it has been hypothesized that, under an energy restriction, decreases in these futile cycles may occur, decreasing the ATP consume and, consequently, EE. Nevertheless, information is still scarce and good-design studies are needed to understand the influence of these cycles on the ability to lose weight and maintaining it throughout time.

A detailed description of compensatory changes that occur in each EE component is described below.

Resting Energy Expenditure (REE)

Decreases in REE after a WL intervention are well stated in the literature (Muller et al., 2016). Since REE is mainly determined by body composition, mainly FFM (Frings-Meuthen et al., 2021), an individual with higher values of FFM presents higher values of this EE component when compared to height and weight-matched individuals with lower FFM (Egan & Collins, 2022). Therefore, decreases in FM and FFM will lead to a decrease in this EE component, as a smaller body needs to spend less energy to maintain essential body functions.

Alongside with this expected decrease, AT has been considered in several studies, especially in REE, not only in lifestyle interventions (Bosy-Westphal et al., 2009; Byrne et al., 2018; Camps et al., 2013b, 2015; de Jonge et al., 2012; Goele et al., 2009; Gomez-Arbelaez et al., 2018; Karl et al., 2015; Martins et al., 2020; McNeil et al., 2015; Müller et al., 2015; Nymo, Coutinho, Torgersen, et al., 2018; Pourhassan et al., 2014; Rosenbaum & Leibel, 2016; George Thom et al., 2020) but also after WL surgeries (Bettini et al., 2018; Browning et al., 2017; Carrasco et al., 2007; Coupaye et al., 2005; Tam et al., 2016; Wolfe et al., 2018).

One of the most well-known studies involves the Biggest Loser's population, where participants lost a large amount of weight with relative preservation of FFM, due to an intensive exercise (Johannsen et al., 2012). In this study, an AT of ~500kcal/day occurred after 6 years, with participants that presented the greatest weight loss displaying the greatest slowing of REE (Fothergill et al., 2016). However, this comprised a unique population in a distinctive WL intervention, as participants had little or no contact with the "real" world and their day was entirely focused on losing weight. Also, the Biggest Loser's participants showed a higher WL when compared to the "conventional" diet and/or exercise interventions, resembling to the WL achieved by bariatric surgeries. Moreover, some methodological concerns as well as potential errors in key variables has been reported (Kuchnia et al., 2016).

Nevertheless, after bariatric surgery, WL is usually accompanied by a larger FFM loss (~30% of the weight loss), compared to the Biggest Loser participants (16% of weight loss as FFM) (Knuth et al., 2014). Also, the last group underwent several sessions of exercise, which should preserve (at least partially) the FFM (Calbet et al., 2017). As FFM being a major predictor of REE, a large reduction of this component would lead to higher decreases in REE (Browning & Evans, 2015). Therefore, it would be expected that bariatric surgery's patients present a higher AT when compared to The Biggest loser's participants. Yet, bariatric surgery patients showed a lower AT (~300kcal/day vs ~500kcal/day from the Biggest loser's participants) (Knuth et al., 2014). Then, it seems that a relative preservation of FFM is not enough to attenuate AT and may even accentuate the need to spare energy and consequently the magnitude of this phenomenon. Anew, this population is not representative of "real life" WL interventions, as participants mostly achieved a moderate rather than a massive WL.

When considering lifestyle interventions that are more representative to what happens in free-living conditions (diet-only, exercise-only and combined diet and exercise interventions), a higher-than-expected decrease in REE was found by most authors (Bosy-Westphal et al., 2009; Bosy-Westphal et al., 2013; Byrne et al., 2018; Camps et al., 2013b, 2015; de Jonge et al., 2012; Goele et al., 2009; Karl et al., 2015; Martins et al., 2020; McNeil et al., 2015; Müller et al., 2015; Nymo, Coutinho, Torgersen, et al., 2018; Rosenbaum & Leibel, 2016; George Thom et al., 2020), as only 3 studies did not show AT after WL (Doucet et al., 2001; Gomez-Arbelaez et al., 2018; Pourhassan et al., 2014). Nevertheless, AT values varied widely from minimal to extreme values, which can be a result of the large discrepancy among the chosen interventions, resulting in different WL values. More specifically, while some participants underwent severe energy restrictions [such as very low-calorie diets (Gomez-Arbelaez et al., 2018; Nymo, Coutinho, Torgersen, et al., 2018; Pourhassan et al., 2014)], others undertook less

restrictive diets (Goele et al., 2009; Martins et al., 2020; George Thom et al., 2020), resulting in a lower (but substantial) WL. Although it has been suggested that the magnitude of WL is somehow associated with the degree of AT (Johannsen et al., 2012; McNeil et al., 2015), other authors have reported contradictory findings (Martins et al., 2020; Muller et al., 2016), which highlights the uncertainty of this association.

Considering the energy expended during sleeping, only two studies addressed metabolic compensations in this component (Lecoultre et al., 2011; Marlatt et al., 2017). In both studies a higher-than-expected decrease in sleeping energy expenditure was observed in groups that underwent a WL intervention [diet-only (Lecoultre et al., 2011; Marlatt et al., 2017) or combined diet-exercise intervention (Lecoultre et al., 2011)]. Nevertheless, evidence is not strong enough to fully understand the impact of WL on this EE component.

Although there is a considerable number of studies considering AT in REE, its existence is debatable, as some studies did not show compensatory decreases in any EE component even after a considerable WL (Bosy-Westphal et al., 2013; Doucet et al., 2001; Hopkins et al., 2014; Jebb et al., 1996). Plus, understanding AT's influence on long-term WL maintenance is important, as some authors found that AT seems to be attenuated or even disappeared after a period of weight stabilization (Gomez-Arbelaez et al., 2018; Marlatt et al., 2017; Martins et al., 2020; Novaes Ravelli et al., 2019; Wolfe et al., 2018). These widely variable findings might be a reflection of several factors, such as the lack of standardization among study designs, methodologies, participants' characteristics and other variables. A detailed description of these issues will be further detailed.

Physical Activity Energy Expenditure (PAEE)

PAEE is the second most significant contributor to total EE, which includes the energy expended in both exercise (EiEE) and other activities [daily life activities that are not

considered exercise, such as fidgeting, posture maintenance and non-specific ambulatory activities (NEAT)] (Levine et al., 1999).

As some studies showed that the energy cost of weight-bearing activities and light-intensity activities was proportional to body weight (Levine et al., 2000; Schoeller & Jefford, 2002), it is rational to think that a "smaller" body will have less energetic costs while performing a specific activity when compared to a heavier one. Indeed, decreases in this component as a response to a negative EB are also described in the literature (Muller et al., 2016) and explained by a combination of 1) Behavioral compensations, such as decreases in non-exercise PA and/or increases in sedentary behavior as a response to an increase in exercise and/or a decrease in EI (King et al., 2007; Melanson et al., 2013), and 2) increases in muscular efficiency, i.e., the amount of work that can be performed by the muscles per unit of energy expended (Coutinho, Halset, et al., 2018; Rosenbaum et al., 2018; Rosenbaum et al., 2003).

There is little evidence considering the effect of energy restriction on PA (Drenowatz, 2015). Nevertheless, decreases in PA have been associated to decreases in EI (Camps et al., 2013a; Martin et al., 2007; Redman et al., 2009). According to a systematic review, a reduction in NEPA as a response to a negative EB occurred in more than a half of the diet-only interventions (~63%) (Silva et al., 2018). Although this compensatory response in PA is actually a survival advantage to a prolonged negative EB (as it preserves energy) (Keys et al., 1950), it may undermine the WL success by attenuating the negative EB. Together with a compensatory increase in EI (Myers et al., 2019; Stubbs et al., 2002), decreases in NEPA may also explain why exercise-only interventions do not lead to significant amounts of WL (Colley et al., 2010; Drenowatz et al., 2015; Schutz et al., 2014).

Considering changes in NEPA, the results are not consistent, as in the aforementioned systematic review, reductions in this component only occurred in 27% of combined diet and exercise interventions and in 23% of exercise-only interventions (Silva et al., 2018).

More recently, Liu et al observed that short-time exercise (40min/session, 3-day exercise intervention) induced an increase in NEPA, while a longer exercise duration (2x40min/session, 3-day exercise intervention) led to a compensatory decrease in NEPA (Liu et al., 2022). A possible explanation for this observation could be the fatigue associated to a long exercise duration. This goes along with the Shutz et al findings, who observed that the degree of compensation increases progressively as the exercise duration increases (Schutz et al., 2014).

The muscle work efficiency has been studied by some authors (Amati et al., 2008; Coutinho, Halset, et al., 2018; Coutinho, With, et al., 2018; Goldsmith et al., 2010; Nymo, Coutinho, Torgersen, et al., 2018; Rosenbaum et al., 2018; Rosenbaum et al., 2003), including measures of the external mechanical work performed during a specific exercise compared with the metabolic EE during the same activity.

To measure skeletal muscle efficiency, most authors asked participants to undergo a graded cycle ergometer session with a fixed pedal rate at 60rpm, to generate 10, 25 or 50W of power. Together with the cycle ergometry, Rosenbaum et al also measured muscular efficiency (gross mechanical efficiency) through nuclear magnetic resonance spectroscopy in gastrocnemius, calculating the ratio of phosphate (Pi) to phosphocreatine (PCr) (Rosenbaum et al., 2003). This ratio indicates the high-energy phosphate bond flux between ATP and PCr, providing an indirect measurement of the rate at which skeletal muscle consumes ATP (Vandenborne et al., 1995). Therefore, while cycle ergometry measures the whole-body skeletal muscle work efficiency - calculated as the ratio of generated power (kcal/min) to change in EE above REE (kcal/min) -, nuclear magnetic resonance spectroscopy isolates the gastrocnemius muscle to examine specifically its energy consumption during the prescribed exercise, eliminating any possible artifacts of energy consumption that are not directly involved in the prescribed exercise. Additionally, Rosenbaum et al (for a small subset) and Goldsmith et al performed a magnetic resonance spectroscopy, offering a direct

measurement of the ATP cost per muscle contraction, as it measures the levels of high-energy phosphate compounds, such as ATP in skeletal muscle.

Furthermore, the definition of skeletal muscle work efficiency is not the same among studies, as it can be expressed as net mechanical efficiency (ratio of power generated to calories consumed) (Coutinho et al., 2014; Coutinho, Halset, et al., 2018; Nymo, Coutinho, Torgersen, et al., 2018), delta mechanical efficiency (changes in net mechanical efficiency between two points during the contraction-relaxation cycle) or gross mechanical efficiency (ratio of generated power to change in EE above REE) (Amati et al., 2008; Goldsmith et al., 2010) net mechanical efficiency assumes that REE, which is included in the measurement of calories consumed, is constant, which is not true as this EE component change as a function of WL. On the other hand, gross mechanical efficiency corrects for the influence of changes in REE resulting from WL on the power generated per calorie expended (Leibel et al., 1995).

Decreases in EiEE after WL were reported at 10W (Coutinho, Halset, et al., 2018; Coutinho, With, et al., 2018; Nymo, Coutinho, Torgersen, et al., 2018), 25W (Coutinho, Halset, et al., 2018; Coutinho, With, et al., 2018; Nymo, Coutinho, Torgersen, et al., 2018) and 50W (Coutinho, Halset, et al., 2018; Nymo, Coutinho, Torgersen, et al., 2018), as well as increases in skeletal muscle efficiency at 10W and 25W (Amati et al., 2008; Goldsmith et al., 2010; Rosenbaum et al., 2003). Maintaining a reduced weight was also associated with a decrease in the ratio Pi/Pcr for low workloads (Rosenbaum et al., 2003), suggesting a decline in the rate of flux of high-energy phosphate bonds for the same amount of generated power, and with a decrease in the ATP cost per muscle contraction. Moreover, these changes in skeletal muscle efficiency explained a significant portion of the variance in changes in non-resting EE, which also decreased after WL, suggesting that the decrease in this EE component is not only due to a decrease in energy cost of weight-bearing activities due to a lower mass.

Although the mechanisms underlying the increased efficiency are still unclear, some evidence suggests that changes in SERCA and myosin heavy chains (MHCs) are involved (Baldwin et al., 2011). The SERCA is a key regulator of cellular calcium homeostasis, driving free calcium ions from the cytosol into the sarcoplasmic reticulum by coupling ATP hydrolysis to the translocation of calcium ions (de Meis et al., 2005). Plus, it is known that muscle fibers are generally classified by MHC isoforms characterized by slow to fast contractile speeds (Plotkin et al., 2021). Type I muscle fibers are slow-twitch, MHC I and SERCA2 predominant and with low ATPase activity, being more efficient. On the other hand, fast-twitch type II fibers are less efficient, SERCA1 predominant and with a high myosin ATPase activity and glycolytic capacity (Herbison et al., 1982). Moreover, it is known that SERCA1 has the unique ability to uncouple ATP hydrolysis from Ca^{2+} transport, where the energy derived from ATP hydrolysis is converted into heat (de Meis et al., 2005).

Therefore, it has been hypothesized that the maintenance of a weight reduced state is associated with changes in the activity of glycolytic and oxidative enzymes which lead to an overall increase in the relative expression of the more efficient MHC I and SERCA2 isoforms of skeletal muscle. Indeed, the maintenance of a reduced body weight has been associated with alterations in muscle enzyme activities *in vitro,* characterized by a decline in the activity in skeletal muscle of the glycolytic enzyme (phosphofructokinase, PFK) (Goldsmith et al., 2010) and by a decrease in the ratio of PFK to cytochrome *c* oxidase (COX) (at low levels of exercise) which expresses the ratio of glycolytic to fatty acid oxidative enzyme activity, as well as changes in the proportions of fast- vs. slow-twitch fiber types (Jaworowski et al., 2002). Also, a negative correlation was found between the skeletal muscle efficiency and the ratio PFK/COX, which suggests that this ratio can be a predictor of skeletal muscle efficiency. Then, by changing muscle fiber types, namely the increase of type I fibers, through the increase in the relative expression of MHC I and SERCA 2 isoforms, it is expectable an increase in skeletal muscle efficiency. Nevertheless, this emerging area of research needs more

consideration, as more studies are needed to understand the mechanisms underlying the increased muscular efficiency.

Overall, it seems that skeletal muscle efficiency changes after WL towards compromising the maintenance of the new weight-reduced state. After losing weight (considering that there is a maintenance of PA levels), the body will became more “efficient” by expending less energy for the same performed activity, leading to a reduction in PAEE (Ravussin et al., 2021). This phenomenon, especially if coupled with behavioral compensations comprising decreases in PA and/or exercise levels, may exert an influence towards weight regain, undermining WL success.

Thermic effect of feeding (TEF)

When someone undergoes a dietary restriction to lose weight, it is expected that their food consumption changes in terms of quantity but also quality (macronutrients proportion). Then, if someone decreases their food intake, it is expectable that TEF also decreases, as the amount of energy needed to digest, absorb, and metabolize the ingested food will be lower. Likewise, changes in macronutrients’ proportion will also affect TEF, as each macronutrient has different energy costs due to different requirements during metabolism and storage (Westerterp, 2004). Protein is the macronutrient with a higher energy cost (20-30% of ingested intake), followed by carbohydrates (5-10%) and lastly fat (0-3%) (Westerterp, 2004). Therefore, if the diet’s macronutrient composition changes during an energy restriction, it will also affect this EE component.

Additionally, it has been contemplated a possible higher-than-expected decrease in this component after losing weight. In fact, few studies have studied possible compensations in TEF by assessing this component after a pre-defined meal (in terms of energy content and macronutrient distribution) before and after WL (Luscombe et al., 2003; Racette et

al., 1995; Rosenbaum et al., 2003). However, the results are not consistent, as a decrease in TEF after WL was only reported in one study (Racette et al., 1995). Moreover, it is a matter of debate if these data reflect the effect of WL per se on TEF or if can be considered a metabolic compensation, i.e., a greater than predicted decline in TEF. Furthermore, as the gut microbiota composition suffers structural changes due to energy restriction and/or PA (Jumpertz et al., 2011; Santacruz et al., 2009), likely changing the calorie absorption and its processing/portioning, it cannot be assured if the difference between TEF measurements (before and after WL) should be considered a metabolic adaptation.

Then, the evidence regarding AT in TEF is not strong enough to assure the existence of this compensatory response. Nevertheless, as TEF has a small contribution among the main EE components, it is highly unlikely that decreases in this EE component will undermine WL and contribute to weight regain.

To summarize this section, these findings highlight the existence of metabolic and behavioral compensations that may occur as a response to a negative EB. These compensatory responses work towards energy conservation, undermining the ability of losing weight and maintaining it throughout time. However, the literature is not consistent and there is still uncertainty in some findings. Considering metabolic compensations, there is a need to understand the mechanisms underlying AT, as well as exploring the methodological issues that are behind this phenomenon, in order to improve the WL success.

The **figure 2.6.** briefly depicts an overview of the topics that were addressed in detail so far and how they are connected. This image summarizes what is the current evidence regarding body weight regulation, suggesting possible areas of intervention that will be addressed in this thesis.

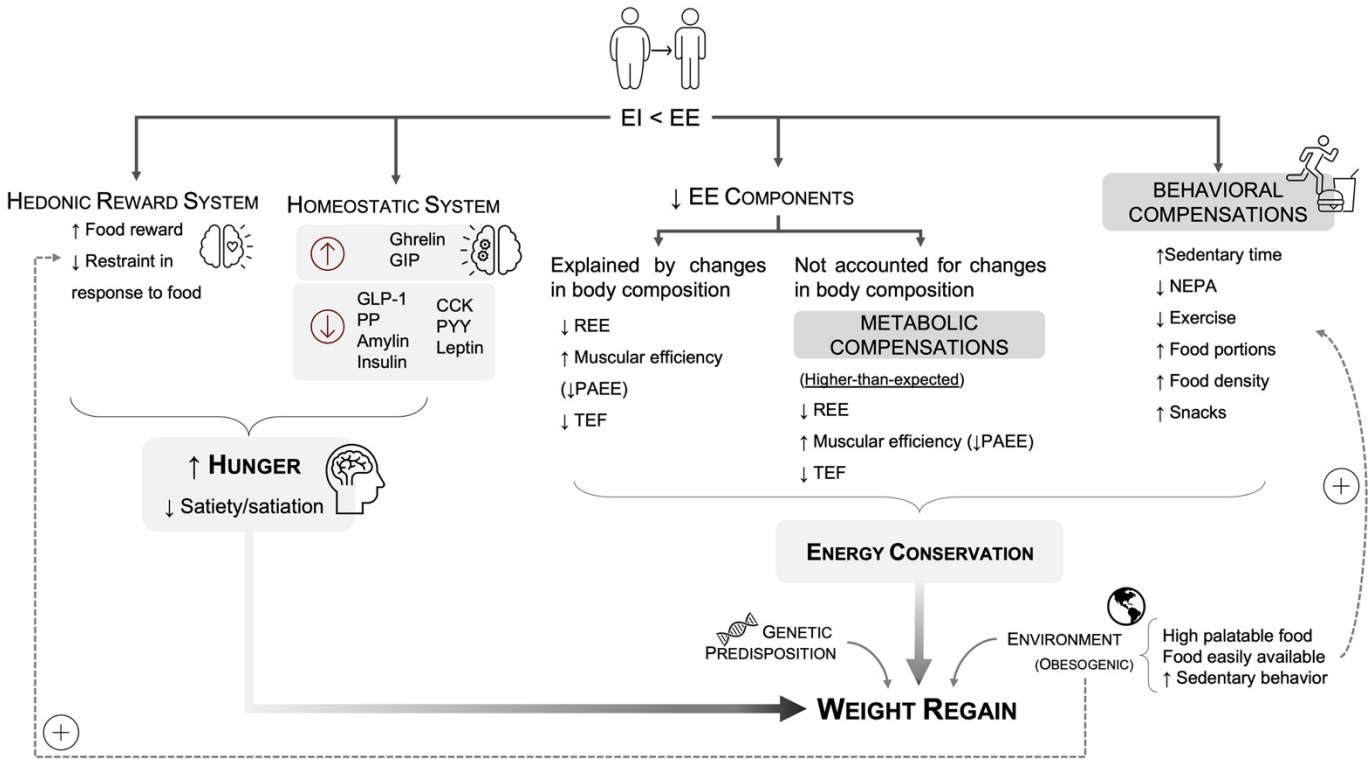

Figure 2.6. Graphical representation of the mechanisms underlying body weight regulation.

Legend: EI – energy intake, EE – energy expenditure, GIP – Gastric inhibitory polypeptide/ glucose-dependent insulinotropic polypeptide, GLP-1 – glucagon-like peptide 1, PP – pancreatic polypeptide, CCK – cholecystokinin, PYY – peptide YY, REE – resting energy expenditure, PAEE – physical activity energy expenditure, TEF – thermic effect of feeding, NEPA – Non exercise physical activity.

Adaptive thermogenesis – real or a fairy tale?

Studying the existence of metabolic and behavioral compensations as a response to an energy restriction can be challenging, as there are several factors that influence the EB regulation and WL outcomes. Indeed, to study the real effectiveness of a lifestyle WL intervention, it is necessary to consider some possible confounding factors that might compromise WL success. Despite most studies involving people living with overweight/obesity, the reason why participants gained weight, as well as their weight history are usually not considered. It is known that weight gain is common with aging,

mostly due to changes in PA patterns, i.e., increases in sedentary behavior and decreases in PA (exercise and other activities). However, weight gain may be a consequence of other factors, such as certain medical conditions or a genetic predisposition. For instance, developing obesity during early childhood might be a result of a strongly genetic predisposition, as some genetic mutations exert a powerful effect on body weight regulation (with little or no environmental influence), usually resulting in childhood obesity (Rankinen et al., 2006). Therefore, these factors need to be considered when selecting the population to study metabolic and behavioral adaptations to WL.

These confounding effects can be somewhat controlled by including individuals that were active and did not live with overweight/obesity during their childhood and early adulthood but gained weight when changed their diet and PA patterns. By excluding people who developed obesity during early childhood, the possibility of having a strongly genetic predisposition to weight gain is excluded, assuring that weight gain occurred mostly due to changes in PA patterns and an inadequate diet rather than genetic and hormonal effects. Similarly, when submitted to a WL intervention, changes in weight and the consequent compensations will also be explained by changes in their diet and PA patterns, emphasizing the preponderant role of environment and behavior on weight management and dismissing any significant influence of genetics or homeostatic disorder. In sum, choosing people who were active and within an adequate BMI range during their childhood and the beginning of adulthood is highly recommended as it will reduce the possible confounding effects of genetics and/or hormones.

Former athletes are a specific population that easily fits these requirements. During their career, which may begin during childhood, it is required for athletes to match their energy demands with an adequate EI to ensure a good performance (American Dietetic et al., 2009; Loucks, 2004). However, when the transition to post career occurs, there is a need to adjust their EI to bridge the decrease in EE due to decreases in PA. Therefore, as athletes dramatically reduce their PAEE when retiring from their sports career, it is

expected a proportional reduction in EI. However, according to Stubbs et al., this reduction in PA levels does not induce an equivalent reduction in EE (Stubbs et al., 2004). Consequently, a positive EB is created and maintained, resulting in weight gain, and increasing the risk of developing obesity-related adverse health effects. Thus, former athletes generally experienced an undesired weight gain and a transition to a sedentary state throughout adulthood (Griffin et al., 2016).

Although the results might not be representative of the general population at first sight, studies revealed that former athletes are not protected against any risk factors or have health-related benefits when compared to a non-athletic population if they do not continue the same (or similar) diet and PA patterns that had during their sport career (Griffin et al., 2016; Laine et al., 2016). Also, former athletes with a higher body mass are highly susceptible to developing metabolic syndrome, dyslipidemia, elevated fasting plasma glucose, and elevated blood pressure (Griffin et al., 2016). Moreover, the reported weight gain after an athletic retirement was of a similar magnitude to what was observed in studies with non-athletic population (Dutton et al., 2016). Moreover, and despite athletes being expected to present different body composition when compared to non-athletic population, namely a higher percentage of FFM, non-athletic individuals who were active in their youth may present a similar body composition. Also, body composition varies according to the sports modality, with values for %FM ranging from 10.4 (in hockey rink) to 18.5 (in rugby) in male athletes and from 18.0 (in athletics) to 27.3 (in handball) in female athletes (Santos et al., 2014).

Additionally, former athletes were used to follow specific nutrition and PA recommendations, which can be a facilitator for the intervention adherence. As WL interventions are known to have a higher attrition rate and/or lower adherence to the intervention (Franz et al., 2007), implementing lifestyle interventions on this specific group may be advantageous as they are more willing to engage in the recommended PA and diet patterns.

Therefore, choosing an adequate population – i.e., people who were active and without overweight/obesity until their adulthood, without any medical condition - to study compensatory responses to a negative EB is paramount to exclude (or at least attenuate) any possible confounding factors and to achieve more accurate and reliable findings.

As it was stated before, the findings regarding the existence of AT are contradictory, as some studies did not show ´compensatory decreases in any EE component even after a considerable WL (Bosy-Westphal et al., 2013; Doucet et al., 2001; Hopkins et al., 2014; Jebb et al., 1996). Also, even if AT exists, it is unclear if this disproportionate decrease in all EE components exerts an influence that is strong enough to undermine WL and its maintenance.

The observed inconsistencies among studies may be the result of a lack of standardization regarding the methods used to assess AT, varying on how REE is calculated and in body composition assessments (Müller & Bosy-Westphal, 2013). The main issues about AT assessment and its existence are stated at **table 2.4.**

Methodological issues

As AT is defined as a higher-than-expected decrease in an EE component (considering REE), the assessment of this phenomenon will go through a comparison between an expected REE, i.e., a predicted value that is calculated based on changes in FM and FFM, and the “real” REE (usually measured with the reference method). Then, in the current literature, AT is calculated through several mathematical approaches, varying in how REE is predicted and/or how AT is assessed.

Table 2.4. Main issues regarding AT assessment and its existence

"Gaps to fill" and issues regarding AT	
Methodological issues	• Lack of a concrete definition of AT; • Lack of standardization among methodologies to predict REE; • Lack of standardization among methodologies to assess AT;
Other issues	• If AT exists after a moderate WL; • If AT occurs if assessed during a period of a neutral EB; • If AT exists in all EE components; • More studies with better designs (RCT).

Legend: AT – adaptive thermogenesis, REE – Resting Energy Expenditure, WL – weight loss, EB – Energy Balance, EE – Energy Expenditure, RCT – Randomized controlled trial.

While the indirect calorimetry is considered the gold standard method to assess REE (measured REE) (Delsoglio et al., 2019), predicting REE from organ/tissue masses tied to their specific metabolic rates seems to be the most accurate method to assess predicted REE (Muller et al., 2016). However, as this methodology is time consuming and is associated with higher costs, only few studies used it to predict REE (Bosy-Westphal et al., 2009; Bosy-Westphal et al., 2013; Müller et al., 2015). Therefore, as an alternative, the most common method to predict REE is through regression models. These models are usually created by developing an equation based on the baseline information from the population included in the study, such as FM and FFM, but also other variables such as sex, age and ethnicity (Martins et al., 2020; Nymo, Coutinho, Torgersen, et al., 2018). Then, to predict REE after WL, the same equation will be used but with the post-WL values for FM and FFM (and for the other variables, if applicable). Other alternatives were performed, such as using an already created and previous validated equation (Byrne et al., 2018; Marzullo et al., 2018) or by adjusting the measured REE (for FM and/or FFM) before and after a WL intervention (Byrne et al., 2018).

Since FM and FFM are included in the REE prediction, the methodology to assess them is also a matter of debate. It is known that the 4-compartment model, a technique involving dual energy X-ray absorptiometry (DXA), body volume by using air-displacement plethysmography/underwater weighing and isotopic dilution (deuterium), is the gold standard for FM assessment (Heymsfield et al., 1997). However, this approach requires considerable time and cost, and consequently, studies including this methodology are scarce (Martins et al., 2020; Pourhassan et al., 2014). Then, DXA is a valid alternative to 4-compartment models, being the most used methodology to assess FM and FFM (Coupaye et al., 2005; Fothergill et al., 2016; Gomez-Arbelaez et al., 2018; Johannsen et al., 2012; McNeil et al., 2015; Rosenbaum & Leibel, 2016; Wolfe et al., 2018). Still, some studies performed other methodologies with other devices such as MRI (Müller et al., 2015; George Thom et al., 2020), bioimpedances (Bettini et al., 2018; Marzullo et al., 2018; Tam et al., 2016), air displacement plethysmography - BodPod (Byrne et al., 2018; Karl et al., 2015; Nymo, Coutinho, Torgersen, et al., 2018) and hydrodensitometry (Doucet et al., 2001; Dulloo & Jacquet, 1998). Therefore, the accuracy of these measurements is dependent on the performed methodology.

Considering the AT assessment, the most common approach is by simply subtracting the predicted REE to the measured REE after WL (mREE minus pREE) (Gomez-Arbelaez et al., 2018; Martins et al., 2020; George Thom et al., 2020). However, some concerns have been raised regarding the large discrepancy between predicted and measured REE at baseline. For example, if an individual showed a large difference between the measured and predicted REE at baseline, the same might occur after WL, which can be attributed to the predictive power of the model rather than the existence of AT. Consequently, other studies performed a similar approach but considering the baseline residuals (measured minus predicted REE at baseline) (Browning et al., 2017; Ten Haaf et al., 2018).

In sum, REE can be predicted through several approaches, with the use of predictive equations as the most common method. Regarding AT assessment, most studies subtract between the predicted with the measured REE, which also raised some questions due to the large difference between both values at baseline. In order to solve this issue, some studies considered the residuals when calculating AT as a form of "adjustment" for the baseline values. Therefore, the discrepant findings regarding AT among studies can be in part due to differences in their methodologies, being strongly dependent on the accuracy of the technique used to predict REE and to assess AT.

Other issues

Together with the lack of standardization regarding methodologies to assess AT, other problems should be considered when comparing studies regarding this phenomenon. Firstly, although it seems that studies that reported higher magnitudes of AT were also those who showed higher WL (bariatric surgeries or severe WL interventions) (Bettini et al., 2018; Johannsen et al., 2012; Tam et al., 2016), this association between the magnitude of WL and the degree of AT has been criticized by other authors (Martins et al., 2020; Muller et al., 2016). Indeed, some authors reporting substantial WL did not find a higher-than-expected decrease in REE or any other EE component (Coupaye et al., 2005; Gomez-Arbelaez et al., 2018). Therefore, these discrepancies among studies are likely to be explained by other factors rather than the magnitude of WL.

Additionally, as regards to studies comprising moderate WL, the results are not consistent, as some studies showed that a disproportionate decrease in REE occurred during WL and may have persisted during the weight-reduced state (Fothergill et al., 2016; Rosenbaum et al., 2008), but others did not find a higher-than-expected decrease in any of the EE components (Bosy-Westphal et al., 2013; Hopkins et al., 2014). As most WL interventions utilizing a reduced-energy diet and/or exercise strategy result in a

moderate WL (<10%), it is crucial to understand if AT still occurs in this condition, as well as its impact on WL and its maintenance.

Alongside with the magnitude of WL, most studies assessed AT immediately after the WL intervention (under a negative EB) (Browning et al., 2017; Coupaye et al., 2005; de Jonge et al., 2012; Gomez-Arbelaez et al., 2018; Karl et al., 2015; Marlatt et al., 2017; Novaes Ravelli et al., 2019; Pourhassan et al., 2014; Wolfe et al., 2018). Therefore, the AT existence on long-term weight management has been recently questioned, as only few studies have assessed AT after WL and after a period of WL maintenance (Byrne et al., 2018; Fothergill et al., 2016; Karl et al., 2015; Redman et al., 2009). As some authors showed that, after a period of weight stabilization, this "phenomenon" seems to be attenuated or even disappeared (Gomez-Arbelaez et al., 2018; Marlatt et al., 2017; Martins et al., 2020; Novaes Ravelli et al., 2019; Wolfe et al., 2018), future studies should include a follow-up period - where participants are weight stabilized-, in order to understand if AT still occurs under a neutral EB and its influence on WL management outcomes.

AT has been widely discussed in REE, but its existence in other EE components is still a matter of debate, partially explained by the lack of specific protocols to assess it. For instance, studies who were included and observed a lower than decreased TEF after an intervention were not specifically designed to assess the existence of AT, but to understand the effect of a lifestyle WL intervention in TEF (Luscombe et al., 2003; Racette et al., 1995; Rosenbaum et al., 2003). Therefore, none of the studies defined AT during their methodology. Although it can be hypothesized that, in response to the same meal (i.e., with the same energy and macronutrient composition), if TEF is lower after WL, the difference between measurements could be considered a metabolic compensation.

Regarding muscular efficiency, it is not clear how some studies separate the effect of achieving a lower body weight on the energy cost of performing a certain activity from the real muscular efficiency. Also, it is important to standardize how muscular efficiency

should be defined, as the net mechanical efficiency assumes that REE remains the same throughout the intervention, when it is well-stated that it changes accordantly to weight changes. Conversely, gross mechanical efficiency takes into account the impact of REE changes caused by WL on the energy produced per unit of calorie burned (Leibel et al., 1995). Therefore, the comparison among studies with different definitions for muscular efficiency must be carried out carefully. Lastly, and similar to REE, most studies comprised short-term WL intervention and consequently, it is still unclear whether these decreases in PAEE, as well as increases in muscular efficiency remain significant at a long-term.

Lastly, the current literature on this topic consists in mostly observational studies or controlled trials without a control group, where studies with strong designs such as randomized controlled trials (RCT) are scarce. For instance, the inclusion of a control group is important to understand if AT occurs as a result of the WL intervention rather than other external factors. Moreover, the use of good-quality design studies minimizes the bias, which enhances the validity and reliability of the findings.

Overall, although the existent literature regarding AT yielded some important insights, assessing this phenomenon can be challenging. In fact, some issues have been raised, such as the lack of standardization on the methodologies to predict REE and to assess AT, the participants' characteristics and also if AT occurs in other conditions, namely in moderate WL and/or in other EE components. Moreover, the variability among individuals must be considered, in order to identify possible predictors of the AT existence and therefore to understand why some people are more prone to regain weight while others do not. Therefore, more studies are needed to fully understand its mechanisms and develop effective strategies for WL maintenance.

2.4. AIM OF THE INVESTIGATION

The present dissertation presents six research studies conducted under the scope of the energy balance regulation.

The studies included in this thesis (except study 1) are a secondary analysis from the Champ4life project, a self-determination theory (SDT) 1-year lifestyle intervention aimed to WL that comprised former elite athletes who lived with overweight/obesity and became inactive (Silva et al., 2021; Silva et al., 2020).

Study 1 (Chapter 4) is a systematic review aimed to understand the current evidence regarding the existence of adaptive thermogenesis in some EE components, namely REE, SEE and total EE. This was fundamental to compile all the evidence regarding this topic, as the findings are not consistent, as well as to point out some methodological concerns and gaps that need to be look further.

Considering the methodological issues that were raised in the study 1, **study 2** (chapter 5) was conducted to understand the discrepancy among methodologies to assess AT, by comparing 13 approaches varying in how REE is predicted and/or how AT is assessed.

Moving beyond the methodological issues and considering that studies regarding the existence of AT after a moderate WL, as well as studies including a follow up period (under a neutral EB after WL) are scarce, the aim of **study 3** (chapter 6) was to understand if AT occurred not only after 4 months of a moderate WL but also after 8 months of WL maintenance. This study also aimed to investigate if AT is associated with changes in body composition, hormones and EI.

Study 4 (chapter 7) was conducted to understand if AT occurs in other EE components rather REE, namely NEAT. Also, an interindividual variability was found in previous studies regarding changes in REE and AT after WL. Then, this study also aimed to

analyze if a large variability among participants was observed in this EE component, as well as if there are any associations between these compensations and WL.

As all previous studies tackled the issues related with metabolic compensations, **study 5** (chapter 8) analyze behavioral compensatory responses, namely the associations between EI and PA during a WL intervention. The interindividual variability in the observed changes in EI and PA (exercise and non-exercise) was also explored.

Lastly, **study 6** (chapter 9) aimed to analyze changes in intuitive eating and food reward, in order to understand if eating behavior changes as a response to WL, as well as associations between these changes and body composition.

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CHAPTER 3

METHODOLOGY

3. METHODOLOGY

This chapter addresses all the methods used in **study 2-6**, as well as the sample size and the study protocol. If applicable, specific details are described in the respective study (chapter 5 to 9).

The **study 1** is a systematic review and all the details regarding the used methodology are described in **Chapter 4**.

3.1. Study design and sampling

This thesis and the respective studies (except the first study – Chapter 4) were conducted within a project entitled "**Champ4life**" (clinicaltrials.gov ID: NCT03031951), funded by the Portuguese Institute of Sports and Youth and by the International Olympic Committee, under the Olympic Solidarity Promotion of the Olympic Values Unit (Sports Medicine and Protection of Clean Athletes Programme). This project was also supported by national funding from the Portuguese Foundation for Science and Technology within the R&D units UIDB/00447/2020.

The **table 3.1.** summarizes the characteristics of each study regarding sampling and design.

3.1.1. The Champ4life project

The Champ4life project was a 1-year lifestyle intervention targeting inactive former elite athletes who were living with overweight/obesity, divided in 4 months of an active weight loss phase followed by 8 months of weight loss maintenance. A total of 94 (42.4 ± 7.3 years, 34% females) participants were recruited and randomly divided in intervention (IG) (n=49) and control group (CG) (n=45). Participants from the IG attended an initial nutrition appointment presented by a certified dietitian to create a moderate caloric reduction (~300-500kcal/day) and to provide a well-balanced personalized diet plan.

Table 3.1. Design and sampling of each study.

Study	Design	Sample	N	Population characteristics	WL intervention
1	Systematic review	Healthy adults	33 studies 2528 individuals	18-65y	Diet-only, exercise-only, diet-and-exercise, surgery
2	RCT*	Former elite athletes with overweight/ obesity and inactive	94	BMI: 31.1(4.3)kg/m^2; age: 43.0(9.4)y; 34% females	4 months of active WL
3	RCT*				4 months of an active WL followed by 8 months of WL maintenance
4	RCT*				
5	RCT*		81	BMI: 31.2(4.4)kg/m^2, Age: 42.8(9.4)y, 37% females	4 months of active WL
6	RCT*		94	BMI: 31.1(4.3)kg/m2; age: 43.0(9.4)y; 34% females	4 months of an active WL followed by 8 months of WL maintenance

Abbreviations: BMI – Body Mass Index, RCT – Randomized Clinical Trial, F – Female, M – Male.

* Secondary analysis of a RCT aimed to WL that comprised former elite athletes who lived with overweight/obesity and became inactive (Silva et al., 2021; Silva et al., 2020)

Follow-up appointments were scheduled to adjust individual energy requirements. As this project is based on the Self-Determination theory, IG also underwent 12 educational sessions throughout the 4 months of the intervention, addressing topics regarding physical activity, weight management, and nutrition. On the other hand, participants of the CG were placed on a waiting list and were asked to maintain their physical activity and nutrition routines. At the end of the program (12 months), after they completed all measurements (baseline, 4 and 12 months), and if they were still interested, they

undertook the Champ4life intervention. A schematic description of the project is presented in **figure 3.1**.

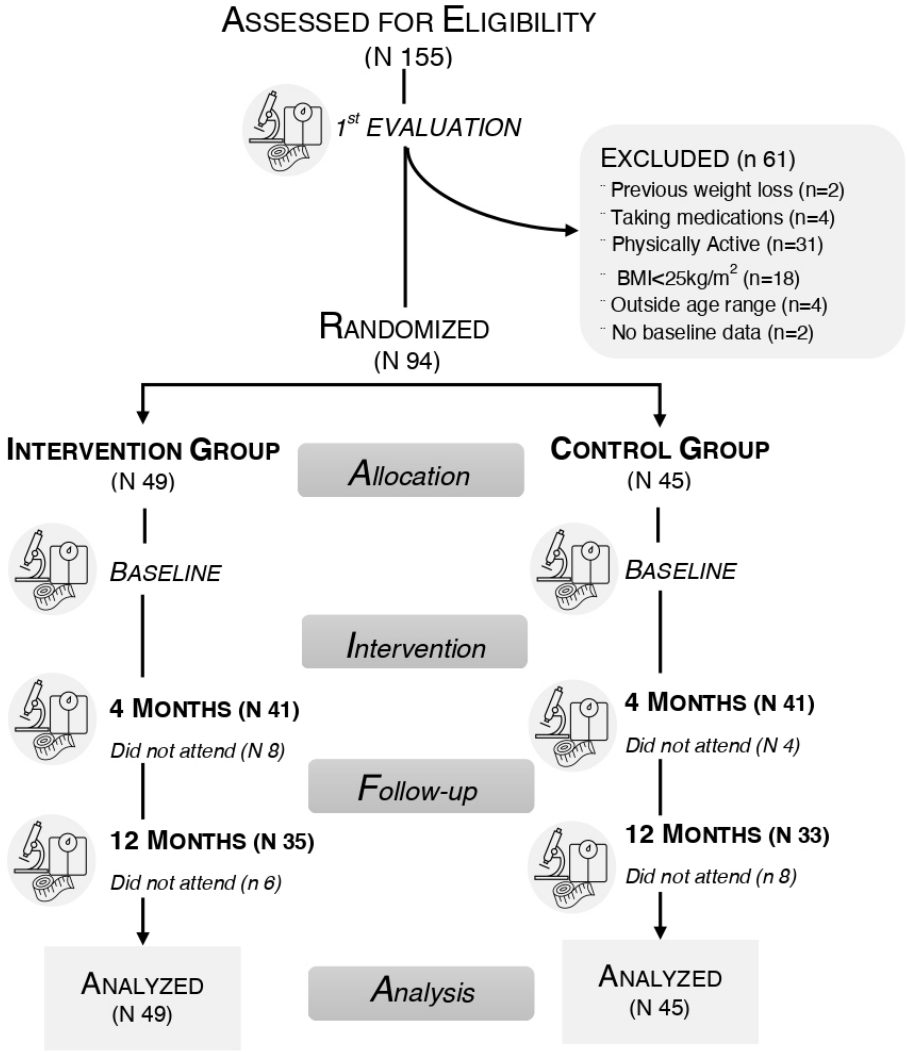

Figure 3.1. Schematic description of the Champ4life project (Silva et al., 2021).

The programme was effective in reducing not only weight, but also total and abdominal fat mass, with a relative preservation of the fat-free mass at the end of the project. Participants of the IG also showed improvements in cardiovascular risk markers, quality-of-life dimensions, and other secondary outcomes (**figure 3.2.**).

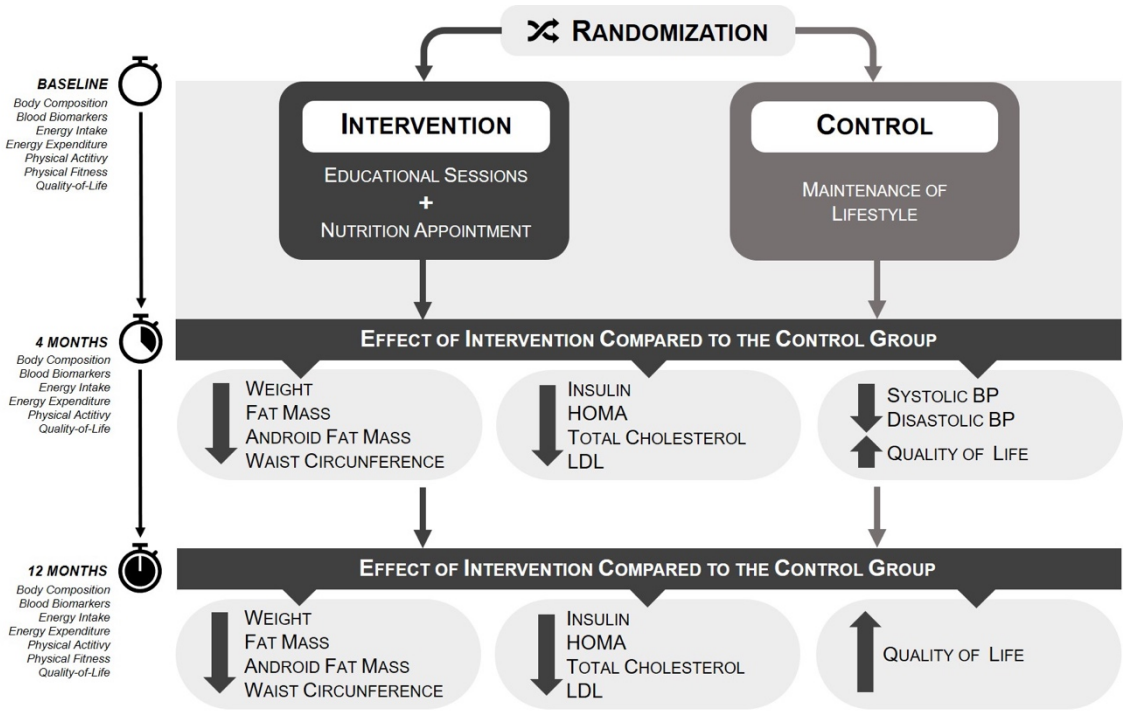

Figure 3.2. Main results of the Champ4life project (Silva et al., 2021).

Legend: BP – Blood pressure, LDL – Low density lipoprotein, HOMA – Homeostatic model assessment

A detailed description of the study protocol and the main results of this project were already published elsewhere (Silva et al., 2021; Silva et al., 2020).

3.2. Body composition measurements

Body composition measurements were performed at three time points: Baseline, after the active weight loss phase (4 months) and after the 8-months of follow up (12 months).

Anthropometry

Weight and height were measured with the participants in bathing suits and no shoes to the nearest 0.01 kg and 0.1 cm, using a weight scale and a stadiometer (Seca, Hamburg, Germany), respectively. BMI was calculated as weight (kg) divided by the square of the

height (m) and the cutoffs of the World Health Organization (WHO) were used (Weir CB & A., [Updated 2019 Apr 20].).

Dual-Energy X-ray Absorptiometry

Total FM and FFM were assessed by dual-energy X-ray absorptiometry (DXA; Hologic Explorer-W, Waltham, MA, USA), according to the established protocols described elsewhere (Park et al., 2002). The calibration procedures were performed according to the manufacturer's instructions (Lewiecki et al., 2016). A whole-body scan was performed, and the attenuation of X-rays pulsed between 70 and 140kV 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 determined at the android region, by identifying a specific region of interest within the analysis program. The specific DXA region of interest (ROI) was defined as follows: from the upper edge of the second lumbar vertebra (approximately 10 cm above the L4 to L5) to above the iliac crest and laterally encompassing the entire breadth of the abdomen, and thus determining total abdominal FM. The reliability of the measurements were tested by performing a test–retest on 10 participants, where the coefficient of variations in our laboratory for FM, FFM, and abdominal FM (android region) were 1.7%, 0.8%, and 0.01%, respectively (Pimenta et al., 2013; Santos et al., 2013). All the assessments (before and after the intervention) were performed by the same professional.

3.3. Calculation of energy balance (EB)

In order 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:

$$ES_{(kcal/d)} = EI_{(kcal/d)} - EE_{(kcal/d)}$$

It is recognized that EB is negative 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. ES 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 (Merril; & Watt.) and FFM (Dulloo & Jacquet, 1999), the following equation was applied:

$$ES_{(kcal/d)} = 1020\frac{\Delta FFM}{\Delta t} + 9500\frac{\Delta FM}{\Delta t}$$

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

3.4. Energy expenditure measurements

Resting Energy Expenditure (REE)

Measured REE

Measured REE (mREE) was obtained in the morning when fasted (7.00–10.00 a.m.), in a room maintained at an environmental temperature of approximately 22ºC and humidity of 40-50%. The MedGraphics CPX Ultima indirect calorimeter (MedGraphics Corporation, Breezeex Software, Italy) was used to measure breath-by-breath oxygen consumption ($\dot{V}O2$) and carbon dioxide production ($\dot{V}CO2$) 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 were asked to rest in a supine position for 15 minutes, covered with a blanket. The calorimeter device was then

attached to the mask, and breath-by-breath measurements of V̇O2 and V̇CO2 were collected for 30 minutes, with a total test duration of 45 minutes.

The first and the last 5 min of data collection were discarded. Steady state intervals were defined as 5-minute periods with ≤10% CV for V̇O2 and V̇CO2 and Respiratory Exchange Ratio between 0.7 and 1.0 (Compher et al., 2006). The mean V̇O2 and V̇CO2 of 5 min steady states was used in Weir equation (Weir, 1949) and the period with the lowest REE was considered for data analysis.

Predicted REE

REE was also predicted (pREE) by creating a predictive equation using baseline characteristics of the Champ4life participants as independent predictors. The independent predictors were FM and FFM and, for some equations, age and sex were also included. For study 2 (chapter 5), pREE was also assessed 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 (Hayes et al., 2002).

Physical Activity (PA, min/day)

PA was objectively measured using a tri-axial accelerometer (ActiGraph GT3X+, Pensacola, FL). Participants were instructed to wear the accelerometer on the right side of the hip for 7 consecutive days, removing it only during sleep and water-based activities (e.g., bathing and swimming). The accelerometers were initialized on the morning of the assessment day and data were recorded in 15-s epochs and reintegrated into 60-s epochs and using a frequency of 100Hz. Periods of at least 60 consecutive minutes of zero counts were considered as non-wear time. A valid day was defined as having ≥600 min of monitor wear per day. Only participants with at least three valid days (with at least one weekend-day) were included in the analysis. Levels of PA were expressed as

minutes per day and classified according the proposed PA cut points: as sedentary, <100 counts/min [≤1.5 metabolic equivalent of task (METs)]; light-intensity PA, 100–2019 counts/min (1.5-2.9 METs); moderate-intensity PA, 2020–5998 counts/min (3–5.9 METs); vigorous-intensity PA, ≥5999 counts/min (≥6 METs) (Troiano et al., 2008). The time spent in different levels of PA, excluding the time spent in exercise, was considered to determine NEPA levels. By contrast, the time excluded for NEPA analysis plus registered information from structured PA in which the participants did not use the accelerometer (e.g., water-based activities) was used to determine overall levels EPA. Participants were asked to record daily waking and sleeping hours, as well as the timings and reasons for not using the accelerometer.

Exercise-induced Energy Expenditure (EiEE, kcal/d) and Non-Exercise Activity Thermogenesis (NEAT, kcal/d)

The caloric expenditure of both structured and unstructured PA was calculated from Freedson Combination' 98 algorithm (Sasaki et al., 2011), which considers the Work-Energy Theorem and the Freedson' 98 equation to calculate EE under 1951 and above 1952 counts, respectively. The EE of NEPA (i.e., NEAT) was calculated by applying the algorithm over the time spent in different levels of PA excluding time spent in exercise. On the other hand, the EE of exercise (EiEE) was assessed from the combination of the data excluded in the NEAT analysis and additional data of PA that participants reported when the accelerometer was not used. The EiEE that was not recorded with the accelerometer was calculated using specific PA METs of the 2011 Compendium of Physical Activities (Ainsworth et al., 2011).

Total Daily Energy Expenditure (TEE)

Total EE was estimated as:

$$\text{total EE}_{(\text{kcal/d})} = \text{REE}_{(\text{kcal/d})} + \text{NEAT}_{(\text{kcal/d})} + \text{EiEE}_{(\text{kcal/d})} + \text{TEF}_{(\text{kcal/d})},$$

As the TEF is assumed to accounts for 10% of total EE (Weststrate, 1993), total EE was estimated as the sum of REE, NEAT and EiEE, divided by 0.9.

3.5. Adaptive thermogenesis assessment

AT was assessed through different approaches based on previous studies, such as:

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 (Byrne et al., 2018);

B) AT was assessed simply by subtracting pREE from mREE (indirect calorimetry), at the specific time points (after WL and after WL maintenance) (Byrne et al., 2018; Martins et al., 2020; Thom et al., 2020);

C) AT was calculated as: a) subtracting pREE from mREE after WL or after WL maintenance, b) subtracting pREE from mREE at baseline and therefore subtracting the result of b) from the result of a) (Browning et al., 2017; Ten Haaf et al., 2018);

D) %AT was calculated as 100 × [(mREE / pREE) – 1) after WL or after WL maintenance and therefore AT is assessed as (%AT / 100) x mREE at baseline (Borges et al., 2019; Silva et al., 2017).

For all situations, negative values indicate a higher-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) (Thomas et al., 2012).

3.6. Energy intake measurements

Food Diaries

Three-day food records (including one-weekend day) was collected to characterize macronutrient composition of the diet in the 3 assessment times using a software package (Food Processor SQL, ESHA Research, Salem, OR, USA) by a registered dietitian. Comprehensive written instructions using specific guidelines were given to all participants in face-to-face debriefing sessions, including pictures of portion sizes used for a better recording of food intake, and examples of common errors in recording dietary intake. At the end of the recording period, a registered dietitian reviewed the record with the participant to clarify potential omissions and ambiguities and to assure that additional information is provided to improve the accuracy of the macronutrient composition of the diet.

Intake-balance method

EI was also estimated by the "intake-balance method" (Rosenbaum et al., 1996). This method has been previously validated (Racette et al., 2012; Shook et al., 2018) and has been shown to provide valid estimated of EI through changes in body energy stores such FM and FFM, together with total EE. The following equation was used:

$$EI_{(kcal/d)} = EE_{(kcal/d)} - ES_{(kcal/d)},$$

Where EE represents the total daily energy expenditure measured by accelerometry and the ES the energy stores (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 changes in ES = 0, and therefore EI = EE.

3.7. Eating behavior

Food reward

To measure food preferences and food reward, including explicit liking/wanting and implicit wanting, the Leeds Food Preference Questionnaire (LFPQ) (Finlayson et al., 2008; Finlayson et al., 2007) was used. The LFPQ consists of two sub-tasks that are counterbalanced within the test. The first sub-task involves an explicit evaluation of food images randomly presented from a pre-validated array of photographs using VAS. The second sub-task requires participants to quickly choose between paired combinations of food images from different categories (Oustric et al., 2020). Participants were able to practice the two tasks before starting the questionnaire.

Two composite scores – Fat Bias and Taste Bias – were computed for each component of food reward (explicit liking and wanting and implicit wanting). Fat Bias score was calculated by subtracting the mean for low-fat scores from the mean for high-fat scores, while Taste Bias was calculated by subtracting mean savory values from mean sweet values. In both cases, a higher score indicates a stronger preference for high fat/sweet foods compared to low fat/savory foods, respectively (Oustric et al., 2020).

Intuitive eating

Intuitive eating was evaluated using the Intuitive Eating Scale – 2 (IES-2) (Tylka & Diest, 2013). IES-2 is a 23-item questionnaire that assesses the extent to which individuals eat in response to physiological eating cues, comprising 4 subscales: eating for physical rather than emotional reasons (Cronbach's α =0.92), unconditional permission to eat (Cronbach's α=0.81), reliance on hunger and satiety cues (Cronbach's α=0.85), and body-food choice congruence (Cronbach's α =0.83) (Tylka & Diest, 2013). Participants respond to the questionnaire "For each item, please check the answer that best characterizes your eating attitudes or behaviors" on a 5-point Likert scale ranging from 1 ("strongly disagree") to 5 ("strongly agree").

3.8. Blood samples

Blood samples were collected according to the standard procedures by venipuncture from the antecubital vein into ethylenediaminetetraacetic 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 -80ºC for posterior analyses.

Measurements of glucose and lipid profiles, including total cholesterol, high-density lipoprotein (HDL), and low-density lipoprotein (LDL), were performed in serum samples using colored enzymatic tests, in an automated analyzer (Cobas Integra 400, Roche Diagnostics, Portugal). Glycated hemoglobin (HbA_{1C}) was assessed by high-performance liquid chromatography in an autoanalyzer (HA 8160, A.Menarini Diagnostics, Portugal). The thyroid panel [including Thyroid-Stimulating Hormone (TSH) free triiodothyronine (FT3) and free thyroxine (FT4)] and insulin were assessed by immunoquimioluminescence (ECLIA) in a different automated analyzer (Cobas e411, Roche Diagnostics, Portugal). Serum levels of leptin were assessed by ELISA (enzyme-linked immunosorbent assay) by using commercial kits (DIAsource ImmunoAssays, Belgium).

3.9. Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics (SPSS Inc., an IBM Company, Chicago, Illinois, USA) version 25.0 (studies 2 and 3) or 27.0 (Studies 4, 5 and 6). The main study (Silva et al., 2021) was originally powered on changes in total body fat assessed by DXA (using the software GPower version 3.1.9.2). A type I error of 5% and a power of 80% were considered to detect an effect size of 0.58 for statistically significant differences in total body fat as reported elsewhere (Huseinovic et al., 2016).

The normality of the variables was tested using the Kolmogorov-Smirnov test. Data was presented as mean (SD), except when linear mixed models were used, being presented

as estimated marginal means, standard error (SE) and 95% confidence intervals. Statistical significance was set at a two-sided $p < 0.05$ (two-tailed).

Changes in body composition and other variables (appetite-related hormones) 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 (intervention vs control), time [baseline—0 months, post-intervention—4 months and after follow-up – 12 months (for studies 3, 4 and 6)] and treatment-by-time interaction. The covariance matrix for repeated measures within subjects over time was modeled as compound symmetry.

Model residual distributions were examined graphically and by using the Kolmogorov-Smirnov test. Differences-in-differences (DiD) were calculated between the IG and CG throughout time, calculated as the difference between changes for IG and changes for CG.

For study 2 and 3 (chapter 5 and 6), baseline differences between IG and CG were assessed by independent two sample t test. To test the significance for AT (if it is different from zero), one-sample t tests were performed.

The typical error (TE) was calculated for AT (study 3) and for WL and NEPA (Study 4), by dividing the SD of the changes for the CG by $\sqrt{2}$, representing the technical error of measurement as well as the within-subject variability (study 3). For study 4, the TE was used to classify participants as “responders” and “non responders”, where a “responder” is considered an individual who showed beneficial changes that were greater than TE (Swinton et al., 2018).

Considering study 4 (chapter 7), chi-square tests were performed to compare the response rates between IG and CG. NEAT was predicted by performing multiple linear regression models with the baseline characteristics of all participants to generate

equations to predict NEAT. AT in NEAT was calculated according to the approach c) in the "adaptive thermogenesis assessment" section, namely:

$$\mathbf{AT_{(kcal/d)}} = (\text{measured NEAT}^{4mo/12mo}{}_{(kcal/d)} - \text{predicted NEAT}^{4mo/12mo}{}_{(kcal/d)}) - (\text{measured NEAT}^{baseline}{}_{(kcal/d)} - \text{predicted NEAT}^{baseline}{}_{(kcal/d)}),$$

The interindividual differences were calculated in study 4 and 5 by calculating the SD of individual response (SD_{IR}) according to Atkinson and Batterham (Atkinson & Batterham, 2015):

$$SD_{IR} = \sqrt{{SD_{IG}}^2 - {SD_{CG}}^2}$$

The smallest worthwhile change (SWC) was calculated by multiplying 0.2 by the SD of CG at baseline (Hecksteden et al., 2018). A SD_{IR} > SWC suggests meaningful interindividual differences, while a SD_{IR} < SWC insinuates that interindividual differences are irrelevant (Atkinson & Batterham, 2015). Ninety-five percent confidence intervals (95%CI) were estimated by using the following equation (Hopkins, 2015):

$$95\%CI = \sqrt{{SD_{IR}}^2 \pm 1.96 \times \sqrt{2 \times \left(\frac{{SD_{IG}}^4}{n_{IG} - 1} + \frac{{SD_{CG}}^4}{n_{CG} - 1}\right)}}$$

Pearson's correlations were performed to examine the association between AT and body composition, blood samples and adherence to the diet (study 3), between EE components and body composition (study 5) and between changes in food reward/intuitive eating domains and changes in body composition outcomes (study 6)

3.10. References

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CHAPTER 4

DOES ADAPTIVE THERMOGENESIS OCCUR AFTER WEIGHT LOSS IN ADULTS?

A SYSTEMATIC REVIEW [1]

[1] **Nunes, C. L.,** Casanova, N., Francisco, R., Bosy-Westphal, A., Hopkins, M., Sardinha, L. B., & Silva, A. M. (2022, Feb 14). Does adaptive thermogenesis occur after weight loss in adults? A systematic review. Br J Nutr, 127(3), 451-469. https://doi.org/10.1017/S0007114521001094

DOES ADAPTIVE THERMOGENESIS OCCUR AFTER WEIGHT LOSS IN ADULTS? A SYSTEMATIC REVIEW

Catarina L. Nunes, Nuno Casanova, Ruben Francisco, Anja Bosy-Westphal, Mark Hopkins, Luís B. Sardinha, Analiza M. Silva

4.1. ABSTRACT

Adaptive thermogenesis (AT) has been proposed to be a compensatory response that may resist weight loss (WL) and promote weight regain. This systematic review examined the existence of AT in adults after a period of negative energy balance (EB) with or without a weight stabilization phase. Studies published until 15 May 2020 were identified from PubMed, Cochrane Library, EMBASE, MEDLINE, SCOPUS and Web of Science. Inclusion criteria included statistically significant WL, observational with follow-up or experimental studies, age > 18y, sample size ≥10 participants, intervention period ≥ 1week, published in English, objective measures of total daily energy expenditure (EE) (TDEE), resting EE (REE) and sleeping EE (SEE). The systematic review was registered at PROSPERO (2020 CRD42020165348). A total of thirty-three studies comprising 2528 participants were included. AT was observed in twenty-seven studies. Twenty-three studies showed significant values for AT for REE (82·8 %), four for TDEE (80·0 %) and two for SEE (100 %). A large heterogeneity in the methods used to quantify AT and between subjects and among studies regarding the magnitude of WL and/or of AT was reported. Well-designed studies reported lower or non-significant values for AT. These findings suggest that although WL may lead to AT in some of the EE components, these values may be small or non-statistically significant when higher-quality methodological designs are used. Furthermore, AT seems to be attenuated, or non-existent, after periods of weight stabilization/neutral EB. More high-quality studies are warranted not

only to disclose the existence of AT but also to understand its clinical implications on weight management outcomes.

Key-words*:* Energy balance, metabolic adaptation, metabolic compensations, behavioral compensations, weight loss.

4.2. INTRODUCTION

Weight loss (WL) occurs when a negative energy balance is sustained over time (Hall & Guo, 2017). However, despite its apparent simplicity, energy balance represents a complex and dynamic system in which its components (i.e., energy intake (EI) and energy expenditure, (EE)) fluctuate over time (Edholm et al., 1970) and change in response to perturbations in either side of the equation (Casanova et al., 2019; Melby et al., 2017).

Although a clinically meaningful WL is usually achieved, levels of recidivism and weight regain are high (Greaves et al., 2017; Wadden et al., 2011). It has been postulated that difficulties in maintaining a reduced body weight arise not only from a lack of adherence to dietary and physical activity (PA) recommendations (Heymsfield et al., 2007), but also due to metabolic, psychological and behavioral compensatory responses that occur during periods of negative energy balance. Some of these proposed compensatory responses include reductions in EE (Thomas et al., 2012), PA behaviors (Levine et al., 1999), and increases in EI (Dulloo et al., 2012). These compensatory responses may act to undermine adherence to the diet and/or PA recommendations, prompting an individual to regain the weight lost.

Adaptive thermogenesis (AT) represents a greater than predicted decrease in EE beyond what would be predicted from the changes in fat mass (FM) and fat-free mass (FFM) occurring during WL (Dulloo et al., 2012; Major et al., 2007). It has been postulated to be a compensatory response that resists WL and promotes weight regain (Fothergill et al., 2016; Johannsen et al., 2012; Tremblay et al., 2007; Tremblay et al., 2013), but

its influence on longer-term weight management has been recently questioned (Martins et al., 2020). AT in resting EE (REE) has been previously documented in lifestyle (Bosy-Westphal et al., 2009; Bosy-Westphal, Schautz, et al., 2013; Byrne et al., 2018; Camps et al., 2013, 2015; de Jonge et al., 2012; Doucet et al., 2001; Dulloo & Jacquet, 1998; Goele et al., 2009; Gomez-Arbelaez et al., 2018; Karl et al., 2015; Martins et al., 2020; McNeil et al., 2015; Müller et al., 2015; Nymo et al., 2018; Pourhassan et al., 2014; Rosenbaum & Leibel, 2016; Thom et al., 2020) and surgical (Bettini et al., 2018; Browning et al., 2017; Carrasco et al., 2007; Coupaye et al., 2005; Tam et al., 2016; Wolfe et al., 2018) interventions. However, some studies have reported contrasting findings as they have not observed a significant value for AT (Bosy-Westphal, Schautz, et al., 2013; Doucet et al., 2001; Hopkins et al., 2014).

Several narrative reviews examining the topic of AT in REE have been previously published (Casanova et al., 2019; Dulloo et al., 2012; Major et al., 2007; Müller & Bosy-Westphal, 2013; Muller et al., 2016; Rosenbaum & Leibel, 2010; Tremblay et al., 2007; Tremblay et al., 2013; Trexler et al., 2014). However, no systematic reviews have been conducted specifically on this topic, and some of these narrative reviews have also focused exclusively on the occurrence of AT in REE during lifestyle interventions.

Therefore, this is the first systematic review examining the occurrence of AT in resting energy expenditure (REE), total daily energy expenditure (TDEE), and sleeping energy expenditure (SEE) during or after WL induced by diet and/or exercise, bariatric surgery or pharmacological therapy, followed by weight stabilization in adults.

4.3. METHODOLOGY

This systematic review was conducted according to the PRISMA guidelines (Liberati et al., 2009) and was registered on PROSPERO (PROSPERO 2020 CRD42020165348).

Eligibility criteria

This systematic review included scientific articles published in peer-reviewed journals on or before May 15th, 2020, that reported WL induced by diet and/or exercise, bariatric surgery or pharmacological therapy, and reported values for AT. All studies were evaluated according to the following inclusion criteria: 1) The study should include an intervention aimed to reduce weight that resulted in a statistically significant weight loss; 2) Observational with follow-up or experimental study; 3) Conducted in adults (>18 years); 4) A total sample size of at least 10 participants; 5) Intervention period of at least 1-week; 5) Published in English; 6) Objective measures of total daily EE, REE and SEE (indirect calorimetry, metabolic chamber, doubly labeled water, accelerometer and combined heart rate and motion sensor); and 7) Objective measures of FM and FFM (Dual-energy X-ray Absorptiometry, DXA; Air displacement plethysmography; Bioelectrical impedance analysis; and/or multicompartment molecular models (e.g. 4-compartment models, including combination of several techniques such as DXA, isotope dilution and air displacement plethysmography). Articles were excluded if they did not meet all of the inclusion criteria and/or had an exclusion criterion, such as the inclusion of participants with the following: 1) Cancer; 2) Thyroid diseases; 3) Diabetes; 4) Pregnancy or breastfeeding; 5) Total parenteral nutrition; 6) Organ transplant; 7) Acute illnesses, such as infections or traumatic injury and 8) Other medical conditions and/or the use of medications known to affect energy balance.

Information Sources and Search Strategy

A comprehensive search of peer-reviewed articles published until May 15th, 2020 (including online ahead of print publications) was conducted in the following electronic databases: PubMed, Cochrane Library, EMBASE, MEDLINE, SCOPUS and Web of Science. Searches included all meaningful combinations of the following sets of terms: i) terms concerning the intervention(s) of interest (e.g. diet or caloric restriction, bariatric surgery, physical activity or exercise, pharmacotherapy); ii) terms representing the

outcomes of interest (e.g. adaptive thermogenesis, metabolic adaptation, energy metabolism, resting energy expenditure, metabolic compensation); iii) terms representing the population of interest (e.g. adults); and iv) terms representing body composition components of interest (e.g. fat mass, fat-free mass, lean mass). Manual cross-referencing of the literature cited in prior reviews and hand-searches of the content were conducted to strengthen the systematic review. A search strategy example for PubMed is provided as a supplementary file (Supplementary file 1).

Study selection and data processing

Based on the initial abstracts retrieved, duplicates were removed, and 25 were added from manual searching. Abstracts identified from the literature searches were screened for potential inclusion by two authors (C.L.N. and N.C.) and a third author (R.F.) when there was a disagreement between the first two. One-hundred and two articles were assessed for eligibility and 33 were included in this review. Data extraction was conducted by C.L.N. according to the PRISMA statement for reporting systematic reviews (Liberati et al., 2009) and included information about each article, such as: authors, year, study design, participants' information (e.g. demographics and BMI), type of intervention (diet only, exercise only, diet + exercise, bariatric surgery or pharmacological), length of active intervention and/or the duration of follow up, methodology, outcome measures and main results.

Study quality and Risk of Bias

To assess the study quality, the Quality Assessment Tool for Quantitative Studies checklist was used (Armijo-Olivo et al., 2012). This procedure was performed by two authors (C.L.N. and R.F.). The checklist evaluates six key methodological domains: study design, blinding, representativeness (selection bias), representativeness (withdrawals/dropouts), confounders and data collection. From the interpretation of the scores of each section (classified as strong, moderate or weak methodological quality),

an overall score was given to each article. The quality assessment for each study is presented as supplementary material (Supplementary file 2).

4.4. RESULTS

A total of 1332 articles were retrieved by the aforementioned databases. From those, 612 duplicates were removed, and 25 articles identified through other sources were added, leading to a total of 745 articles for title and abstract screening. Six hundred and forty-three articles were excluded during title and abstract screening and 102 full texts were further assessed for eligibility. In this phase, 69 were excluded (Supplementary file 3) and 33 were included in this systematic review. The PRISMA flow chart of the study selection is presented in **Figure 1.**

The studies included in this review comprised 2528 participants and were divided by each component of EE as follows:

- Resting energy expenditure (REE) – 29 studies;
- Total daily energy expenditure (TDEE) – 7 studies;
- Sleeping energy expenditure (SEE) – 2 studies;

Some articles included more than 1 intervention type and/or assessed AT in more than one EE component.

From the included studies, 6 (20.7%) were randomized controlled trials (RCT), 2 (6.9%) were randomized trials without a control group (RT), 12 (41.4%) were non-randomized trials (NRT), 3 (10.3%) were retrospective observational (RO) studies and 10 (34.5%) were considered prospective observational (PO) studies. A summary of the results reported in each study, divided by study type and %WL is presented in **table 4.1.**

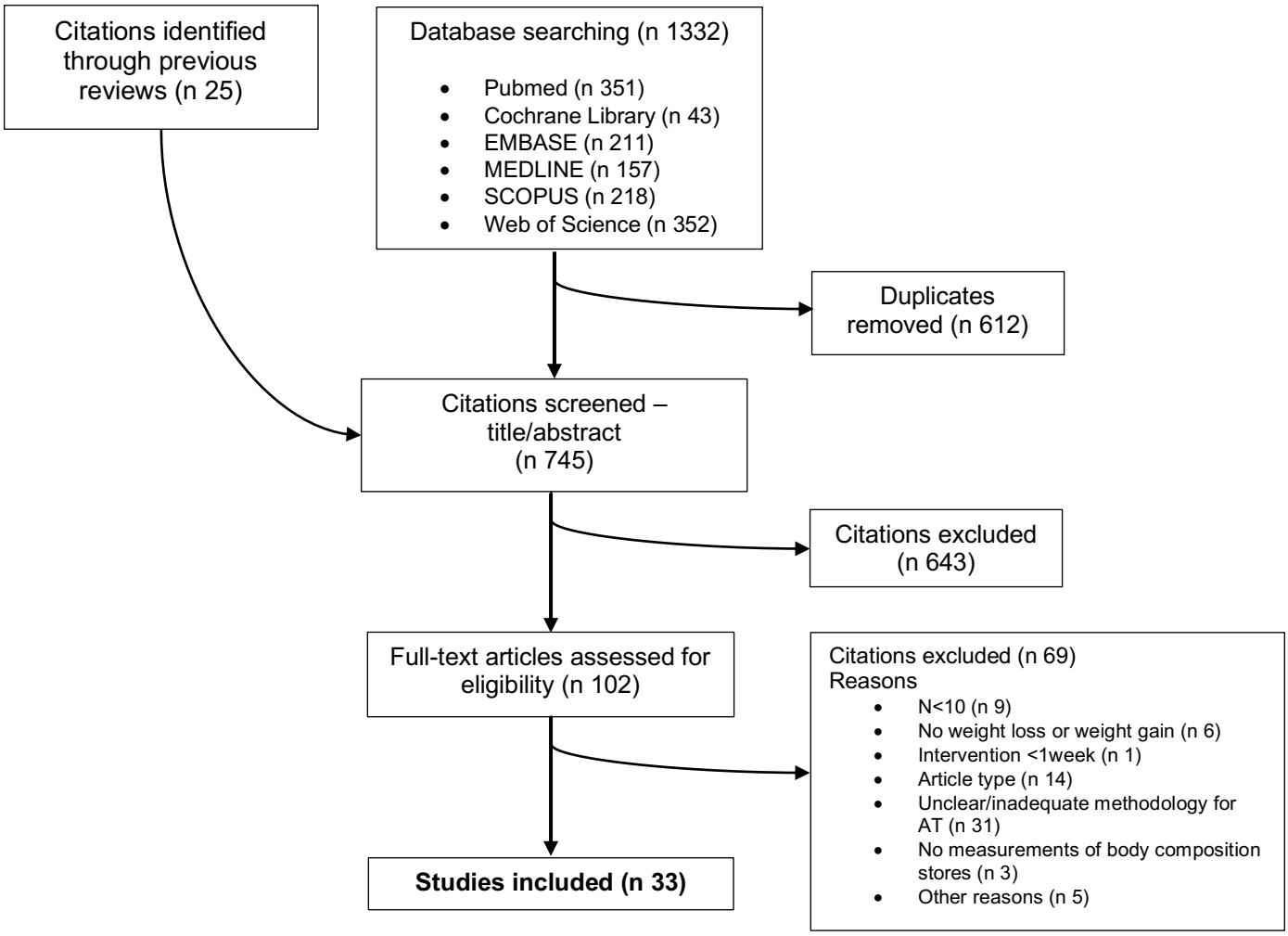

Figure 4.1. Flow diagram of studies' selection.

Table 4.1. Summary of the results

	%WL		REE		TDEE		SEE
			WL	WM	WL	WM	WL
RCT	<10%	(Marzullo et al., 2018)	ⓓ				
		(de Jonge et al., 2012)	ⓓ				
		(Karl et al., 2015)	ⓓ	✕			
	10 – 15%	(Doucet et al., 2001)	ⓓ	ⓓ Men ✕ Women			
		(Byrne et al., 2018)	ⓓ	✕			
		(Redman et al., 2009)			ⓓ CR and LCD ✕ Exercise	✕ (CR)	
		(Lecoultre et al., 2011)			ⓓ CR and LCD ✕ Diet and Exercise		ⓓ (CR)
NRT	<5%	(Hopkins et al., 2014)	✕				
		(Bosy-Westphal et al., 2009)	ⓓ				
	5 a 10%	(Müller et al., 2015)	ⓓ				
		(Camps et al., 2013)	ⓓ				
		(Goele et al., 2009)	ⓓ				
		(Camps et al., 2015)	ⓓ				
	10-20%	(Bosy-Westphal, Schautz, et al., 2013)		ⓓ (weight regainers)			
		(Thom et al., 2020)	ⓓ				
		(Nymo et al., 2018)	ⓓ				
	>20%	(Gomez-Arbelaez et al., 2018)	✕				
		(Rosenbaum & Leibel, 2016)	ⓓ				
		(Dulloo & Jacquet, 1998)	ⓓ				
RT	<10%	(McNeil et al., 2015)	ⓓ				
Observational	<10%	(Ten Haaf et al., 2018)	ⓓ				
	10-20%	(Pourhassan et al., 2014)	✕				
		(Marlatt et al., 2017)			✕		ⓓ
		(Martins et al., 2020)	ⓓ				
		(Coupaye et al., 2005)	✕				
	20-30%	(Wolfe et al., 2018)	ⓓ	✕	ⓓ	✕	
		(Tam et al., 2016)	ⓓ	✕			
		(Browning et al., 2017)	✕				
		(Novaes Ravelli et al., 2019)			ⓓ	✕	
	>30%	(Bettini et al., 2018)	ⓓ				
		(Carrasco et al., 2007)	ⓓ				
		(Johannsen et al., 2012)	ⓓ				
		(Fothergill et al., 2016)	ⓓ	ⓓ			

Legend: WL – Weight loss; WM – Weight Maintenance; CR – Caloric restriction; LCD – Low-calorie diet; ⓓ reported a higher-than-expected decrease for REE/TDEE/SEE (AT), ✕ Did not report AT

Resting Energy Expenditure (REE)

A total of 29 studies reporting changes in REE were included in this review (Bettini et al., 2018; Bosy-Westphal et al., 2009; Bosy-Westphal, Schautz, et al., 2013; Browning et al., 2017; Byrne et al., 2018; Camps et al., 2013, 2015; Carrasco et al., 2007; Coupaye et al., 2005; de Jonge et al., 2012; Doucet et al., 2001; Dulloo & Jacquet, 1998; Fothergill et al., 2016; Goele et al., 2009; Gomez-Arbelaez et al., 2018; Hopkins et al., 2014; Johannsen et al., 2012; Karl et al., 2015; Martins et al., 2020; Marzullo et al., 2018; McNeil et al., 2015; Müller et al., 2015; Nymo et al., 2018; Pourhassan et al., 2014; Rosenbaum & Leibel, 2016; Tam et al., 2016; Ten Haaf et al., 2018; Thom et al., 2020; Wolfe et al., 2018) (**table 4.2**), divided in: RCT=4 (13.8%); NRT=12 (41.4%); RT=2 (6.9%); PO=8 (27.6%); RO=3 (10.3%).

Table 4.2. Resting Energy Expenditure (REE)

Study	Study type	Sample	Intervention's description	Length + follow up	Measurements	AT definition and measurement	Results	AT
Diet-only intervention								
Martins et al, 2020	O (retrospective)	n=171 females BMI=28.3±1.3 kg/m^2 Age=35.2±6.3y 3 groups: Diet only Diet + aerobic training Diet + resistance training	Diet: ~3.3 MJ/d: 20–22% fat, 20–22% protein 56–58% CHO	2y follow up	Body composition: 4C model (BODPOD, DXA (DPX-L Lunar) and isotope dilution) REE: Indirect calorimetry (Delta Trac II)	**AT was tested with t-tests by comparing mREE with pREE.** pREE was achieved by a **predictive equation** (predictors: age, sex, race, FM and FFM) AT was measured after a 4-week period of weight stabilization	WL= −12.2 ± 2.6 kg (−15.7% ± 2.9%); No metabolic adaptation was seen at 1- and 2-y follow-up in all participants	AT= −226 ± 439 kJ/d AT is minimal when measurements are taken under conditions of weight stability
Thom et al 2020	NRT	N=15 females BMI=39.4± 4.3 Age=46.3±9.5y	Diet only: 3.5–3.7 MJ/d; 59% CHO, 13% fat, 26% protein, 2% fiber	6mo + 18mo follow up	Body composition: MRI; REE: Computerised open-circuit ventilated hood system (Oxycon Pro). Leptin, PYY, ghrelin, GLP-1 - ELISA kits	Sample-specific linear **regression equation** to predict REE (predictors: total adipose tissue - TAT (kg), skeletal muscle mass residuals (SMM) (kg) and age) AT is considered the **difference between measured and predicted REE + t-test** AT was measured immediately after WL	WL =−13.8 ± 6.3 kg (−13,5%); Significant reductions in TAT (-11.5 ± 4.9kg) with preservation of SMM. Reductions in Leptin and GLP-1. Increases in Ghrelin.	AT=−628 ± 678 kJ/d Large inter-individual variability in adaptive thermogenesis.
Nymo et al, 2018	NRT	N=31 (18 males) BMI = 36.7±4.5 kg/m^2 Age = 43±10y	Diet only: VLCD 2.3-2.8MJ/d 42 % CHO, 36% PRO, 18% Fat and 4% fiber.	8 weeks + 4 weeks follow up	Body Composition: BodPod; REE: Indirect Calorimetry (Vmax Encore 29N); PA - Armbands (BodyMedia); Exercise-Induced	REE was predicted by an **equation** using FM, FFM, sex, age and height. AT was present when **mEE** (REE or EIEE) **was lower than pEE**, given the body composition (FM and FFM) measured at each time point. AT was measured immediately after WL and after a 4-week period of weight stabilization.	WL: (week 9) -18.7±4.1kg FM and FFM was reduced by 5% and 9% WL in all participants, respectively.	Evidence of AT-REE only after 10%WL AT = -465 (SEM 691) kJ/d
Gomez-Arbelaez et al, 2018	NRT	N=20 (8 males) BMI = 35.5±4.4 kg/m^2 Age = 47.2±10.2y	Diet only: ketogenic diet; VLCD (2.5-3.3MJ/day), <50g/d HC and only 10g olive oil per day. Protein 0.8-1.2g/kg/day	4mo	Body composition: DXA (GE healthcare lunar) and MF-BIA (InBody 720) REE: Indirect calorimetry (FitMate PRO);	pREE predicted through an **equation** using baseline values of FM and FFM. **AT = mREE-pREE** AT was measured immediately after WL	WL: -20.7±6.9; (~-21%) Significant reductions for FM and FFM. Severe reductions for leptin.	Non-significant AT.
Byrne et al, 2018	RCT	N=36 males Age: 25-54y. 2 groups: - Continuous energy restriction (CER) n=19 BMI = 34.3±3.0 kg/m^2 Age = 41.2±5.5y - Intermittent energy restriction (IER) n=17 BMI 34.1±4.0 kg/m^2 Age = 39.5±8.4y	Diet only: ~67% of individual weight maintenance energy requirements IER: 2 weeks of ER + 2 weeks EB CER: Continuous ER	CER: 28weeks IER: 42weeks + 8 weeks weight maintenance	Body Composition: Air displacement plethysmography (BodPod). REE - Ventilated hood system (TrueOne 2400 Metabolic System).	pREE calculated using 3 approaches: Adjustment for changes in FM and FFM; Group-specific equations using baseline data in function of age, FM and FFM; Equation published by Muller et al (49). AT was achieved by comparing mREE and pREE. AT was measured after WL	CER: WL: -9.2±3.7kg (~-8.4%); IER: WL: -14.1±5.6kg (~-12.9%) Significant reductions for FM in both groups.	Significant AT only for CER group (~-209kJ/d). No information about AT after weight maintenance phase.

Table 4.2. Continued

Study	Study type	Sample	Intervention's description	Length + follow up	Measurements	AT definition and measurement	Results	AT
Rosenbaum et al, 2016	NRT	N=17 (3 males) BMI = 44.6 ±11.2 kg/m^2 Age = 28.4±8.8y	Diet only 3.3 MJ/d liquid formula diet; 40% fat, 45% CHO, 15% protein + mineral supplementation	7-13weeks to achieve 10% WL + 8-14weeks to achieve 20%	Body composition: DXA; TEE - Doubly labeled water REE - Indirect calorimetry (beckman MMC Horizon Metabolic Cart).	Regression equation to predict REE using weight, FFM and FM. The **observed-minus-predicted values** were test if they differed from zero to calculate AT. AT was measured after 10% and 20% WL	Significant WL (~80% were fat). Reductions in FM but not in FFM.	10%WL = -795±870kJ/d 20%WL = -778±983 kJ/d
Müller et al, 2015	NRT	N=32 men BMI: 20.7-29.3 kg/m^2 Age: 20–37 y	Diet-only: CR: 50% of energy needs. Protein intake: 49±6g/d. food and drinks provided	6weeks (1week overfeeding, 3weeks CR, 2weeks overfeeding)	Body composition: MRI (ECHOMRI-AH) REE: Indirect Calorimetry (Vmax Spectra, SensorMedics); PA: 24h heart rate and accelerometry.	pREE was based on the **sum of 7 body compartments multiplied by their corresponding specific tissue respiration rates**. AT =**REEadj at caloric restriction - REEadj after CR** AT was measured after WL and after refeeding.	WL= -4.22±0.873kg (~-8%); Decreases in FM (~-18%) Leptin decreased. No associations between hormones and AT.	AT= -301±481kJ/d. Considerable between-subject variance in AT and weight- loss. Non-significant after refeeding
McNeil et al, 2015	RT w/ no CG	N=93 women BMI = 32.1±4.3 kg/m^2 Age = 58.1±4.8y 2 groups: Diet-only (n=65) Diet + exercise (n=28)	Diet: REE x 1.4 and then ~3.3MJ was subtracted from this result. 30% lipids and 15%proteins. resistance training 3x week	6mo	Body composition: DXA (General Electric Lunar Prodigy) REE: indirect calorimetry TEE: doubly-labeled water	pREE by a multiple regression analysis using age, FFM, leptin and PYY. AT was achieved **by comparing pREE with mREE via a repeated-measures ANOVA.** AT was measured after WL.	Both interventions decreased weight and FFM. Diet only: WL=-4.8±4.6kg Diet + Exercise: WL=-6.7±4.5kg Leptin and PYY were not significant predictors of the differences between pREE and mREE.	Greater predicted vs. measured REE was noted post-intervention (data not shown, ~126kJ/d). This significant effect disappeared after correcting for the degree of caloric restriction.
Karl et al, 2015	RCT	N=91 (39 males) BMI = 28-38 kg/m^2 Age = 45-65y	Diet only: Phase 1 - 5weeks of weight maintenance 12.2 MJ/d with 48% CHO, 16% PRO and 36% fat Phase 2 - 4 different diets differed by its carbohydrate content: 55%, 60%, 70% or 80% CHO, 67% of phase 1 EI) Phase 3 – Weight maintenance.	22weeks (5weeks phase 1 + 12 weeks phase 2 + 5weeks phase 3) + 12mo ad libitum-diet follow-up period	Body composition: BODPOD; REE: portable metabolic cart (Deltatrac metabolic monitor, SensorMedica)	pREE for each phase was calculated by a regression model developed from baseline vales of age, sex, FM, FFM, and REE. AT was calculated as the **difference between mREE and pREE** for that phase. AT was calculated after WL and after weight maintenance phase.	The 4 groups lost weight (~-7,5%) ~80% WL was FM No difference in CHO content	Existence of AT after WL (-226kJ/d [95%CI: -314 kJ/d, -138kJ/d]) but not after 5weeks of weight stabilization.
Camps et al, 2015	NRT	N=82 (23 males) BMI = 31.9±3.0 kg/m^2 Age = 41±8y;	Diet-only: VLCD 2.1 MJ/d; 51.9g of protein, 50.2 g of carbohydrates and 6.9 g of lipids	8 weeks	Body composition: Siri's 3C Model; BodPod System. REE: open-circuit ventilated hood-system + Brouwer's formula. TEE - Doubly labeled water;	REE was predicted (REEp) by an equation using FM and FFM. AT was calculated as **REEm divided by REEp.** AT was calculated after WL	WL=-10.7 ± 4.1% Reductions in FM and FFM. Reductions in Leptin	mREE/pREE= 0.96±0.07. Six percent of the variation in REEm/REEp after the diet was explained by the decrease in leptin.

Table 4.2. Continued

Study	Study type	Sample	Intervention's description	Length + follow up	Measurements	AT definition and measurement	Results	AT
Pourhassan et al, 2014 *(information only about WL group)*	O (prospective)	N=30 BMI = 33.6 ± 5.4 kg/m^2 Age = 36.9±8.4y	Diet-only: Very low-calorie diet	6mo	Body composition: Fuller 4C model. (BodPod + deuterium dilution + DXA (QDR4500A Hologic Inc)); MRI REE - Indirect Calorimetry (Vmax Spectra 29n)	pREE from individual organ and tissue masses by using constant specific metabolic rate. AT was calculated as **REEm minus REEp.** AT was calculated after WL.	36% of the sample had significant WL (-11.2±4.9kg), which ~-72% was FM. Reductions in T3 and T4.	Non-significant AT (0.01 ± 0.93 MJ/d)
Camps et al, 2013	NRT	N=91 (22 males) BMI = 31.9±3.0 kg/m^2 Age = 40±9y	Diet-only: VLCD (2.1 MJ/d) 51.9 g PRO, 50.2 g CHO, 6.9 g lipids	8week + 44week follow up	Body composition - Siri's 3C model. BODPOD and deuterium diluition. REE - Open circuit ventilated hood system;	pREE was calculated through an equation using FM and FFM. AT= **mREE/ pREE.** AT was calculated after WL and after a weight maintenance period.	8weeks: WL = -9.6±4.1kg (~-10%) 52weeks: WL = -6.0±5.7kg (~-7%)	8 weeks: AT = 0.967 ± 0.007 52 weeks: AT = 0.979 ± 0.007
Bosy-Westphal et al, 2013	NRT	N=47 (11 males) 2 groups: Weight stable (n=20) Weight regainers (regain >30% of their weight) (n=27)	Diet-only: Low calorie diet (3.3 – 4.2 MJ/d)	13 ± 3 weeks	Body composition: BODPOD, MRI, DXA (Hologic); REE: Indirect calorimetry (Vmax Spectra 29n).	pREE was based on the sum of eight body compartments (brain, heart, liver, kidneys, skeletal muscle mass, bone mass, adipose tissue and residual mass) x the specific tissue metabolic rate. AT calculated as **mREE minus pREE**. AT was calculated after WL and after a follow up period.	Weight stable: WL = -12.3 ± 3.3kg. Weight regainers: WL = -9.0 ± 4.3kg. Decreases in T3 only for weight regainers after WL and follow up.	Significant AT only at weight regainers after WL (-0.39 ± 0.57 MJ/d).
de Jonge et al, 2012	RCT	N=811 (296 males) BMI from 25 - ≤40 kg/m^2 Age from 30–70 y	Diet-only: 4 types of caloric restriction: (i) 20% fat/15% PRO (ii) 20% fat/25% PRO (iii) 40% fat/15% PRO (iv) 40% fat/25% PRO	6months + 18 months follow up	Body composition: methodology not shown. REE: metabolic cart (Deltatrac II Metabolic Monitor)	Predicted REE was achieved by an equation using weight, age and sex. AT calculated as **mREE minus pREE**. AT was calculated after WL and after a follow up period.	6 months: Significant WL for all groups. From -6.37±0.42 (iii) to -6.80±0.42 (ii). 24mo: From -3.26±0.56 (i) to -5.03±0.58 (ii).	6 months: Only groups (i) and (ii) reported significant values for AT. AT = −76 ± 28 kJ/d 24 months: +91 ± 42 kJ/d
Goele et al, 2009	NRT	N=48 women BMI = 35.4 ± 4.4 kg/m^2 Age = 31.5 ± 6.1y	Diet-only: 4.2 MJ/day (2 meals of a formula diet and a low-fat meal per day)	13.9 ± 2.4 weeks	Body composition: BODPOD REE: Indirect calorimetry (Vmax Spectra 29n) PA: Pedometers (walking Style pro, OMRON) TEE: PAL * REE	AT was calculated by a comparison between mREE and mREE adjusted for FFM. AT was assessed after WL.	WL= –8.4 ±3.9 kg (~-8.4%)	Significant AT in 26 of 48 women (–13.4 ± 5.0 kJ/kg FFM).
Bosy Westphal et al, 2009	NRT	N=45 women BMI from 28.7-46.8 kg/m^2 Age from 22-46y	Diet-only: Low calorie diet (3.3 – 4.2 MJ/d)	12.7 ± 2.2 weeks	Body composition – 4C model BODPOD, DXA (Hologic Inc). MRI REE: indirect calorimetry (Vmax Spectra 29n)	pREE was based on the sum of eight body compartments (brain, heart, liver, kidneys, skeletal muscle mass, bone mass, adipose tissue and residual mass) x the specific tissue metabolic rate. AT was assessed after WL.	WL=9.5±3.4kg (~-4%) Decreases in Leptin and T3	AT was 230 ± 650 kJ/d Correlations with T3 concentrations.

Table 4.2. Continued

Study	Study type	Sample	Intervention's description	Length + follow up	Measurements	AT definition and measurement	Results	AT
Doucet et al, 2001	RCT	N=35 (15 males) Age = 44.3±1.7y (males) and 41.4±1.1y (females)	Diet + pharmacological therapy: 2 groups: 60mg/d fenfluramine (n=27) Non-macronutrient-specific energy restriction of approximately 2.9 MJ/d.	15 weeks + 2-4 weeks follow up	Body composition: hydrodensitometry %BF: Siri formula REE - Indirect calorimetry.	Predictive equation using FM and FFM. AT was considered as the difference between the changes in pREE from the reference equations and the changes in mREE. AT was calculated after WL and after a follow up period.	Significant WL and FM.	Non significant AT after the weight stabilization.
Dulloo et al, 1998	NRT	N= 32 males Age: 25 ± 4 y Weight: 69.4 ± 5.8 kg	Diet-only: Control period: 15.1 MJ/d: 13% PRO, 37% fat, 50% CHO. Semistarvation: 6.1 MJ/d: 25% PRO, 17% fat and 58% CHO	12w baseline + 24w semistarvation + 12weels refeeding	Body composition: hydrodensitometry. BMR - rate of oxygen consumption.	Total thermogenic economy (adaptive reduction in BMR) assessed by an equation using ΔFFM and ΔFM. AT was calculated after WL and after the refeeding period.	Each man lost ~25% of his initial body weight.	12 week: AT =-1491 ± 514 kJ/d S24 week: AT = -1706 ± 477 kJ/d Refeeding: AT =-693 ± 464 kJ/d Huge variability in BMR reductions
Exercise only and combined exercise and diet interventions								
Martins et al, 2020	O (retrospective)	n=171 females BMI=28.3±1.3 kg/m^2 Age=35.2±6.3y 3 groups: Diet only Diet + aerobic training Diet + resistance training	Diet + exercise: Aerobic exercise training OR resistance training (3x week)	2 years of follow up	Body composition: 4C model (BODPOD, DXA (DPX-L Lunar) and isotope dilution) REE: Indirect calorimetry (Delta Trac II)	**AT was tested with t-tests by comparing mREE with pREE**. pREE was achieved by a **predictive equation** using age, sex, race, FM and FFM. AT was measured after a 4-week period of weight stabilization	WL= −12.2 ± 2.6 kg (−15.7% ± 2.9%); No metabolic adaptation was seen at 1- and 2-y follow-up in all participants	AT= −226 ± 439 kJ/d AT is minimal when measurements are taken under conditions of weight stability and does not predict weight regain up to 2 years follow-up.
Ten Haaf et al, 2018	O (retrospective)	N=254 (88 males) BMI=31.7 ± 4.4 kg/m^2 Age=51±14 y 2 groups: Younger adults (n=122) BMI=31.0 ± 4.4 kg/m^2 Age=40±9 y Older adults (N=132) BMI=32.5 ± 4.3 kg/m^2 Age=62±5 y	Diet + exercise: All subjects went through a hypocaloric diet (30% lipids, 52% CHO, and 18%PRO). A subgroup completed and exercise program.	8 to 13 weeks	Body composition: Air displacement plethysmography (BodPod) + Siri Equation REE: Indirect Calorimetry (Vmax Encore n29).	pREE achieved by a **linear regression** with baseline data of FFM, FM, age, gender and FFM*age interaction. **AT = pREE-mREE** and corrected for measured versus predicted REE differences at baseline. AT was calculated after WL	Young adults: WL=-2.8±3.3kg; FM=-3.0±3.6kg. Older adults: WL: -3.2±3.0kg; FM=-3.4±3.3kg.	Significant AT in older adults (-278±774 kJ/d) but not in younger adults. Whole sample: -176 ± 715 kJ/d
Marzullo et al, 2018	NRT	N=100 (50 males) BMI = 45.1±4.8 kg/m^2 Age = 40.4±12.7y	Diet + exercise: 75% of mREE. 30% lipids, 52% CHO, 18% PRO. Aerobic PA - 2 sessions of 30min for 5days/week.	4 weeks	Body composition: Bioimpedance (BIA 101/S Akern); Thyroid ultrasonography; REE - Indirect Calorimetry (Sensormedics)	pREE was calculated by the **Harris-Benedict formula** and was employed to calculate the **mREE/pREE** ratio as a proxy of thermogenic potential, set as normal at 100%. AT was calculated after WL.	Significant WL (-5.5±1.8%) Significant reductions for FM and FFM only for men.	REEm/REEp = 91.8±10.2% (<100%) Association between REE and thyroid hormones

Table 4.2. Continued

Study	Study type	Sample	Intervention's description	Length + follow up	Measurements	AT definition and measurement	Results	AT
Fothergill et al, 2016	O (prospective)	N=14 (6 males) BMI = 49.5±10.1 kg/m^2 Age = 34.9±10.3y.	Diet + exercise: Restricted diet (~70% of their baseline energy requirements) Physical activity: 6x a week, 90min/d of supervised vigorous circuit training and/or aerobic training.	6y follow up	Body composition: DXA (iDXA, GE Lunar) REE - Indirect calorimetry (TrueOne Metabolic cart) TEE - double labeled water	pREE calculated through **linear regression** equation as a function of FFM, FM, age and sex. **Differences between mREE and pREE** defined the magnitude of metabolic adaptation which was considered to be present if the **REE residuals were significantly different from zero.** AT was calculated after WL and after the follow up period.	Severe WL WL= -58.3±24.9kg. Decreases in FM and FFM. Increases of PA Significant decreases in leptin, T4 and TG. At 6y, 41.0±31.3 of the lost weight was regained.	Presence of AT after 30weeks of competition (-1150 ± 866 kJ/d) and after 6y (-2088 ± 866 kJ/d).
McNeil et al, 2015	RT w/ no CG	N=93 women BMI = 32.1±4.3 kg/m^2 Age = 58.1±4.8y 2 groups: Diet-only (n=65) Diet + exercise (n=28)	Diet: REE x 1.4 and then 3.3 MJ was subtracted from this result. 30% lipids and 15%proteins. Supervised resistance training 3x week	6mo	Body composition: DXA (General Electric Lunar Prodigy) REE: indirect calorimetry TEE: doubly-labeled water	pREE by a multiple regression analysis using age, FFM, leptin and PYY. AT was achieved **by comparing pREE with mREE via a repeated-measures ANOVA.** AT was calculated after the WL intervention.	Both interventions decreased weight and FFM. Diet only: WL=-4.8±4.6kg Diet + Exercise: WL=-6.7±4.5kg Significant time x group interaction for FM. Greater decrease in FM for diet + exercise group. Decreases in Leptin and increases in PYY at both groups. Leptin and PYY were not significant predictors of the differences between pREE and mREE.	Greater predicted vs. measured REE was noted post-intervention (data not shown, -126kJ/d). Participants with higher caloric restriction saw greater decreases in their mREE vs pREE. This significant effect disappeared after correcting for the degree of caloric restriction.
Hopkins et al, 2014	NRT	N=30 women BMI = 30.6±3.6 kg/m^2 Age = 40.6±9.1y	Exercise-only: Supervised aerobic exercise designed to expend 10.5 MJ/week	12weeks	Body composition: Air displacement plethysmography (BODPOD). REE - Indirect calorimetry (GEM)	pREE by a regression equation from a reference population using FM and FFM. AT was achieved when **residuals between pREE and mREE** were different from zero. AT was calculated immediately after the WL programme.	Small but significant WL (84.3±10.3 to 83.7±10.7 (week 6) and to 83.0±11.2 (week 12)) No significant loss of FFM Decrease in Leptin.	Non significant AT Highly variability between subjects
Johannsen et al, 2012	O (prospective)	N=16 (7 males) BMI = 49.4±9.4 kg/m^2 Age = 33±10y	Diet + exercise: Restricted diet (~70% of their baseline energy requirements) Physical activity: 6x a week, 90min/d of supervised vigorous circuit training and/or aerobic training.	30weeks	Body composition: Dual-energy x-ray absorptiometry (GE Lunar). REE - Indirect Calorimetry (Max II metabolic cart); Total daily energy expenditure (TEE) - Double labeled water.	pREE calculated by an equation for predicting REE based on FFM, FM, age, and sex at baseline. AT was considered if the **REE residuals were negative and different from zero.** AT was assessed immediately after the WL programme.	6 weeks: WL=-15.0±4.9kg (>-10%) 30 weeks: WL=-57.6±23.8kg (~-38%) Decreases in leptin and T3. Increases in adiponectin.	6 weeks: AT = -1021 ± 967 kJ/d 30weeks AT= -2109 ± 715 kJ/d No association between changes in T3 and AT.

Table 4.2. Continued

Study	Study type	Sample	Intervention's description	Length + follow up	Measurements	AT definition and measurement	Results	AT
Surgery								
Wolfe et al, 2018	O (prospective)	N= 25 (3 males) BMI = 47±6 kg/m^2 Age = 45±11y	Bariatric Surgery (88% Roux-em-Y Gastric Bypass, 8% adjustable gastric banding and 4% biliopancreatic bypass with duodenal switch).	24mo	Body composition: DXA (Discovery A, Hologic Lunar); REE: Indirect calorimetry (Columbus Instruments); TDEE - DLW.	**Regression equation** using baseline FFM as the independent variable to predict REE and TDEE. AT was calculated as the **residuals between measured REE/TDEE and predicted REE/TDEE**. AT was measured after 6mo and 24mo.	6mo: WL = -24%±5%; FM = -37%±8%; FFM = -11±4%. 24mo: WL = -27±10.2kg	Presence of AT at 6mo (REE = -674 ± 582 kJ/d; but not at 24mo.
Bettini et al, 2018	O (prospective)	N=154 (56 males) BMI =45.5 ± 7.2 kg/m^2 Age = 45.1 ± 11.6y	Sleeve Gastrectomy	12mo	Body composition: bioimpedance (Soft Tissue Analyzer, Akern); REE - Indirect Calorimetry (Vmax).	pREE was calculated through a **preditive equation** using FM, FFM and sex. **AT calculated as mREE minus pREE** and was assessed after 12mo.	Significant WL (~-30%) Reductions in FM (~45%) and FFM (~-14%) Decreases of Leptin and Insulin	Significant AT (-833 ± 996 kJ/day) No significant correlations between AT and metabolic variables.
Browning et al, 2016	O (retrospective)	N= 13 (3 males) BMI = 46.4±5.8 kg/m^2 Age = 46.2±12.7y	Roux-em-Y gastric bypass (n=8) and laparoscopic adjustable gastric banding (n=5)	6mo	Body composition: DXA (Hologics discovery Wi) REE - Indirect calorimetry (SensorMedics)	pREE from LBM, FM, age, and sex using least squares linear regression. AT was calculated using the equation: (6-monthREEp -baselineREEp) - (6-month REEm - baselineREEm). AT was assessed after 6mo.	Significant WL; Reductions on FM and FFM.	Non-significant AT. AT was highly variable across individuals, ranging from -598 to 891 kJ/day.
Tam et al 2016	O (prospective)	N=35 (9 males) BMI=42.1±6.5 kg/m^2 Age=46±11 y	Gastric band (GB, n=8), sleeve gastrectomy (SG, n=13) or Roux-em-Y Gastric bypass (RYGB, n=14)	24mo	Body composition: Bioimpedance (Impedimed, HydexDF50) REE: Indirect Calorimetry (Medgem, Microlife)	AT was calculated as the **difference between mREE and the pREE** from fat-free mass, age and sex on the basis of equations established at baseline. AT was calculated after 6 weeks and 3, 6, 12 and 24mo.	GB: WL = -16.1±3.2% SG: WL = -30.7±2.6% RYGB: WL = -32.9±2.7 % Similar and significative reductions on FFM (~-31%)	For GB, AT occurred at 6 week (-469 ± 285 kJ/d) and 3mo (−741 ± 289 kJ/d) Insignificant after 6mo. For Sleeve, AT was significant from week 6 to 24mo (-1448 ± 247 kJ/d) For RYGB, AT was significant from week 6 to 24mo (- 1167 ± 259 kJ/d).
Carrasco et al, 2007	O (prospective)	N = 31 (4 males) BMI 44.4 ± 4.8 kg/m^2 Age = 37.3 ± 11.1 y	Roux-em-Y Gastric Bypass	6mo	Body composition: TBW - Deuterium dilution REE: Indirect calorimetry (Deltatrac) PA - Physical activity survey. Cardio-frequency monitor (Polar Vantage NV).	pREE calculated through a regression equation among REE and FFM before surgery. AT was calculated after 6 months.	WL= -33.4 ± 7.6kg BF ~-77% of WL.	AT = -348 ± 517 kJ/d Great dispersion of the difference between pREE and mREE.
Coupaye et al, 2005	O (prospective)	N= 36 females BMI = 47.2 ± 8.5 kg/m^2 Age = 42.7 ± 8.7y	Laparoscopic adjustable gastric banding	12mo	Body composition: DXA (Hologic QDR 2000) REE - Indirect calorimetry (Deltatrac II)	pREE - Regression equations relating REE to LBM and FM at initial weight before surgery. AT = residual values (observed-minus-predicted values) different from zero. AT was calculated after 1 year.	WL= -23.7±11.6kg (-19%); Decreases in leptin (-42%)	Non significant AT

O – Observational; NRT - Non-randomized Trial; RCT – Randomized Clinical Trial; RT – Randomized trial; CG – Control group; FM – Fat Mass; FFM – Fat Free Mass; WL – Weight Loss; AT – Adaptive thermogenesis; CHO – Carbohydrates; PRO – Protein; CR – Caloric Restriction; VLCD – Very Low Calorie Diet; LCD – Low Calorie Diet; CER – Continuous Energy Restriction; IER – Intermittent Energy Restriction; TDEE – Total Daily Energy Expenditure; BF – Body Fat; GB – Gastring Banding; SG – Sleeve Gastrectomy; RYGB – Roux-en-Y Gastric Bypass.

Diet-only interventions

Eighteen studies using a diet-only intervention were included (Bosy-Westphal et al., 2009; Bosy-Westphal, Schautz, et al., 2013; Byrne et al., 2018; Camps et al., 2013, 2015; de Jonge et al., 2012; Doucet et al., 2001; Dulloo & Jacquet, 1998; Goele et al., 2009; Gomez-Arbelaez et al., 2018; Karl et al., 2015; Martins et al., 2020; McNeil et al., 2015; Müller et al., 2015; Nymo et al., 2018; Pourhassan et al., 2014; Rosenbaum & Leibel, 2016; Thom et al., 2020). From those, one used a pharmacological therapy together with caloric restriction (Doucet et al., 2001).

Participants' characteristics. These studies involved 1780 participants (559 males). Only 3 studies had a mean BMI<30kg/m^2 (Dulloo & Jacquet, 1998; Martins et al., 2020; Müller et al., 2015), while the majority of the studies included participants with obesity (Bosy-Westphal et al., 2009; Byrne et al., 2018; Camps et al., 2013, 2015; de Jonge et al., 2012; Doucet et al., 2001; Goele et al., 2009; Gomez-Arbelaez et al., 2018; Karl et al., 2015; McNeil et al., 2015; Nymo et al., 2018; Pourhassan et al., 2014; Rosenbaum & Leibel, 2016; Thom et al., 2020). The amount of weight lost varied between studies, with 10 studies reporting a WL > 10% (Byrne et al., 2018; Camps et al., 2013, 2015; Dulloo & Jacquet, 1998; Gomez-Arbelaez et al., 2018; Martins et al., 2020; Nymo et al., 2018; Pourhassan et al., 2014; Rosenbaum & Leibel, 2016; Thom et al., 2020) and 7 reporting moderate WL (<10%) (Bosy-Westphal et al., 2009; de Jonge et al., 2012; Doucet et al., 2001; Goele et al., 2009; Karl et al., 2015; McNeil et al., 2015; Müller et al., 2015).

Diet type. Six studies used a very-low calorie diet (<3.3 MJ/d) in order to lose weight (Camps et al., 2013; Doucet et al., 2001; Gomez-Arbelaez et al., 2018; Nymo et al., 2018; Pourhassan et al., 2014; Rosenbaum & Leibel, 2016) and 5 used a low calorie diet (3.3 – 5.0 MJ/d) (Bosy-Westphal et al., 2009; Bosy-Westphal, Schautz, et al., 2013; Camps et al., 2015; Goele et al., 2009; Thom et al., 2020). Other studies calculated the prescribed EI as a percentage of participant's energy needs (calculated as measured REE x PAL): ~67% (Byrne et al., 2018; Karl et al., 2015) and 50% (Müller et al., 2015).

McNeil et al. multiplied each participant's REE by 1.4 and then subtracted 3.3MJ from that result (McNeil et al., 2015).

The macronutrient distribution was different among studies. Three reported a high protein intake (>25% or >1.2g/kg) (Dulloo & Jacquet, 1998; Nymo et al., 2018; Thom et al., 2020). A ketogenic diet was used by Gomez-Arbealez et al. (Gomez-Arbelaez et al., 2018). Karl and colleagues used 4 types of diets differing in carbohydrate (CHO) content: 55%, 60%, 70% or 80% CHO (Karl et al., 2015). Jonge et al. also divided the sample in 4 types of caloric restriction diets differing in fat and/or protein content: (i) 20% fat/15% protein (PRO); (ii) 20% fat/25% PRO; (iii) 40% fat/15% PRO and (iv) 40% fat/25% PRO (de Jonge et al., 2012). Dulloo et al. prescribed a 6.1MJ/day diet, consisting of 25% PRO, 17% fat and 58% CHO (Dulloo & Jacquet, 1998). Some studies did not report any information about the diet (Martins et al., 2020) or the macronutrient composition of the diet (Bosy-Westphal et al., 2009; Bosy-Westphal, Schautz, et al., 2013; Byrne et al., 2018; Camps et al., 2013; Goele et al., 2009; Martins et al., 2020; Pourhassan et al., 2014).

Methodology to assess adaptive thermogenesis. Thirteen studies used a predictive equation to estimate resting energy expenditure (pREE) and then calculated AT by comparing the pREE with a measured REE (mREE) using a statistical approach such as t-test or ANOVA (Byrne et al., 2018; Camps et al., 2013, 2015; de Jonge et al., 2012; Doucet et al., 2001; Dulloo & Jacquet, 1998; Gomez-Arbelaez et al., 2018; Karl et al., 2015; Martins et al., 2020; McNeil et al., 2015; Nymo et al., 2018; Rosenbaum & Leibel, 2016; Thom et al., 2020). Byrne et al. also used an additional two approaches: i) an equation developed by Muller et al. (Müller et al., 2004) to predict REE and ii) adjusted REE to FM and/or FFM followed by a comparison between baseline and post-intervention adjusted baseline values (Byrne et al., 2018). Bosy-Westphal, Pourhassan and Muller, used the sum of 7 tissue-level components obtained by magnetic resonance imaging (MRI) multiplied by their tissue-specific metabolic rates to predict REE and then

subtracted the baseline REE with the post-intervention REE (Bosy-Westphal et al., 2009; Bosy-Westphal, Schautz, et al., 2013; Müller et al., 2015; Pourhassan et al., 2014).

Adaptive thermogenesis. A significant value for AT was observed in 15 studies (Bosy-Westphal et al., 2009; Bosy-Westphal, Schautz, et al., 2013; Byrne et al., 2018; Camps et al., 2013, 2015; de Jonge et al., 2012; Dulloo & Jacquet, 1998; Goele et al., 2009; Karl et al., 2015; Martins et al., 2020; McNeil et al., 2015; Müller et al., 2015; Nymo et al., 2018; Rosenbaum & Leibel, 2016; Thom et al., 2020). Only 3 studies did not report a significant AT after WL (Doucet et al., 2001; Gomez-Arbelaez et al., 2018; Pourhassan et al., 2014). Byrne et al. (Byrne et al., 2018), which compared a continuous energy restriction (CER) versus an intermittent energy restriction (IER), only reported AT for the CER group (~209kJ/d), which lost ~8.4% of their initial weight. For the IER group, AT was not significant despite a greater WL (~-12.9%). Jonge et al. compared 4 types of caloric restriction diets varying in fat and/or protein (PRO) content (de Jonge et al., 2012). AT was only presented for the 20% fat/15%PRO and 20%fat/25%PRO groups, while the other 2 groups (40% fat/15%PRO and 40% fat/25%PRO) did not report AT despite significant WL. Despite the evidence for AT when measured immediately after the WL intervention, some intervention studies reported that this disappeared or was attenuated after a period of weight stabilization (measured after the follow up period) (Camps et al., 2013; de Jonge et al., 2012; Karl et al., 2015). Those three studies had participants with similar characteristics and methodologies to assess pREE (although de Jonge et al. created a regression equation without using FM and FFM as variables). Furthermore, Camps et al. also used a different methodology to assess AT (mREE/ pREE).

Exercise only and combined exercise and diet interventions

Since only 1 article reported an exercise-only intervention (Hopkins et al., 2014), its results will be analyzed with combined diet and exercise interventions, comprising 7 articles (Fothergill et al., 2016; Hopkins et al., 2014; Johannsen et al., 2012; Martins et al., 2020; Marzullo et al., 2018; McNeil et al., 2015; Ten Haaf et al., 2018).

Participants' characteristics. A total of 678 participants were involved (151 males). Only 1 study comprised participants with a BMI<25kg/m^2 (Martins et al., 2020). Half of the studies reported a >10% WL (Fothergill et al., 2016; Johannsen et al., 2012; Martins et al., 2020), while the others reported moderate amounts of WL (<10%)(Hopkins et al., 2014; Marzullo et al., 2018; McNeil et al., 2015; Ten Haaf et al., 2018).

Intervention type. The study related to an exercise-only intervention (Hopkins et al., 2014) consisted of a supervised aerobic exercise designed to create an energy deficit of ~10.5 MJ per week. The type of exercise was divided into aerobic (Hopkins et al., 2014; Marzullo et al., 2018), resistance training (McNeil et al., 2015) or both (Fothergill et al., 2016; Johannsen et al., 2012; Martins et al., 2020). One study did not add any information about the type of exercise (Ten Haaf et al., 2018).

Methodology to assess adaptive thermogenesis. A predictive equation to estimate REE was created in 5 studies (Fothergill et al., 2016; Johannsen et al., 2012; Martins et al., 2020; McNeil et al., 2015; Ten Haaf et al., 2018). Hopkins et al. also used a predictive equation to estimate REE but did not use their own sample but an independent population including women with overweight/obesity that did not participate in the intervention (Hopkins et al., 2014). All of the mentioned studies calculated AT by comparing pREE with mREE using a statistical approach such as t-test or ANOVA. Marzullo et al. used the Harris-Benedict equation to estimate REE (pREE), dividing mREE by pREE to calculate a ratio (Marzullo et al., 2018).

Adaptive thermogenesis. AT was reported in 6 studies (Fothergill et al., 2016; Johannsen et al., 2012; Martins et al., 2020; Marzullo et al., 2018; McNeil et al., 2015; Ten Haaf et al., 2018). Hopkins et al. study was the only study that did not report a significant value for AT (Hopkins et al., 2014), being the only exercise-only intervention in which participants lost a small amount of weight (-1.3 ± 2.7 kg). Despite having AT after WL, 1 study reported an attenuation after 1-2y of follow up (Martins et al., 2020). The values for AT ranged between 126-418 kJ/d except for 2 studies (Fothergill et al., 2016; Johannsen et al., 2012). These studies reported significant weight losses (WL = -

58.3±24.9 kg (Fothergill et al., 2016) and WL = -57.6 ± 23.8 kg (Johannsen et al., 2012)) and showed a larger AT (~837-1255 kJ/d which increased during follow up for ~2092kJ/d) (Fothergill et al., 2016; Johannsen et al., 2012).

Bariatric Surgery

For bariatric surgery, six studies were included in this review (Bettini et al., 2018; Browning et al., 2017; Carrasco et al., 2007; Coupaye et al., 2005; Tam et al., 2016; Wolfe et al., 2018), with the study length ranging from 6 to 24 months.

Participants' characteristics. A total of 294 participants (75 males) underwent bariatric surgery. Baseline characteristics were similar among studies, with all including participants with obesity (mean BMI>30kg/m^2). All of the studies presented a mean WL of ~30% except for those who underwent gastric banding (~15-20%).

Intervention type. The following weight reduction surgeries were conducted: Roux-en-Y gastric bypass (Browning et al., 2017; Carrasco et al., 2007; Tam et al., 2016; Wolfe et al., 2018), sleeve gastrectomy (Bettini et al., 2018; Tam et al., 2016), gastric band (Browning et al., 2017; Carrasco et al., 2007; Coupaye et al., 2005; Wolfe et al., 2018) and biliopancreatic bypass with duodenal switch (Wolfe et al., 2018).

Methodology to assess adaptive thermogenesis. A predictive equation was created and used for all the studies, calculating AT by comparing the pREE with a mREE using a statistical approach such as t-test or ANOVA. Browning et al. calculated AT by a different approach [(6-monthREEp-baselineREEp)-(6-monthREEm-baselineREEm)](Browning et al., 2017).

Adaptive thermogenesis. A significant value for AT was reported in 4 of the 6 studies (Browning et al., 2017; Coupaye et al., 2005). In two of these studies, AT only remained significant after 6 months, disappearing throughout time (Tam et al., 2016; Wolfe et al., 2018). AT values were slightly lower for those who had gastric band surgery when compared to other surgeries such as sleeve gastrectomy or Roux-en-Y gastric bypass (Tam et al., 2016). Studies in which participants underwent gastric banding did not report

significant values for AT (Browning et al., 2017; Coupaye et al., 2005). Both studies assessed AT by comparing the residuals (i.e., difference between measured REE and estimated based on the predictive equation) at baseline and after WL. A high variability between individuals was highlighted in two studies (Browning et al., 2017; Carrasco et al., 2007).

Total Daily Energy Expenditure

A total of 5 studies reporting changes in TDEE were included in this review (Lecoultre et al., 2011; Marlatt et al., 2017; Novaes Ravelli et al., 2019; Redman et al., 2009; Wolfe et al., 2018), with 2 RCTs (40%) and 3 prospective observational studies included (60%) (**table 4.3**).

From those, 1 was related to a diet-only intervention (Marlatt et al., 2017), 2 to a diet-only vs. a combined diet and exercise intervention (Lecoultre et al., 2011; Redman et al., 2009) and 2 to bariatric surgery (Novaes Ravelli et al., 2019; Wolfe et al., 2018). Due to the small number of studies, all intervention types were analyzed together.

Participants' characteristics. The 5 studies comprised 164 participants (53 males). Participants from the studies related to lifestyle interventions had a BMI ranging from 25 to 30kg/m^2 (Lecoultre et al., 2011; Marlatt et al., 2017; Redman et al., 2009). For studies that used bariatric surgeries, BMI was above 40kg/m^2 (Novaes Ravelli et al., 2019; Wolfe et al., 2018). All of the studies reported a WL >10%.

Intervention type. Marlatt et al. created a caloric deficit of 25% based on each participant's energy needs (Marlatt et al., 2017), while the other two authors used two different approaches: i) a low calorie diet (~3.7 MJ/d) until each participant had reached a WL of 15% of their initial weight or ii) an individual diet based on individual EI targets (Lecoultre et al., 2011; Redman et al., 2009).

Table 4.3. Total Daily Energy Expenditure (TDEE)/24h Energy Expenditure (24hEE)

Study	Study type	Sample	Intervention's description	Length + follow up	Measurements	AT definition and measurement	Results	AT
Diet-only intervention								
Marlatt et al, 2017 (50)	O (prospective)	N=29 (10 males) 2 groups: Caloric restriction n=18 BMI = 25.7 ± 1.6 kg/m² Control n=11 BMI = 25.7 ± 1.1 kg/m²	Diet only 25% of their energy needs	2y	Body composition: DXA (Hologic QDR 4500A), EE: 24h respiratory chamber; TDEE: 14d DLW. Sleeping metabolic rate: through PAL and/or Activity related energy expenditure.	Predictive equation using BSA, age and sex to calculate pEE. AT in 24hEE and SEE are expressed as changes in residual values. AT was assessed at 12mo and 24mo	After 2y of CR: WL: -9.0±0.6kg. 54% of the weight was regained 2y later.	No significant changes in 24hEE were observed.
Lecoultre et al, 2011(51)	RCT	N= 46 (20 males) BMI = 27.8±0.7 kg/m² Age = 36.8±1.0y	Diet-only or diet + exercise: 4 groups: 25% calorie restriction; 12,5% calorie restriction + exercise LCD 3.7 MJ/d until a 15% reduction in BW 1 control group (weight maintenance diet)	6 months	Body composition: DXA (hologics QDR 4500 A); 24hEE: Metabolic chamber SEE: microwave motion sensors (02h-05h am)	Predicted values of 24hSedEE and SEE: stepwise multivariate regression with FM, FFM, age, and sex as independent variables. **AT is calculated by m24hEE/mSEE minus p24hEE/SEE.** AT was calculated after the WL intervention (6mo).	WL=-11.4±0.6%; Decreases in Leptin (independent of the type of CR. Decreases in T3 and T4, related to the change in leptin, controlling for baseline leptin.	AT was observed in 6mo for CR groups for 24hEE (-527 ± 105 kJ/d).
Redman et al, 2009 (52)	RCT	N= 46 (20 males) BMI = 27.8±0.7 kg/m² Age = 36.8±1.0y	Diet-only or diet + exercise: 4 groups: 25% calorie restriction; 12,5% calorie restriction + exercise LCD 3.7 MJ/d until a 15% reduction in BW 1 control group (weight maintenance diet)	6 months	Body composition: DXA (hologics QDR 4500 A) 24hSedEE: Metabolic chamber SEE: microwave motion sensors (02h-05h am) TDEE: 14-day doubly labeled water; PA: PAL=TDEE/SMR OR mTDEE-mSMR.	Predicted values of 24hSedEE and SEE: stepwise multivariate regression with FM, FFM, age, and sex as independent variables. **AT is calculated by mTDEE minus pTDEE.** AT was calculated at 3 and 6mo (after WL intervention)	Calorie restriction WL = -8.3±0.8 (-10%), Calorie restriction + exercise WL = -8.4±0.8 (-10%) LCD WL = -11.2±0.6 kg (-14%)	3months: Significant AT for CR group (-1552± 314 kJ/d) and for LCD (-2075 ± 285 kJ/d). 6months: Significant AT for LCD (-1151 ± 531 kJ/d)
Exercise only and combined exercise and diet interventions								
Lecoultre et al, 2011(51)	RCT	N= 46 (20 males) BMI = 27.8±0.7 kg/m² Age = 36.8±1.0y	Diet-only or diet + exercise: 4 groups: 25% calorie restriction; 12,5% calorie restriction + exercise LCD 3.7 MJ/d until a 15% reduction in BW 1 control group (weight maintenance diet)	6 months	Body composition: DXA (hologics QDR 4500 A); 24hSedEE: Metabolic chamber SEE: microwave motion sensors (02h-05h am)	Predicted values of 24hSedEE and SEE: stepwise multivariate regression with FM, FFM, age, and sex as independent variables. **AT is calculated by m24hEE/mSEE minus p24hEE/SEE.** AT was calculated after the WL intervention (6mo).	WL=-11.4±0.6%; Decreases in Leptin (independent of the type of CR. Decreases in T3 and T4, related to the change in leptin, controlling for baseline leptin.	Non-significant AT for the diet + exercise group.

Table 4.3. Continued

Study	Study type	Sample	Intervention's description	Length + follow up	Measurements	AT definition and measurement	Results	AT
Redman et al, 2009 (52)	RCT	N= 46 (20 males) BMI = 27.8±0.7 kg/m² Age = 36.8±1.0y	Diet-only or diet + exercise: 4 groups: 25% calorie restriction; 12,5% calorie restriction + exercise LCD 3.7 MJ/d until a 15% reduction in BW 1 control group (weight maintenance diet)	6 months	Body composition: DXA (hologics QDR 4500 A) 24hSedEE: Metabolic chamber SEE: microwave motion sensors (02h-05h am) TDEE: 14-day doubly labeled water; PA: PAL=TDEE/SMR OR mTDEE-mSMR.	Predicted values o 24hSedEE and SEE: stepwise multivariate regression with FM, FFM, age, and sex as independent variables. **AT is calculated by mTDEE minus pTDEE.** AT was calculated at 3 and 6mo (after WL intervention)	Calorie restriction WL = -8.3±0.8 (-10%), Calorie restriction + exercise WL = -8.4±0.8 (-10%) LCD WL = -11.2±0.6 kg (-14%)	Non-significant AT for the exercise group.
Surgery								
Ravelli et al 2019 (53)	O (prospective)	N=18 females BMI between 40 and 50 kg/m² Age = 20-45y	Roux-em-Y Gastric Bypass	12mo	Body composition: stable isotope dilution technique (Schoeller); TDEE: DLW;	**Predictive equation of TEEp**, as a function of FM (kg), FFM (kg), age (years), and the number of steps (S) adjusted by current body weight (BW) in kilograms (S × W) in multiple linear regression. **AT was considered present when the residual values between mTEE and pTEE after surgery were negative**. AT was assessed at 6 and 12months after surgery.	Significant weight loss at 6mo (≅−27%) and at 12mo (≅−33%). ~10% reduction of FFM and ~12% reduction of FM.	6mo: Presence of AT (−665 ± 2092 kJ/day); 12mo: Non-significant AT
Wolfe et al, 2018 (34)	O (prospective)	N= 25 (3 males) BMI = 47±6 kg/m² Age = 45±11y	Bariatric Surgery (88% Roux-em-Y Gastric Bypass, 8% adjustable gastric banding and 4% biliopancreatic bypass with duodenal switch).	24mo	Body composition: DXA (Discovery A, Hologic Lunar); REE: Indirect calorimetry (Columbus Instruments); TDEE - DLW.	**Regression equation** using baseline FFM as the independent variable to predict REE and TDEE. AT was calculated as the **residuals between measured REE/TDEE and predicted REE/TDEE**. AT was measured after 6mo and 24mo.	6mo: WL = -24%±5%; FM = -37%±8%; FFM = -11±4%. 24mo: WL = -27±10.2kg	Presence of AT at 6mo (TDEE=-950 ± 1423 kJ/d) but not at 24mo.

Methodology to assess adaptive thermogenesis. TDEE were assessed by doubly labeled water method (Novaes Ravelli et al., 2019; Redman et al., 2009; Wolfe et al., 2018) or by a metabolic chamber (Lecoultre et al., 2011; Marlatt et al., 2017). A predictive equation was used to estimate TDEE (pTDEE) and AT was calculated by subtracting pTDEE from mTDEE.

Adaptive thermogenesis. AT was reported in 4 studies (Lecoultre et al., 2011; Novaes Ravelli et al., 2019; Redman et al., 2009; Wolfe et al., 2018). For lifestyle interventions, Redman et al. reported larger values for AT (~-1255 to -2092 kJ/d)(Redman et al., 2009), while Lecoultre reported lower values (-527 ± 105 kJ/d)(Lecoultre et al., 2011). Marlatt et al. did not report any significant changes in TDEE (Marlatt et al., 2017). Both studies that used weight reduction surgeries (Novaes Ravelli et al., 2019; Wolfe et al., 2018) reported a significant AT after 6 months, but not after 12 months (Novaes Ravelli et al., 2019) or 24 months (Wolfe et al., 2018). Studies which did not find AT had a follow up period and had similar methodologies to assess it, using a predictive equation with FM and FFM as variables and comparing the residual values.

Sleeping Energy Expenditure (SEE)

Only two studies reporting changes in SEE were found (Lecoultre et al., 2011; Marlatt et al., 2017) (**table 4.4**). One had a RCT design and 1 was a prospective observational study.

Participants' characteristics. The 2 studies comprised 75 individuals with a mean BMI between 25 and 30 kg/m^2 (30 males). Both studies reported a WL >10%.

Intervention type. Marlatt et al. generated a caloric deficit of 25% based on each participant's energy needs (Marlatt et al., 2017), while Lecoultre et al. used two different approaches: i) a low calorie diet (~3.7 MJ/d) until each participant had reached a WL of 15% of their initial weight or ii) an individual diet based on individual EI targets (Lecoultre et al., 2011).

Methodology to assess adaptive thermogenesis. SEE was assessed in a respiratory chamber using microwave motion sensors. A predictive equation was created to estimate SEE (pSEE) and AT was calculated by subtracting pSEE from measured SEE. *Adaptive thermogenesis.* Both studies reported significant and similar values for AT in SEE (~-335 to -377 kJ/d).

4.5. DISCUSSION

The aim of this systematic review was to examine whether AT occurs after WL and/or a period of weight stabilization phase. Overall, significant values for AT were reported in 27 of the 33 included studies. Most studies reported a large variability between subjects (e.g., when a standard deviation is higher than the respective mean) with regard to the magnitude of WL and/or AT.

Resting Energy Expenditure

The majority of the studies aimed to assess AT in REE. From those, 23 out of 29 reported a significant value for AT in REE (Bettini et al., 2018; Bosy-Westphal et al., 2009; Bosy-Westphal, Schautz, et al., 2013; Byrne et al., 2018; Camps et al., 2013, 2015; Carrasco et al., 2007; de Jonge et al., 2012; Dulloo & Jacquet, 1998; Fothergill et al., 2016; Goele et al., 2009; Johannsen et al., 2012; Karl et al., 2015; Martins et al., 2020; Marzullo et al., 2018; McNeil et al., 2015; Müller et al., 2015; Nymo et al., 2018; Rosenbaum & Leibel, 2016; Tam et al., 2016; Ten Haaf et al., 2018; Thom et al., 2020; Wolfe et al., 2018).

The reduction in REE after WL occurs mainly due to the losses of FFM and FM (Bosy-Westphal et al., 2009; Muller et al., 2016). Furthermore, it is known that WL is accompanied by hormonal changes such as a decrease in circulating leptin and thyroid hormones, and these changes may contribute to AT (MacLean et al., 2011; Major et al., 2007; Rosenbaum et al., 2018).

Table 4.4. Sleeping Energy Expenditure (SEE)

Study	Study type	Sample	Intervention's description	Length + follow up	Measurements	AT definition and measurement	Results	AT
Marlatt et al, 2017 (50)	O (prospective)	N=29 (10 males) 2 groups: Caloric restriction n=18 BMI = 25.7 ± 1.6 kg/m^2 Control n=11 BMI = 25.7 ± 1.1 kg/m^2	Diet only 25% of their energy needs	2y + 2y follow up	Body composition: DXA (Hologic QDR 4500A), EE: 24h respiratory chamber; TDEE: 14d DLW. Sleeping metabolic rate: microwave motion sensors in a respiratory chamber (activity <1%)	Predictive equation using BSA, age and sex to calculate SEE. AT in 24hEE and SEE are expressed as changes in residual values. AT was assessed during follow up.	After 2y of CR: WL: -9.0±0.6kg. 54% of the weight was regained 2y later.	Significant AT was observed between CR (-381 ± 75 kJ/d) and CG (-96 ± 96 kJ/d).
Lecoultre et al, 2011(51)	RCT	N= 46 (20 males) BMI = 27.8±0.7 kg/m^2 Age = 36.8±1.0y	Diet-only or diet + exercise: 4 groups: 25% calorie restriction; 12,5% calorie restriction + exercise LCD 3.7 MJ/d until a 15% reduction in BW 1 control group (weight maintenance diet)	6 months	Body composition: DXA (hologics QDR 4500 A); 24hSedEE: Metabolic chamber Sleeping EE (SEE): microwave motion sensors (02h-05h am)	Predicted values of 24hSedEE and Sleeping EE: stepwise multivariate regression with FM, FFM, age, and sex as independent variables. **AT is calculated by m24hEE/mSEE minus p24hEE/SEE.** AT was calculated after the WL intervention (6mo).	WL=-11.4±0.6%; Decreases in Leptin (independent of the type of CR. Decreases in T3 and T4, related to the change in leptin, controlling for baseline leptin.	AT was observed in CR groups for SEE (-347 ± 71 kJ/d).

O – Observational Study; RCT – Randomized Clinical Trial; TDEE – Total Daily Energy Expenditure; 24hEE – 24h Energy Expenditure; SEE – Sleeping energy expenditure; WL – Weight loss; CR – Caloric Restriction; LCD – Low Calorie Diet; FM – Fat Mass; FFM – Fat Free Mass.

Also, other factors may potentially contribute to AT such as changes in sympathetic nervous system activity and concentrations of insulin and catecholamines after WL (Müller et al., 2015). In this systematic review, some studies reported decreases in leptin (Bosy-Westphal et al., 2009; Camps et al., 2015; Fothergill et al., 2016; Gomez-Arbelaez et al., 2018; Hopkins et al., 2014; Johannsen et al., 2012; McNeil et al., 2015; Müller et al., 2015; Thom et al., 2020) and in thyroid hormones (Bosy-Westphal et al., 2009; Pourhassan et al., 2014). The administration of exogenous leptin and triiodothyronine may restore baseline hormone concentrations (Rosenbaum et al., 2018) and reverse the effects of AT. However, the role of these hormones on AT are still a matter of debate (Müller et al., 2015) as not all studies observe a relationship.

Intervention's type and adaptive thermogenesis

Despite surgeries having a higher percentage of WL, they did not necessarily present higher values for AT, when compared with lifestyle interventions. Weight reduction surgeries differed in the degree of AT, with gastric banding being associated with a lower (or non-existent) AT and smaller amounts of weight loss (~10-20%) compared with sleeve gastrectomy and gastric bypass (~30-40%). No bariatric surgery's studies have included assessments of AT in SEE. Although it remains unknown why different surgeries may lead to different magnitudes of AT, its technical procedure could be a potential explanation. In Sleeve or Gastric bypass surgeries, part of the stomach is removed, while in gastric banding procedures the stomach remains intact, which alter the hormonal responses which may be linked to AT (Beckman et al., 2010).

Although the studies performing bariatric surgeries reported the highest amounts of WL, the Biggest Loser's participants reported similar changes in bodyweight by creating a large energy deficit (Fothergill et al., 2016; Johannsen et al., 2012). In these studies, the magnitude of AT was similar between participants who had lost a similar amount weight through either lifestyle changes or bariatric surgery. However, while in bariatric surgeries AT tended to disappear after a period of 6-24 months, on the Biggest Loser's studies,

AT not only remained present but also increased their value after 6 years. However, as some of the participants lost weight on the 2 weeks prior to the 6-year follow-up measurements, the state of energy balance (energy deficit) could have influenced the assessments of AT.

For lifestyle interventions, it is important to consider that different methodologies (macronutrient composition, degree of energy restriction and inclusion of exercise) to achieve a negative energy balance were utilized. Therefore, heterogeneity in the results reported in these lifestyle interventions was to be expected.

Exercise-only studies usually report lower than expected magnitudes of WL mainly due to compensatory increases in EI and decreases in EE (Thomas et al., 2012). Therefore, there is a lack of exercise-only interventions including both a significant WL and assessments of AT. For this systematic review, only 1 study was included, which did not report a significant mean AT after a 12-week supervised exercise-only intervention (Hopkins et al., 2014), potentially explained by the smaller energy deficit.

Despite the large variability among studies, similar AT was found between bariatric surgeries and lifestyle interventions, regardless of total WL.

Relationship between the magnitude of weight loss and adaptive thermogenesis

It has been previously postulated that a relationship between total WL and degree of AT exists (Johannsen et al., 2012; McNeil et al., 2015). However, some studies have reported contradictory results (Martins et al., 2020; Muller et al., 2016). If a relationship between magnitude of WL and degree of AT existed, it would be plausible that bariatric surgery would lead to a greater AT as total WL is usually larger. However, only Tam et al. reported higher values for AT (>1255 kJ/d) (Tam et al., 2016), when compared to lifestyle interventions. Interestingly, despite large WL (~-20%), two studies did not report a significant value for AT (Browning et al., 2017; Coupaye et al., 2005). Altogether, the findings from this analysis suggest that the amount of WL is not associated with the

magnitude of AT, corroborating the results from previous studies (Martins et al., 2020; Muller et al., 2016).

The influence of the state of energy balance on adaptive thermogenesis

An important consideration when examining the presence of AT is to understand the state of energy balance participants are at the time of the measurements. It has been shown that the state of energy balance may be associated with AT (Drummen et al., 2019). Notably, the majority of the included studies who did not report AT (in at least 1 group) had their participants EE measured under conditions of neutral energy balance (~70%) (Bosy-Westphal, Schautz, et al., 2013; Coupaye et al., 2005; de Jonge et al., 2012; Doucet et al., 2001; Karl et al., 2015; Marlatt et al., 2017; Müller et al., 2015; Novaes Ravelli et al., 2019; Wolfe et al., 2018). Furthermore, some studies reported a minimal AT when measurements were taken under conditions of weight stability (Karl et al., 2015; Martins et al., 2020). For instance, Martins et al. observed AT (~209-251kJ/d) after a 4-week weight stabilization period (Martins et al., 2020). However, it is important to acknowledge that weight stability does not imply the presence of a neutral energy balance, as in this study participants were under a very low caloric ketogenic diet (3.3MJ/d) (Martins et al., 2020) which deplete glycogen stores. Therefore, participants could be in a negative energy balance and lose body fat while replenishing glycogen stores. Indeed, after 4 weeks of stabilization, participants had lost an extra 0.8kg of FM while gaining 0.9kg of FFM.

Despite the potential influence of the state of energy balance on AT (Drummen et al., 2019), most studies are not clear in reporting whether participants were assessed under similar states of energy balance, which could in part explain the conflicting and heterogenous results. Therefore, in order to examine whether AT is present after WL, measurements should be conducted under conditions of neutral energy balance.

Methodological issues

The equivocal findings observed between studies may also be reflective of a lack of consistency regarding the definition and methods used to assess AT. In the current literature, the most common method is the use of regression models to predict REE. This method includes the utilization of a previously validated equation or the development of an equation based on the baseline information from the population included in the study. Then, a comparison between measured and predicted REE is conducted to examine whether these are different. Therefore, examining the existence of AT is strongly dependent on the accuracy of the technique used to measure body composition. The 4-compartment models, constructed from combinations of the reference methods (Fuller et al., 1992), are considered the gold standard method to assess FM (Smith-Ryan et al., 2017; Wilson et al., 2012). Since this model combines the use of several techniques, due to the assessment of bone mineral content (by DXA), total body water (isotopes dilution), body weight and body volume (air displacement plethysmography) (Fuller et al., 1992), it requires considerable time and cost and only a few studies used it. Therefore, the most common methods used in weight management research are 2-compartment models, in which a stable density or hydration of FFM needs to be considered. Since FFM is composed of water, proteins, mineral and glycogen with different densities, any change in its composition during WL will alter the energy density of FFM. During WL, especially during an initial phase, a decrease in nitrogen, glycogen and sodium leads to a negative water balance which changes the density of FFM, and thus compromising the FM obtained by densitometry methods (Müller & Bosy-Westphal, 2019).

Moreover, it is important to acknowledge that FFM represents a heterogeneous group of tissues with different metabolic rates (eliaMüller et al., 2013). This means that changes in the composition of FFM (losses of high-metabolic rate organs vs skeletal muscle vs body water) may dramatically influence the prediction of REE. Therefore, using 2-compartment models to assess FM and FFM presents some limitations for the prediction of REE when comparing individuals before and after WL (Bosy-Westphal, Braun, et al.,

2013). Interestingly, studies that assessed AT using MRI reported lower or non-significant values for AT (Bosy-Westphal et al., 2009; Bosy-Westphal, Schautz, et al., 2013; Müller et al., 2015; Pourhassan et al., 2014). This could be due to the ability to accurately assess tissue-organ components without relying on assumptions, also allowing to account for the specific metabolic rates associated to each tissue (Müller et al., 2013). Therefore, the most accurate method to examine AT may be the estimation of REE based on the data collected from the MRI and the organ's specific metabolic rates (Müller & Bosy-Westphal, 2019). However, MRI is not common in clinical practice due to the high time and cost investment (Bosy-Westphal, Braun, et al., 2013), being used only in a limited number of studies (Bosy-Westphal, Braun, et al., 2013). Overall, the observed variability in AT between studies may be also due to the method used to assess it, as well its assumptions.

Also, it is important to state that AT in REE is generally considered as a greater than predicted decrease in REE after accounting for changes in body composition. However, when it comes to TDEE, AT is usually calculated using a similar method, which could lead to inaccurate calculations as this approach does not account for changes in PA behaviors that could influence EE independently of the presence of AT.

Lastly, comparing weight reduction surgeries, gastric banding seems to be the one associated with the lowest (or non-existent) AT. Although it remains unknown why different surgeries may lead to different magnitudes of AT, its technical procedure could be a potential explanation. This stomach removal in sleeve or gastric bypass surgeries (versus gastric banding procedures) may alter the concentration of hormones related to energy balance regulation or lead to different changes in body composition (different contributions of FM and FFM), and therefore influence AT. Moreover, after these types of surgeries, the digestibility and absorption after a meal are altered (Quercia et al., 2014). In fact, nutritional deficits are one of the major long-term complications of bariatric surgery (Damms-Machado et al., 2012; Lefebvre et al., 2014). Since the stomach undergoes a short cut, the gut receives less processed food, which may decrease

absorption and stimulate defecation (Gregory et al., 2018). Therefore, the metabolizable energy of the food should also be taken into account.

Limitations

There are important limitations that need to be addressed. As expected, a large heterogeneity in the methods used to assess AT was found between studies, which could in part explain the equivocal results. Considering the quality assessment tool, it is important to state that the data included in this review ranged from weak to moderate study designs. Therefore, the need to establish a universal definition and assessment protocol of AT is warranted. Defining how AT is assessed will decrease the risk of bias and strengthen the comparisons between studies.

Recommendations for future studies

Due to the aforementioned limitations, the standardization of the methods to assess AT is crucial in order to fully understand whether this compensatory response occurs during and/or after WL.

Firstly, a regression equation to predict REE should be created based on the population's baseline information and it should provide a good fit for the observations. The use of general predictive equations already published should be avoided since they were made using other population's characteristics. Moreover, apart from precise measurements of FM and FFM, variables such age and sex may be included as they have been shown to influence REE (Johnstone et al., 2005). Furthermore, residuals should be calculated before and after WL. If residuals are statistically different from zero at baseline, it means that participants already have a predicted REE different from the measured value. Therefore, residuals at baseline should be taken into account when assessing AT.

Previous research has demonstrated that AT may be associated with the state of energy balance (Drummen et al., 2019). Therefore, measurements of EE should be conducted in a similar state of energy balance. Furthermore, assessing AT in a neutral energy

balance condition not only will assure a similar condition to baseline but will also eliminate the potential influence of an acute state of energy deficit. However, it is important to note that neutral energy balance and weight stabilization are not synonyms. Since an energy deficit will inevitably lead to glycogen depletion, a neutral energy balance post-WL may lead to a short-term weight gain due to increases in water stores. Therefore, a neutral energy balance should be confirmed by not having FM changes during a period of time, although a small increase in FFM may occur. An alternative method to estimate the state of energy balance is to use the 'intake-balance' method. Based on changes in energy stores (i.e. changes in body weight (Hall & Chow, 2011) or composition (Racette et al., 2012; Shook et al., 2018), it is possible to estimate the state of energy balance.

Despite AT being reported in 27 out of 33 studies, the methodological quality of each study needs to be taken into consideration, since well-designed studies (online Supplementary File 2) reported lower or non-statistically significant values for AT. Furthermore, studies that assessed AT during a period of WL maintenance suggested that its magnitude cannot be a primary driver of weight regain (Martins et al., 2020). In fact, when AT was measured under conditions of weight maintenance, values for AT were found to be reduced or statistically non-significant, comparing to when assessed during conditions of negative energy balance (table 4.1).

Also, studies comprising bariatric surgeries reported that AT tended to disappear throughout time. On the other hand, studies with poorer methodological designs that measured AT immediately after WL (under conditions of negative energy balance) must be interpreted carefully. Although it remains unknown how much time would be needed to reverse the potential occurrence of AT under conditions of energy deficit, a period of several weeks in a true state of neutral energy balance could be necessary.

Conclusions

AT was found in (at least) one of the EE components in 27 out of 33 studies, suggesting that WL may lead to a greater than predicted decrease in EE. Overall, these findings suggest that although weight loss may lead to AT in some of the energy expenditure components despite a high inter-individual variability, these values may be small or non-significant when higher-quality methodological designs are used. Furthermore, AT seems to be attenuated, or non-existent, after periods of weight stabilization or neutral energy balance. Therefore, more high-quality studies are warranted not only to disclose the existence of AT in each energy expenditure component, but to understand its clinical implications on weight management outcomes.

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Supplementary file 1.

PUBMED Search Strategy

Limited search to 1950 - 2020

1. ((weight or fat mass or body weight or fat free mass or fat mass or lean mass or lean body mass or body fat) loss*) or ((weight or body or fat or adipose tissue or fat mass or body composition or body weight or lean mass or lean body mass) change*) or ((weight or body) composition) or (weight regulation) or (weight balance)).ti.ab. (404951)
2. ((adaptive thermogenesis) or ((metabolic or energy) adaptation*) or ((behavioral or metabolic) compensation*) or (exercise or muscle or muscular) efficiency)).tw. (3316)
3. #1 and #2 (795)
4. Limited #3 to “Humans” (362)
5. Limited #4 to “English” (350)

Supplementary file 2.

Table S4.5. Quality Assessment

Study	Selection Bias	Study Design	Confounders	Blinding	Data Collection	Withdrawals	Final Rating
Martins et al, 2020	Weak	Moderate	strong	Not applicable	Strong	Strong	Moderate
Thom et al 2020	Weak	moderate	Not applicable	Not applicable	Moderate	Moderate	Moderate
Ravelli et al 2019	Weak	moderate	Not applicable	Not applicable	Moderate	strong	Moderate
Wolfe et al, 2018	Weak	moderate	Not applicable	Not applicable	Moderate	moderate	moderate
Bettini et al, 2018	Weak	moderate	Not applicable	Not applicable	moderate	moderate	moderate
Nymo et al, 2018	Moderate	moderate	Not applicable	Not applicable	Strong	Strong	Strong
Ten Haaf et al, 2018	Weak	Weak	Moderate	Not applicable	Moderate	Moderate	Weak
Marzullo et al, 2018	Weak	Moderate	Not applicable	Not applicable	moderate	weak	Weak
Gomez-Arbelaez et al, 2018	weak	moderate	Not applicable	Not applicable	Moderate	Moderate	Moderate
Byrne et al, 2018	Weak	Moderate	strong	Moderate	Moderate	strong	Moderate
Marlatt et al, 2017	weak	Moderate	strong	moderate	Moderate	Moderate	Moderate
Rosenbaum et al, 2016	weak	moderate	strong	Not applicable	Moderate	Moderate	Moderate
Fothergill et al, 2016	weak	moderate	Not applicable	Not applicable	Strong	Moderate	Moderate
Browning et al, 2016	weak	moderate	Not applicable	Not applicable	Moderate	moderate	Moderate
Tam et al 2016	Weak	moderate	Not applicable	Not applicable	Moderate	moderate	Moderate
Müller et al, 2015	moderate	moderate	Not applicable	Not applicable	Strong	Moderate	Moderate
Mcneil et al, 2015	weak	moderate	moderate	Moderate	Moderate	Moderate	moderate
Karl et al, 2015	moderate	strong	strong	strong	strong	strong	Strong
Camps et al, 2015	moderate	moderate	Not applicable	Not applicable	Moderate	Moderate	Moderate
Pourhassan et al, 2014	weak	Weak	Not applicable	Not applicable	Moderate	Not applicable	moderate
Hopkins et al, 2014	Moderate	Moderate	Not applicable	Not applicable	Moderate	moderate	moderate
Camps et al, 2013	moderate	Moderate	Not applicable	Not applicable	Strong	Strong	Strong
Bosy-Westphal et al, 2013	moderate	Moderate	Moderate	Moderate	Strong	Strong	Strong
Johannsen et al, 2012	weak	Moderate	Not applicable	Not applicable	Moderate	Moderate	Moderate
The Jonge et al, 2012	Moderate	Strong	Strong	Moderate	Strong	Moderate	Strong
Lecoultre et al, 2011	Weak	Strong	weak	Moderate	Moderate	weak	Weak
Redman et al, 2009	Moderate	strong	Moderate/strong	Moderate	Moderate	strong	Strong
Goele et al, 2009	Moderate	moderate	Not applicable	Not applicable	moderate	strong	Moderate
Bosy Westphal et al, 2009	moderate	moderate	Not applicable	Not applicable	Strong	strong	Strong
Carrasco et al, 2007	weak	moderate	Not applicable	Not applicable	Moderate	Moderate	Moderate
Coupaye et al, 2005	weak	moderate	Not applicable	Not applicable	Moderate	moderate	Moderate
Doucet et al, 2001	weak	strong	Weak	strong	moderate	weak	Weak
Dulloo et al, 1998	weak	moderate	Not applicable	Not applicable	Moderate	moderate	Moderate

Supplementary file 3.

Table S4.6. Articles that were not included and main reasons for exclusion.

Nr	Authors	Article	Reason
1	**(Drummen et al., 2019)**	High Compared with Moderate Protein Intake Reduces Adaptive Thermogenesis and Induces a Negative Energy Balance during Long-term Weight-Loss Maintenance in Participants with Prediabetes in the Postobese State: A PREVIEW Study	No weight loss / weight gain
2	**(Shaw et al., 2019)**	Effect of a Ketogenic Diet on Submaximal Exercise Capacity and Efficiency in Runners	Sample size <10
3	**(Camps et al., 2019)**	Association of FTO and ADRB2 gene variation with energy restriction T induced adaptations in resting energy expenditure and physical activity	Other reason: Results already published in other paper (Camps et al., 2015)
4	**(Langan-Evans et al., 2019)**	Making weight safely: Assessment of within daily energy balance and manipulation of energy availability without symptoms of RED-S in an elite male Taekwondo athlete	article type
5	**(Corley et al., 2019)**	Changes in resting energy expenditure with intermittent fasting versus continuous daily restriction-a randomised controlled trial	article type
6	**(Borges et al., 2019)**	Adaptive thermogenesis and changes in body composition and physical fitness in army cadets	No weight loss / weight gain
7	**(Beatty & Melanson, 2019)**	Examining changes in respiratory exchange ratio within an 8-week weight loss intervention	No weight loss / weight gain
8	**(Thom et al., 2018)**	Adaptive thermogenesis, leptin and gut hormones during dietary induced weight loss: Impact on long-term weight loss maintenance	article type
9	**(Ostendorf et al., 2018)**	No consistent evidence of a disproportionately low resting energy expenditure in long-term successful weight-loss maintainers	Other reason: Participants had different periods for WL maintenance.
10	**(Redman et al., 2018)**	Metabolic Slowing and Reduced Oxidative Damage with Sustained Caloric Restriction Support the Rate of Living and Oxidative Damage Theories of Aging	Unclear/inadequate methodology for AT
11	**(Nymo et al., 2018)**	Compensatory responses to weight loss and long-term relapse: Is there a link?	article type
12	**(Messias et al., 2018)**	Individual adaptive thermogenesis and body composition changes after weight loss process	article type
13	**(Hintze et al., 2018)**	A one-year resistance training program following weight loss has no significant impact on body composition and energy expenditure in postmenopausal women living with overweight and obesity	Unclear/inadequate methodology for AT
14	**(Heinitz et al., 2018)**	Response of skeletal muscle UCP2-expression during metabolic adaptation to caloric restriction	Unclear/inadequate methodology for AT
15	**(El Ghoch et al., 2018)**	Weight cycling in adults with severe obesity: A longitudinal study.	No weight loss / weight gain
16	**(Clamp et al., 2018)**	Successful and unsuccessful weight-loss maintainers: strategies to counteract metabolic compensation following weight loss	Unclear/inadequate methodology for AT
17	**(Byrne et al., 2018)**	Changes in total and activity energy expenditure accompanying continuous versus intermittent energy restriction: the matador study.	article type
18	**(Trexler et al., 2017)**	Physiological Changes Following Competition in Male and Female Physique Athletes: A Pilot Study	Unclear/inadequate methodology for AT
19	**(Pardue et al., 2017)**	Case Study: Unfavorable But Transient Physiological Changes During Contest Preparation in a Drug-Free Male Bodybuilder	n<10

20	**(Nymo et al., 2017)**	Sustainability of changes in energy expenditure variables at 1 year follow-up after initial weight loss with a very-low energy diet	article type
21	**(Koehler et al., 2017)**	Less-than-expected weight loss in normal-weight women undergoing caloric restriction and exercise is accompanied by preservation of fat-free mass and metabolic adaptations	Unclear/inadequate methodology for AT
22	**(Furber et al., 2017)**	A 7-day high protein hypocaloric diet promotes cellular metabolic adaptations and attenuates lean mass loss in healthy males.	Unclear/inadequate methodology for AT
23	**(Carnero et al., 2017)**	Randomized Trial Reveals that Physical Activity and Energy Expenditure are Associated with Weight and Body Composition after RYGB	Unclear/inadequate methodology for AT
24	**(Tam et al., 2016)**	Energy metabolic adaptation and cardiometabolic improvements one year after gastric bypass, sleeve gastrectomy and gastric band	Sample size <10;
25	**(Pontzer et al., 2016)**	Constrained Total Energy Expenditure and Metabolic Adaptation to Physical Activity in Adult Humans.	No weight loss / weight gain
26	**(Hall et al., 2016)**	Energy expenditure and body composition changes after an isocaloric ketogenic diet in overweight and obese men.	Unclear/inadequate methodology for AT
27	**(Triffoni-Melo et al., 2015)**	Resting energy expenditure adaptation after short-term caloric restriction in morbidly obese women	Unclear/inadequate methodology for AT
28	**(Siervo et al., 2015)**	Imposed rate and extent of weight loss in obese men and adaptive changes in resting and total energy expenditure	Sample size <10
29	**(Nymo et al., 2015)**	Timeline over which compensatory mechanisms are activated during weight loss with a very-low-calorie diet.	Article Type
30	**(Jaime et al., 2015)**	Effect of calorie restriction on energy expenditure in overweight and obese adult women	Unclear/inadequate methodology for AT
31	**(Hume et al., 2015)**	Compensations for Weight Loss in Successful and Unsuccessful Dieters.	Unclear/inadequate methodology for AT
32	**(Herrmann et al., 2015)**	Energy intake, nonexercise physical activity, and weight loss in responders and nonresponders: The Midwest Exercise Trial 2.	Unclear/inadequate methodology for AT
33	**(Hasani et al., 2015)**	Effect of Laparoscopic Gastric Plication Surgery on Body Composition, Resting Energy Expenditure, Thyroid Hormones, and Physical Activity in Morbidly Obese Patients.	Unclear/inadequate methodology for AT
34	**(Bakker et al., 2015)**	Middle-aged overweight South Asian men exhibit a different metabolic adaptation to short-term energy restriction compared with Europeans.	Unclear/inadequate methodology for AT
35	**(Knuth et al., 2014)**	Metabolic Adaptation Following Massive Weight Loss is Related to the Degree of Energy Imbalance and Changes in Circulating Leptin	Other reason: Results already published in other paper (Johannsen et al., 2012)
36	**(Coutinho et al., 2014)**	The impact of speed of weight loss on body composition and compensatory mechanisms activated during weight reduction.	Article type
37	**(Werling et al., 2013)**	Increased Postprandial Energy Expenditure May Explain Superior Long Term Weight Loss after Roux-en-Y Gastric Bypass Compared to Vertical Banded Gastroplasty.	Unclear/inadequate methodology for AT
38	**(Tremblay et al., 2013)**	Adaptive thermogenesis can make a difference in the ability of obese individuals to lose body weight.	Article type
39	**(Byrne et al., 2012)**	Does metabolic compensation explain the majority of less-than-expected weight loss in obese adults during a short-term severe diet and exercise intervention?	Unclear/inadequate methodology for AT
40	**(Kissileff et al., 2012)**	Leptin reverses declines in satiation in weight-reduced obese humans	Sample size <10
41	**(Sumithran et al., 2011)**	Long-term persistence of hormonal adaptations to weight loss	Unclear/inadequate methodology for AT

42	**(Lee et al., 2010)**	Effects of dihydrocapsiate on adaptive and diet-induced thermogenesis with a high protein very low calorie diet: a randomized control trial	Unclear/inadequate methodology for AT
43	**(Johannsen et al., 2010)**	A competitive weight loss program that includes intense daily physical activity results in extreme weight loss despite a large metabolic adaptation.	Article type
44	**(Galgani et al., 2010)**	Leptin Replacement Prevents Weight Loss-Induced Metabolic Adaptation in Congenital Leptin-Deficient Patients	Sample size <10
45	**(Tremblay & Chaput, 2009)**	Adaptive reduction in thermogenesis and resistance to lose fat in obese men.	Sample size <10;
46	**(Fullmer et al., 2009)**	The effect of calorie deficits of 25%, 40% and 55% on adaptation to resting energy expenditure and lean mass in healthy post-menopausal women.	Article type
47	**(Rosenbaum et al., 2008)**	Long-term persistence of adaptive thermogenesis in subjects who have maintained a reduced body weight	Unclear/inadequate methodology for AT
48	**(Martin et al., 2007)**	Effect of Calorie Restriction on Resting Metabolic Rate and Spontaneous Physical Activity	Other reason: Results already published in other article (Lecoultre et al., 2011)
49	**(Abete et al., 2008)**	Energy-restricted diets based on a distinct food selection affecting the glycemic index induce different weight loss and oxidative response	Unclear/inadequate methodology for AT
50	**(Hall, 2006)**	Computational model of in vivo human energy metabolism during semistarvation and refeeding.	Article type
51	**(Heilbronn et al., 2006)**	Effect of 6-month calorie restriction on biomarkers of longevity, metabolic adaptation, and oxidative stress in overweight individuals: a randomized controlled trial	Other reason – already published results
52	**(Tremblay et al., 2004)**	Thermogenesis and weight loss in obese individuals: a primary association with organochlorine pollution	Article type
53	**(Doucet et al., 2003)**	Greater than predicted decrease in energy expenditure during exercise after body weight loss in obese men	Unclear/inadequate methodology for AT
54	**(Hainer et al., 2001)**	A twin study of weight loss and metabolic efficiency.	Unclear/inadequate methodology for AT
55	**(Weyer, Pratley, et al., 2000)**	Energy Expenditure, Fat Oxidation, and Body Weight Regulation: A Study of Metabolic Adaptation to Long-Term Weight Change	No weight loss / weight gain
56	**(Menozzi et al., 2000)**	Resting metabolic rate, fat-free mass and catecholamine excretion during weight loss in female obese patients	Unclear/inadequate methodology for AT
57	**(Weyer, Walford, et al., 2000)**	Energy metabolism after 2 y of energy restriction: the Biosphere 2 experiment.	Sample size N<10
58	**(Agus et al., 2000)**	Dietary composition and physiologic adaptations to energy restriction.	Unclear/inadequate methodology for AT
59	**(Weinsier et al., 2000)**	Energy expenditure and free-living physical activity in black and white women: comparison and after weight loss	Unclear/inadequate methodology for AT
60	**(Wadden et al., 1996)**	Effects of weight cycling on the resting energy expenditure and body composition of obese women.	Unclear/inadequate methodology for AT
61	**(Leibel et al., 1995)**	Changes in energy expenditure resulting from altered body weight	Sample size <10
62	**(Schultink et al., 1993)**	Seasonal weight-loss and metabolic adaptation in rural beninese women - the relationship with body-mass index.	No measurements of body composition stores Body composition - Skinfolds
63	**(Luke & Schoeller, 1992)**	Basal metabolic rate, fat-free mass, and body cell mass during energy restriction.	Unclear/inadequate methodology for AT
64	**(Manore et al., 1991)**	Energy expenditure at rest and during exercise in nonobese female cyclical dieters and in nondieting control subjects.	Unclear/inadequate methodology for AT

65	**(Andersson et al., 1991)**	The effects of exercise training on body composition and metabolism in men and women.	Unclear/inadequate methodology for AT
66	**(Melby et al., 1991)**	Diet- induced weight loss and metabolic changes in obese women with high versus low prior weight loss/regain.	No measurements of body composition stores
67	**(Lemons et al., 1989)**	Selection of appropriate exercise regimes for weight reduction during VLCD and maintenance.	Unclear/inadequate methodology for AT
68	**(Garby et al., 1988)**	Effect of 12 weeks' light-moderate underfeeding on 24-hour energy expenditure in normal male and female subjects	No measurements of body composition stores
69	**(Bessard et al., 1983)**	Energy expenditure and postprandial thermogenesis in obese women before and after weight loss.	Intervention < 1 week

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CHAPTER 5

ADAPTIVE THERMOGENESIS AFTER MODERATE WEIGHT LOSS: MAGNITUDE AND METHODOLOGICAL ISSUES [2]

[2] **Nunes, C. L.,** Jesus, F., Francisco, R., Matias, C. N., Heo, M., Heymsfield, S. B., Bosy-Westphal, A., Sardinha, L. B., Martins, P., Minderico, C. S., & Silva, A. M. (2022, Apr). Adaptive thermogenesis after moderate weight loss: magnitude and methodological issues. Eur J Nutr, 61(3), 1405-1416. https://doi.org/10.1007/s00394-021-02742-6;

ADAPTIVE THERMOGENESIS AFTER MODERATE WEIGHT LOSS: MAGNITUDE AND METHODOLOGICAL ISSUES

Catarina L Nunes, Filipe Jesus, Ruben Francisco, Catarina N Matias, Moonseong Heo, Steven B Heymsfield, Anja Bosy-Westphal, Luis B Sardinha, Paulo Martins, Cláudia S Minderico, Analiza M Silva

5.1. ABSTRACT

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. Ninety-four participants [mean(SD); BMI, 31.1(4.3)kg/m^2; age, 43.0(9.4)y; 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. IG underwent a mean negative energy balance(EB) of 270(289)kcal/d, p<0.001), resulting in a WL of -4.8(4.9)% and a FM loss of -11.3(10.8)%. Regardless of approach, AT occurred in the IG, ranging from ~-65 to ~-230 kcal/d and three approaches showed significant AT in the CG. 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.

Key-words: Metabolic Adaptation, Metabolic Slowing, Resting Energy Expenditure, Energy Balance.

5.2. 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 (Edholm et al., 1970) and change in response to perturbations in either side of the equation (Casanova et al., 2019; Melby et al., 2017).

Interventions aimed at losing weight are abundant in the current literature (Felix & West, 2013; Ma et al., 2017). 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 (Gurevich-Panigrahi et al., 2009). Additionally, the existence of metabolic, behavioral, and psychological compensations that may occur during negative EB, including compensatory changes in EE (Thomas et al., 2012), spontaneous PA (Levine et al., 1999) and increases in EI (Hollstein et al., 2021) have been studied.

Originally called “luxuskonsumption”, evidence regarding the existence of adaptive thermogenesis (AT) was reported at the beginning of the last century (Gulick, 1995; Neumann, 1902). 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 (Hervey & Tobin, 1983; Rothwell & Stock, 1983). In 1995, Leibel et al (Leibel et al., 1995) 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 (Dulloo et al., 2012; Major et al., 2007).

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 (Heinitz et al., 2020) 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 (Heinitz et al., 2020). However, AT's existence has been recently questioned, especially in the long-term weight management (Browning et al., 2017; Gomez-Arbelaez et al., 2018; Marlatt et al., 2017; C. Martins et al., 2020; Catia Martins et al., 2020; Novaes Ravelli et al., 2019; Wolfe et al., 2018), whereas some authors showed that AT may difficult WL and promote weight regain in studies inducing massive WL (Bettini et al., 2018; Carrasco et al., 2007; Tam et al., 2016; Wolfe et al., 2018), others argued that the suppositions regarding AT are exaggerated (Flatt, 2007; Kuchnia et al., 2016).

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 (Müller & Bosy-Westphal, 2013). To our knowledge, only Byrne et al (Byrne et al., 2018) assessed AT using more than 1 approach to calculate changes in REE, using 3 different equations to predict REE. As their goal was to compare 2 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.

5.3. METHODOLOGY

5.3.1. 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) (Silva et al., 2020). A schematic description of the study phases is presented in **Figure 1.**

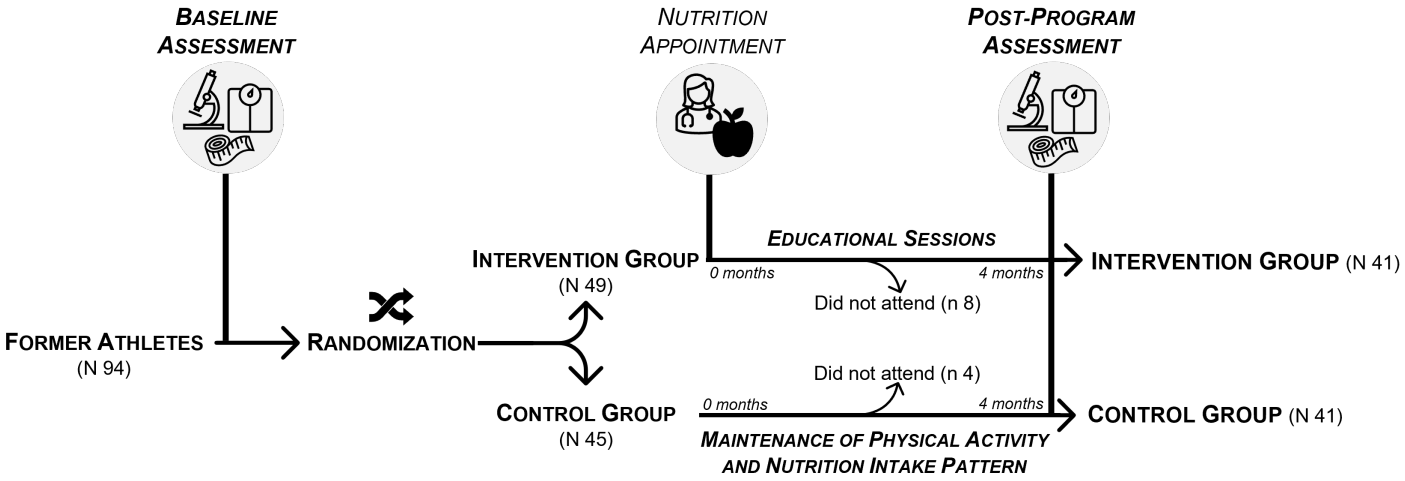

Figure 5.1. Schematic description of the study phases.

A total of 94 healthy participants of both sexes were selected and randomly assigned to 1 of the 2 groups: intervention or control group. All of the participants were overweight/obese (BMI≥ 24.9kg/m^2), inactive (<20min/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 (American College of Sports et al., 2018)), aged 18-65 years and ready to modify their diet in order to achieve a lower body weight. For a more detailed description of inclusion and exclusion criteria, see the study protocol (Silva et al., 2020). In this study, we used measurements made at baseline (0 months) and after the intervention (4 months).

5.3.2. Lifestyle intervention

Nutritional appointments were given by a registered dietitian to each participant. This meeting was intended to provide a well-balanced personalized diet plan, calculated to create a moderate energy restriction from ~300 to 500kcal/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.

5.3.3. Anthropometry

Subjects had their weight and height measured wearing a bathing suit and without shoes to the nearest 0.01kg and 0.1cm, respectively, with a scale and stadiometer (Seca, Hamburg, Germany). Body mass index was calculated using the formula [weight(*kg)*/height^2(m^2)].

5.3.4. 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 140kV 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 program. 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 to 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 (Lewiecki et al., 2016). All the assessments (before and after the intervention) were performed by the same investigator.

5.3.5. 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 22ºC 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 minutes 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 minutes. The first and the last 5 min of data collection were discarded. Steady state intervals were defined as 5-minute periods with ≤10% CV for $\dot{V}O_2$ and $\dot{V}CO_2$ and Respiratory Exchange Ratio between 0.7 and 1.0 (Compher et al., 2006). The mean $\dot{V}O_2$ and $\dot{V}CO_2$ of 5 min steady states was used in Weir equation (Weir, 1949) and the period with the lowest REE was considered for data analysis.

5.3.6. Adaptive Thermogenesis (AT)

In order to detect differences in REE beyond what we would expect from body compositions alterations, AT was assessed through different approaches, varying in how predicted REE ($_{p}$REE) was calculated and/or how AT was assessed **(table 5.1)**.

To identify the 4 used approaches regarding the $_{p}$REE, numbers 1 to 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 (Hayes et al., 2002).

Regarding the assessment of AT, 4 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) (Byrne et al., 2018);

B) AT was assessed simply by subtracting pREE (assessed through one of the 4 aforementioned equations) from mREE (indirect calorimetry), at the end of the intervention (4 months) (Byrne et al., 2018; Catia Martins et al., 2020; Thom et al., 2020);

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) (Browning et al., 2017; Ten Haaf et al., 2018);

D) %AT was calculated as 100 × [(mREE / pREE) – 1) after 4 months and therefore AT is assessed as (%AT / 100) x mREE at baseline (Borges et al., 2019; Silva et al., 2017).

Table 5.1. Methodologies to assess AT

		METHODOLOGY		
Approach		**TO ASSESS AT**		**TO PREDICT REE**
A	***A***	AT(kcal.d^{-1})=$^{4mo}_{m}REE_{adjFM/FFM} - {}^{baseline}_{m}REE_{adjFM/FFM}$	NA	
B.1	***B***	AT(kcal.d^{-1}) = $^{4mo}_{m}REE - {}^{4mo}_{p}REE$	***1***	$_{p}$REE (kcal.d^{-1}) = 581.9 + 17.6×FFM$_{(kg)}$ †
B.2			***2***	$_{p}$REE (kcal.d^{-1}) = 505.2 + 2.8 × FM$_{(kg)}$ + 17.5 × FFM$_{(kg)}$ ‡
B.3			***3***	$_{p}$REE (kcal.d^{-1}) = 604.6 + 17.6×sex$_{(0=male,\ 1=female)}$ – 1.621 × age + 2.902 × FM$_{(kg)}$ + 16.8 × FFM$_{(kg)}$ §
B.4			***4***	According to Hayes *et al.* (Hayes et al., 2002)*
C.1	***C***	AT(kcal.d^{-1}) = [($^{4mo}_{m}REE - {}^{4mo}_{p}REE$) – ($^{Baseline}_{m}REE - {}^{baseline}_{p}REE$)];	***1***	$_{p}$REE (kcal.d^{-1}) = 581.9 + 17.6×FFM$_{(kg)}$ †
C.2			***2***	$_{p}$REE (kcal.d^{-1}) = 505.2 + 2.8 × FM$_{(kg)}$ + 17.5 × FFM$_{(kg)}$ ‡
C.3			***3***	$_{p}$REE (kcal.d^{-1}) = 604.6 + 17.6×sex$_{(0=male,\ 1=female)}$ – 1.621 × age + 2.902 × FM$_{(kg)}$ + 16.8 × FFM$_{(kg)}$ §
C.4			***4***	According to Hayes *et al.* (Hayes et al., 2002)*
D.1	***D***	%AT = 100 × ($\frac{^{4mo}_{m}REE}{^{4mo}_{p}REE} - 1$) AT(kcal.d^{-1}) = $\frac{\%AT}{100} \times {}^{baseline}_{m}REE$	***1***	$_{p}$REE (kcal.d^{-1}) = 581.9 + 17.6×FFM$_{(kg)}$ †
D.2			***2***	$_{p}$REE (kcal.d^{-1}) = 505.2 + 2.8 × FM$_{(kg)}$ + 17.5 × FFM$_{(kg)}$ ‡
D.3			***3***	$_{p}$REE (kcal.d^{-1}) = 604.6 + 17.6×sex$_{(0=male,\ 1=female)}$ – 1.621 × age + 2.902 × FM$_{(kg)}$ + 16.8 × FFM$_{(kg)}$ §
D.4			***4***	According to Hayes *et al.* (Hayes et al., 2002)*

† 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);

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

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

For all situations, negative values indicate a higher-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) (Thomas et al., 2012).

5.3.7. Calculation of Energy Balance (EB)

The EB equation is denoted as follows:

$$\text{ES (kcal/d)} = \text{EI} - \text{EE}$$

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:

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

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.

5.3.8. 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 (Jensen et al., 2014)) *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 modelled as compound symmetry. The one-sample t-test was performed to test the significance for AT.

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

5.4. RESULTS

A total of 94 participants [BMI = 31.1 (4.3)kg/m^2, age = 43.0 (9.4)y, 34% females] were included. Changes in body composition and resting energy expenditure are presented in **table 5.2.** A detailed description of the main results of the Champ4life project is presented elsewhere (Silva et al., 2021).

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, $p<0.05$).

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 a FM loss of -11.3 (10.8)%. The control group presented a EB of 14 (129) kcal/d (not different from zero, $p=0.489$), as no significant WL or changes in body composition stores were observed.

Table 5.2. 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/d)		Baseline	1643 (15)	1645 (15)	**Changes †**	**95%CI**	**p-value**
		Post-programme	1622 (17)	1526 (17)‡	-97	-161 , -33	0.003
$_{p}$REE (kcal/d)	**Eq 1**	Baseline	1644 (3)	1644 (3)	**Changes †**	**95%CI**	**p-value**
		Post-programme	1637 (4)	1626 (4)	-12	-26 , 2	0.089
	Eq 2	Baseline	1643 (4)	1643 (3)	**Changes †**	**95%CI**	**p-value**
		Post-programme	1639 (4)	1617 (4)	-23	-37 , -8	0.002
	Eq3	Baseline	1643 (3)	1643 (3)	**Changes †**	**95%CI**	**p-value**
		Post-programme	1641 (4)	1619 (4)‡	-23	-37 , -9	0.002
	Eq 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).
* All models were adjusted for baseline values and sex.
Abbreviations: SD, Standard deviation; CI, confidence interval.
Eq 1: $_{p}REE\ (kcal.d^{-1}) = 581.9 + 17.6 \times FFM_{(kg)}$
Eq 2: $_{p}REE\ (kcal.d^{-1}) = 505.2 + 2.8 \times FM_{(kg)} + 17.5 \times FFM_{(kg)}$
Eq 3: $_{p}REE\ (kcal.d^{-1}) = 604.6 + 17.6 \times sex_{(0=male,\ 1=female)} - 1.621 \times age + 2.902 \times FM_{(kg)} + 16.8 \times FFM_{(kg)}$
Eq 4: According to Hayes *et al.* (Hayes et al., 2002)
‡ Differences within group between baseline and post-programme, $p<0.05$
† Difference in differences estimated changes
$(\text{Post-programme}_{intervention} - \text{baseline}_{intervention}) - (\text{Post-programme}_{control} - \text{baseline}_{control})$

Adaptive thermogenesis' assessment - comparison among approaches

The results for AT are presented in **table 5.3.**

The intervention group showed a significant AT for all 4 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 ($p<0.05$).

Table 5.3. 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, $p<0.05$.

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. to 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 **Figure 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).**

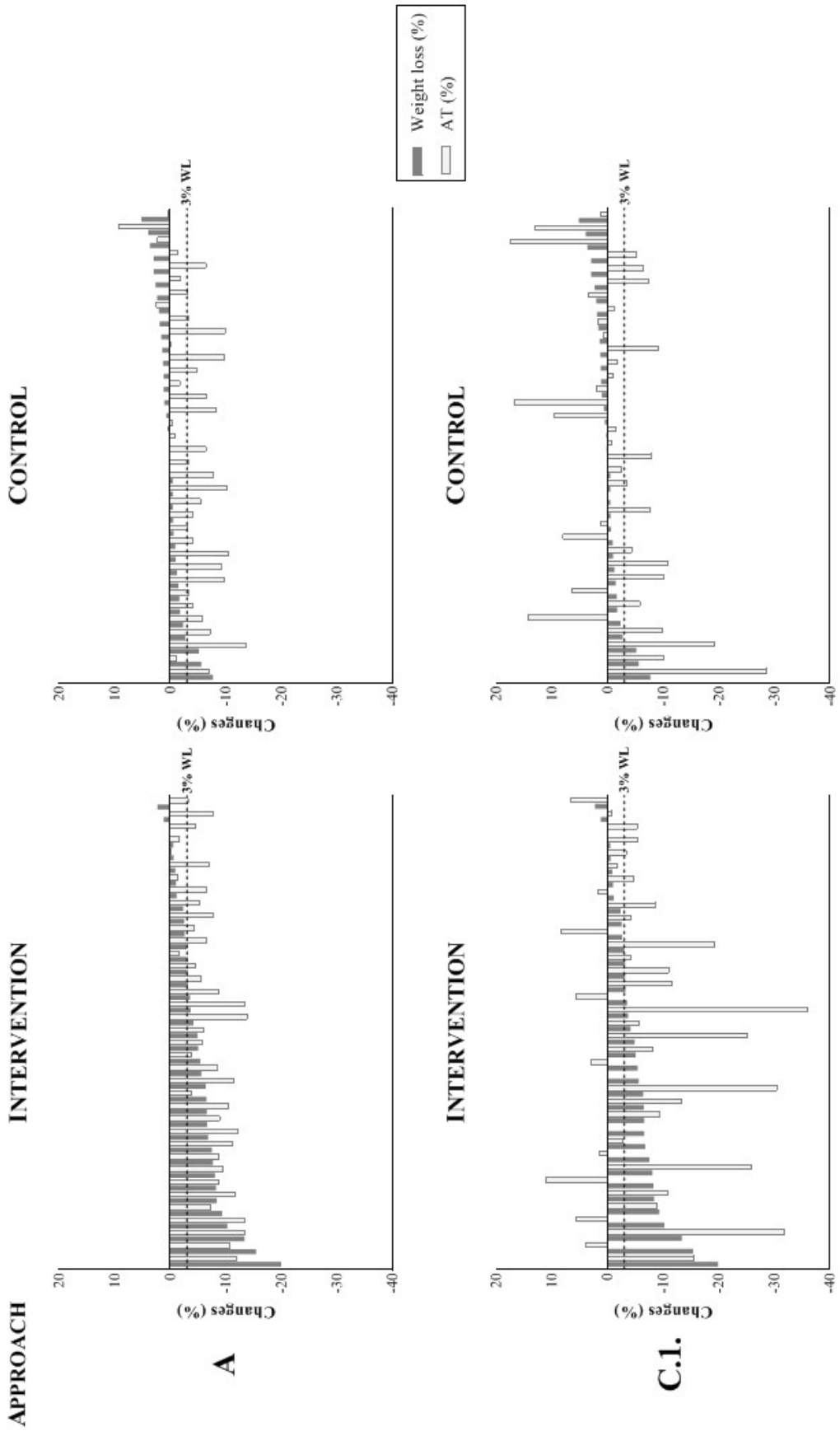

Figure 5.2. Variability of AT (presented as percentage related to post programme REE) and %WL for approach A and C.1 for intervention and control groups.

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 5.4.** 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)y] 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)y], with 91.4 (17.9)kg 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 5.4. 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

5.5. 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/d 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 higher-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) (Gomez-Arbelaez et al., 2018; C. Martins et al., 2020; Thom et al., 2020). Other studies performed a similar approach but considering the baseline residuals (measured minus predicted REE at baseline) (Browning et al., 2017; Ten Haaf et al., 2018). 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) (Byrne et al., 2018) or as described in Thomas et al (Borges et al., 2019; Thomas et al., 2012). 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 (MacLean et al., 2011; Major et al., 2007) and blunted activity of the sympathetic nervous system (Major et al., 2007). A leptin reduction is usually associated with an increase in hunger and consequently increased EI (Mars et al., 2006; Mars et al., 2005), leading to a neutral or even positive EB, jeopardizing WL. Moreover, Tremblay et al (Tremblay et al., 2004), showed that changes in circulating organic pollutants (organochlorines), known for their anti-thermogenic properties, were the main predictor 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 (Pardini, 1971) and they seem to be an independent predictor of the REE (Pelletier et al., 2002). 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 (Casanova et al., 2019). 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 to C.4) showed differences between groups ($p<0.05$). Nevertheless, all approaches showed significant values for AT for those who had a WL $\geq$ 3%. Also, AT seems to be irrelevant for the other group, as only 3 approaches significant AT values.

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 (Browning et al., 2017; de Jonge et al., 2012; Gomez-Arbelaez et al., 2018; Karl et al., 2015; Marlatt et al., 2017; Novaes Ravelli et al., 2019; Pourhassan et al., 2014; Wolfe et al., 2018). 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 (Muller et al., 2016). However, only a few studies used this method due to the considerable time and cost associated (Bosy-Westphal, Kossel, et al., 2009; Bosy-Westphal, Schautz, et al., 2013; Müller et al., 2015). Hayes et al (Hayes et al., 2002) 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 (Gomez-Arbelaez et al., 2018; Karl et al., 2015; C. Martins et al., 2020; Nymo et al., 2018; Thom et al., 2020). 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.d^{-1})=[($^{4mo}_{m}REE - {}^{4mo}_{p}REE$) – ($^{Baseline}_{m}REE - {}^{baseline}_{p}REE$)]) reduces the large discrepancy between data treatment regarding pREE (approaches 1 to 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 (Bosy-Westphal, Braun, et al., 2013; Bosy-Westphal, Müller, et al., 2009). It is recognized that after WL, anatomical and molecular changes on FFM occur. Recently, Müller et al (Müller et al., 2021) 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 (Müller et al., 2021). 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 (Nunes et al., 2021). Firstly, 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 (Johnstone et al., 2005). 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) (Johannsen et al., 2012; Rosenbaum & Leibel, 2016). 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 (Müller, 2019), 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) (Piaggi et al., 2018). 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 higher-than-expected decrease in REE.

Our AT values are consistent with those presented in other similar studies with smaller energy deficit (Bosy-Westphal, Kossel, et al., 2009; Karl et al., 2015; C. Martins et al., 2020; McNeil et al., 2015; Müller et al., 2015; Ten Haaf et al., 2018). 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 (Muller et al., 2016).

Although the current study reveals clear discrepancies between methods to assess AT some limitations should be addressed. Firstly, 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-program 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 (Karl et al., 2015; C. Martins et al., 2020). 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) (Fothergill et al., 2016) 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 (Kuchnia et al., 2016), it is important to underscore that this type of intervention (intensive diet and exercise intervention to promote a massive WL) do 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 two out of the thirteen 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.

Ethics approval

The Ethics Committee of the Faculty of Human Kinetics, University of Lisbon (Lisbon, Portugal), approved the study (CEFMH Approval Number: 16/2016).

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Supplementary File 1.

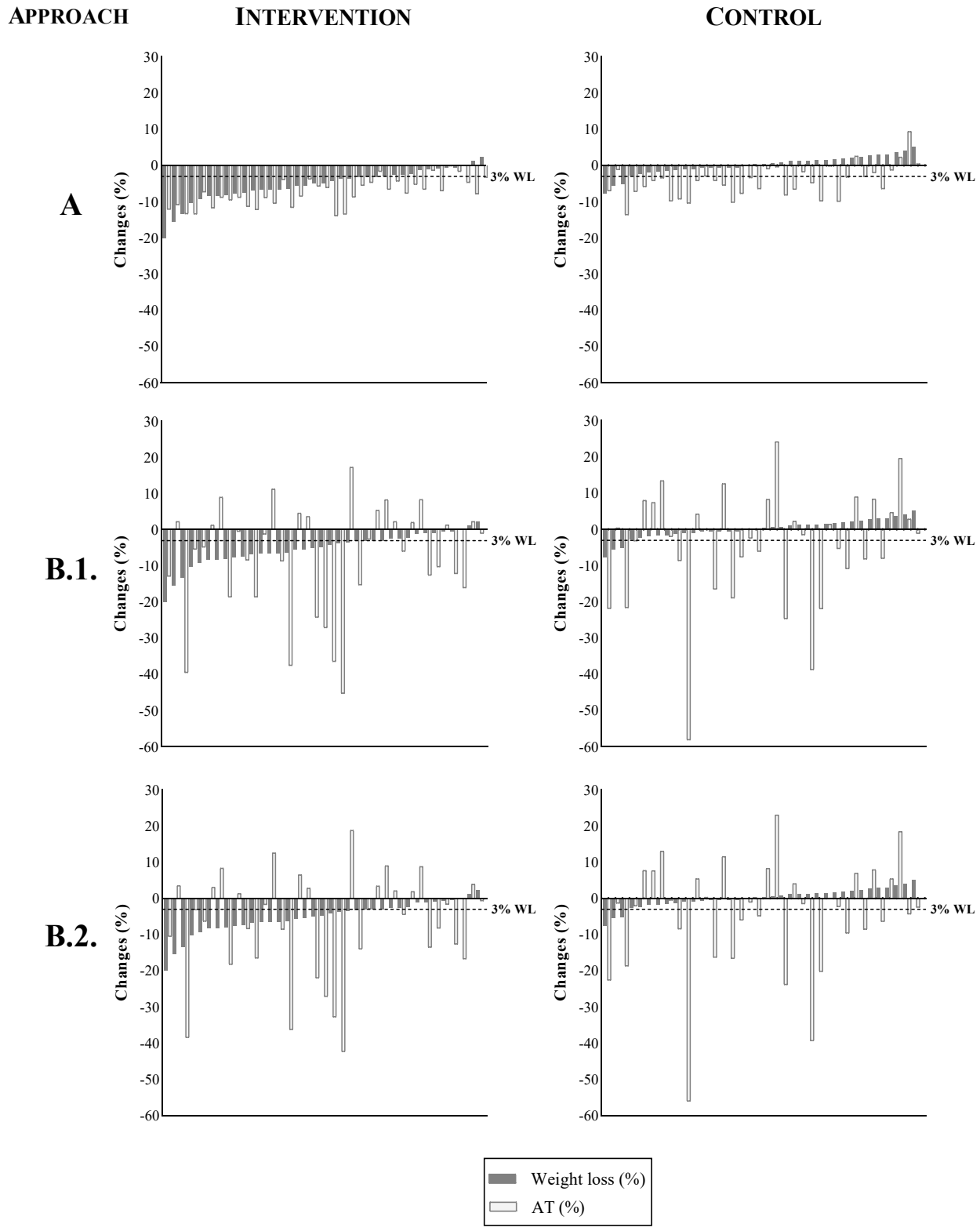

Figure S5.3. Variability of each AT approach (presented as a percentage related to post programme REE) And %WL for intervention and control group (*to continue*).

Figure S5.3. Continued

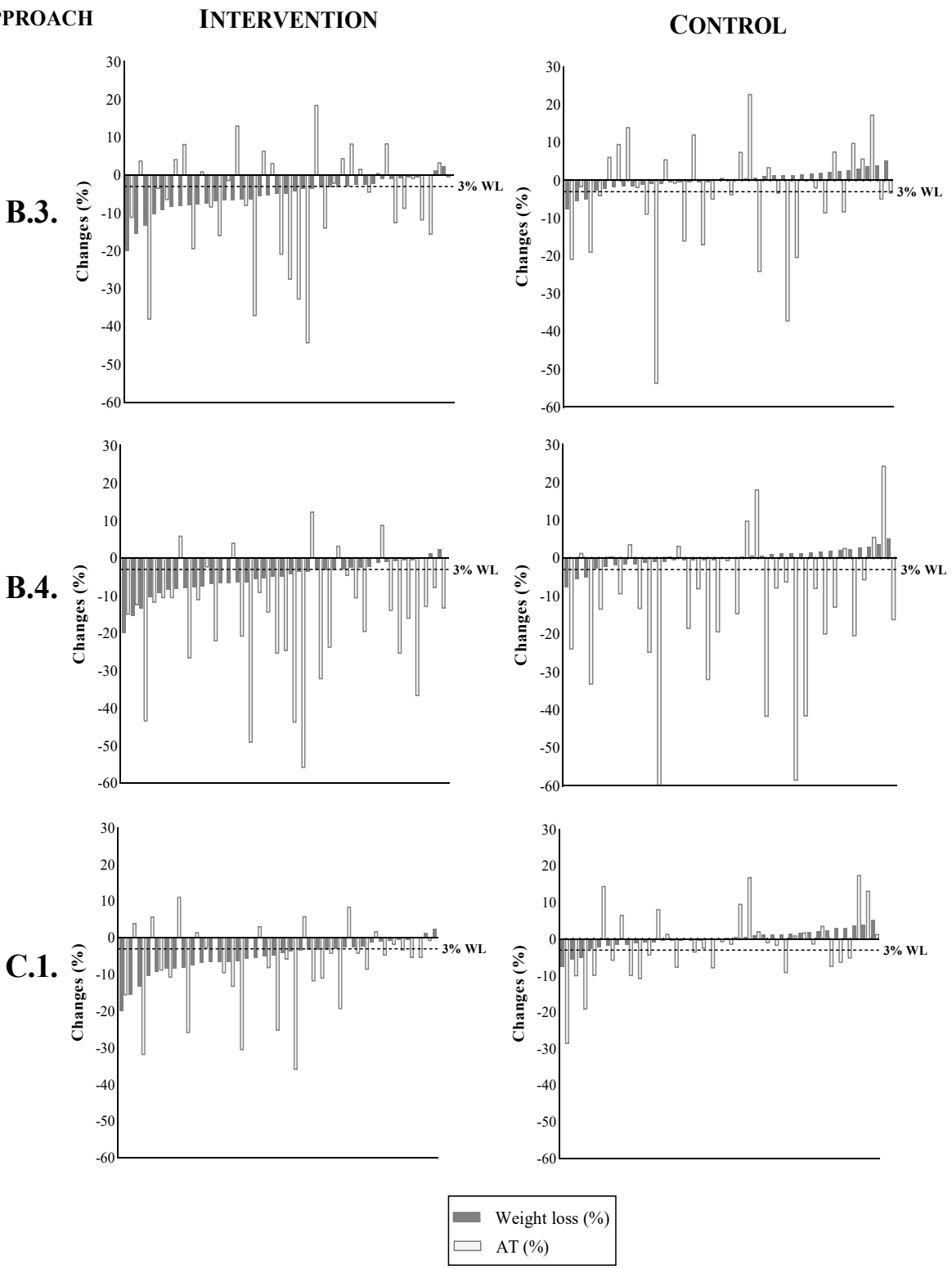

Figure S5.3. Variability of each AT approach (presented as a percentage related to post programme REE) And %WL for intervention and control group (*to continue*).

Figure S5.3. Continued

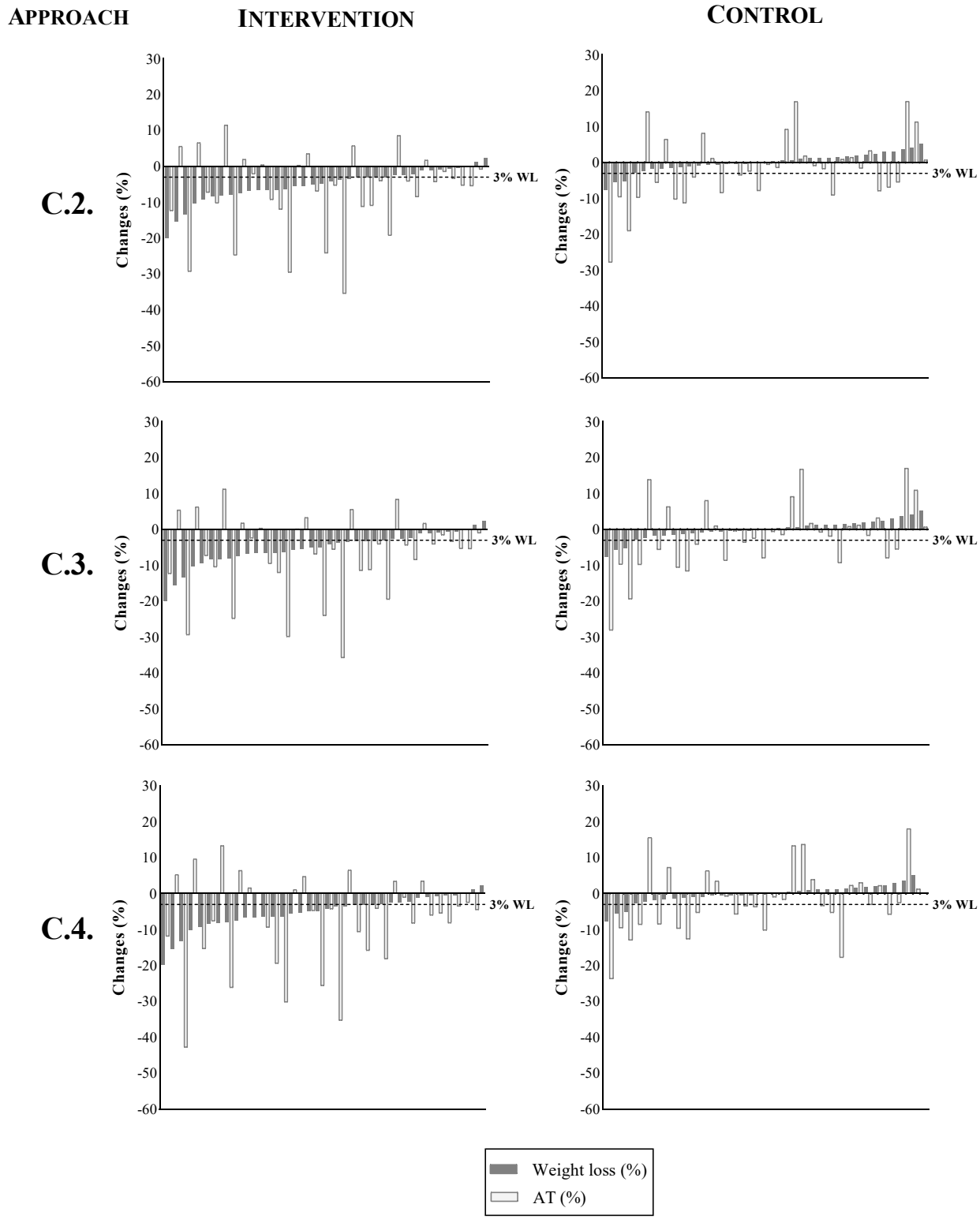

Figure S5.3. Variability of each AT approach (presented as a percentage related to post programme REE) And %WL for intervention and control group (*to continue*).

Figure S5.3. Continued

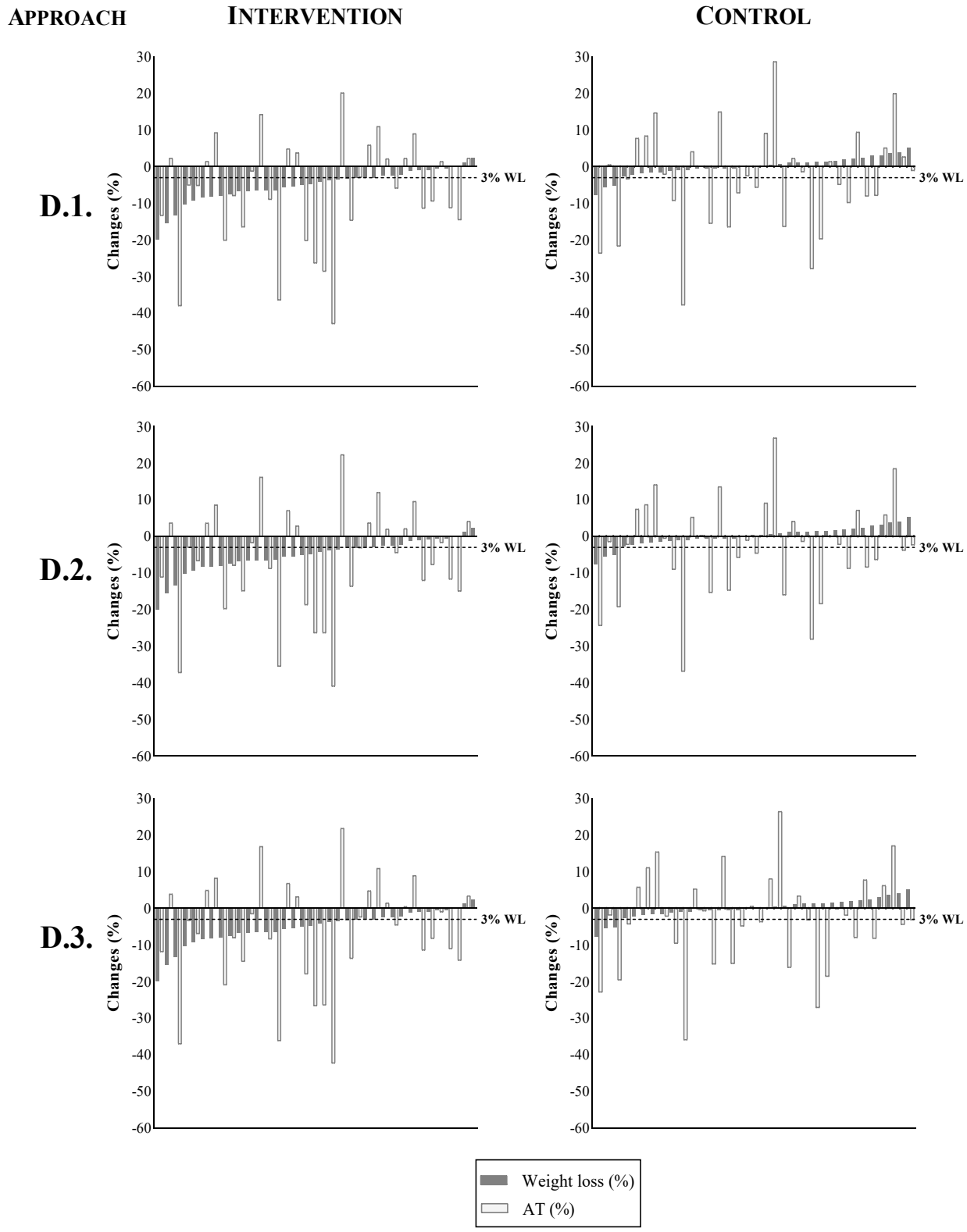

Figure S5.3. Variability of each AT approach (presented as a percentage related to post programme REE) And %WL for intervention and control group (*to continue*).

Figure S5.3. Continued

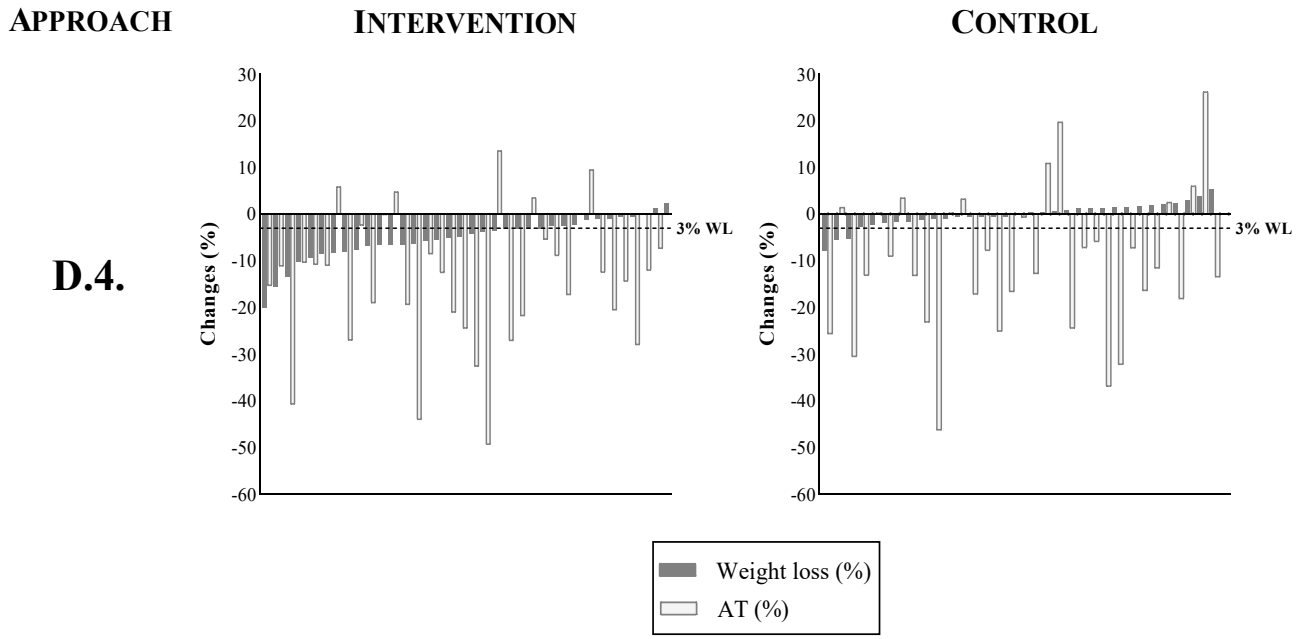

Figure S5.3. Variability of each AT approach (presented as a percentage related to post programme REE) And %WL for intervention and control group.

CHAPTER 6

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 [3]

[3] **Nunes, C. L.,** Jesus, F., Francisco, R., Hopkins, M., Sardinha, L. B., Martins, P., Minderico, C. S., & Silva, A. M. (2022, Dec). 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. Eur J Nutr, 61(8), 4121-4133. https://doi.org/10.1007/s00394-022-02951-7

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 Nunes, Filipe Jesus, Ruben Francisco, Mark Hopkins, Luís B Sardinha, Paulo Martins, Cláudia S Minderico, Analiza M Silva

6.1. ABSTRACT

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). Ninety-four participants [mean(SD); BMI, 31.1(4.3)kg/m^2; 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. 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 where 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. 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.

Key-words: Energy balance, Metabolic adaptation, resting energy expenditure

6.2. 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 (Aronne et al., 2021; Fildes et al., 2015).

During WL, changes in energy expenditure (EE) components are expected to occur as a consequence of changes in FM and FFM (Muller et al., 2016), such as decreases in resting and non-resting energy expenditure (Leibel et al., 1995; MacLean et al., 2011). However, it has been shown that some changes in components of EE occur to a greater extent than would be predicted based on changes in body composition stores (Nunes, Casanova, et al., 2021b). 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) (Dulloo et al., 2012; Major et al., 2007).

While AT after WL has been widely studied and discussed (Nunes, Casanova, et al., 2021a), the lack of concordance among methodologies employed to assess AT and/or how REE is predicted was recently highlighted (Nunes, Jesus, et al., 2021). AT has been studied as a possible barrier specially in WL maintenance, contributing to weight regain (Fothergill et al., 2016; Johannsen et al., 2012; Tremblay et al., 2013). 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 (Gomez-Arbelaez et al., 2018; Marlatt et al., 2017; C. Martins et al., 2020; Novaes Ravelli et al., 2019; Wolfe et al., 2018). Regarding moderate WL, while some studies suggest that a disproportionate decrease in REE appears during WL and may persist during the weight-reduced state (Fothergill et al., 2016; Rosenbaum et al., 2008), others have found no evidence of AT in any of the EE components (Bosy-Westphal et al., 2013; Hopkins et al., 2014). In addition, the limited number of studies available assessing AT during a WL maintenance typically employ weak-to-moderate designs, being mostly observational studies or controlled trials without a control group (Nunes, Casanova, et al., 2021b).

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.

6.3. METHODOLOGY

This is a secondary analysis of the Champ4life project (Silva et al., 2020), 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 (<20min/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 (American College of Sports et al., 2018)) and with a body mass index (BMI) ≥ 24.9kg/m^2. 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 (Silva et al., 2021; Silva et al., 2020).

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.(World Medical Association, 2008) 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).

6.3.1. The Champ4life intervention

The Champ4life was a 1-year intervention SDT-based (Marques & Hagger, 2019), 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 (~300-500kcal.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 (Silva et al., 2020). 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 in order 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 (Silva et al., 2020).

6.3.2. Body composition

Participants had their weight and height measured wearing a bathing suit and without shoes to the nearest 0.01kg and 0.1cm, 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) (Park et al., 2002). FM and LST were also presented for subregions, 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 (Sherman et al., 2011) . Therefore, in 6 participants this technique was considered for the body composition analysis.

6.3.3. 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 22ºC and 40-50%, respectively. The MedGraphics CPX Ultima indirect calorimeter (MedGraphics Corporation, Breezeex Software, Italy) was used to measure breath-by-breath oxygen consumption ($\dot{V}O2$) and carbon dioxide production

($\dot{V}CO2$) using a face mask, for 30 minutes. Before the measurement, participants lay in a supine position for 15 minutes covered with a blanket. The first and the last 5 minutes of data collection were discarded and the mean $\dot{V}O2$ and $\dot{V}CO2$ of 5 min steady states was used in Weir equation (Weir, 1949) and the period with the lowest REE was considered for data analysis. Steady state was defined as a 5-minute period with ≤10% CV for $\dot{V}O2$ and $\dot{V}CO2$ (Compher et al., 2006). 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 (Silva et al., 2020).

6.3.4. Predicted Resting Energy Expenditure ($_p$REE)

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

$$pREE = 505.240 + 2.766 \times FM(kg) + 17.531 \times FFM(kg)$$

(r^2=0.570, p<0.001)

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

6.3.5. 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 (Silva et al., 2021). EE was estimated as the sum of REE, PAEE and thermic effect of food (TEF):

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

The TEF component was assumed as 10% of TDEE (Weststrate, 1993).

6.3.6. Adaptive thermogenesis (AT)

AT was assessed after 4 months WL and 8 months 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(kcal.d^{-1}) = [(${}^{4mo}_{m}REE - {}^{4mo}_{p}REE$) – (${}^{Baseline}_{m}REE - {}^{baseline}_{p}REE$)];

After 8 months of follow-up

AT(kcal.d^{-1}) = [(${}^{12mo}_{m}REE - {}^{12mo}_{p}REE$) – (${}^{Baseline}_{m}REE - {}^{baseline}_{p}REE$)]

Negative values indicate a higher-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) (Thomas et al., 2012).

6.3.7. Energy balance (EB)

In order 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:

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

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 (Merril; & Watt.) and FFM (Dulloo & Jacquet, 1999), the following equation was applied:

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

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.

6.3.8. Energy intake (EI)

EI was estimated by the "intake-balance method" (Rosenbaum et al., 1996). This method has been previously validated (Racette et al., 2012; Shook et al., 2018) 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.

6.3.9. 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 - 500kcal.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 300-500kcal).

Adherence was assessed through the following equation proposed by Racette et al (Racette et al., 2012):

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

6.3.10. Blood Samples

Blood samples were collected according to the standard procedures by venipuncture from the antecubital vein into ethylenediaminetetraacetic 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 -80ºC for posterior analyses.

The thyroid panel [including Thyroid-Stimulating Hormone (TSH) free tri-iodothyronine (FT3) and free thyroxine (FT4)] and insulin were assessed by immunoquimioluminescence (ECLIA) in a different automated analyzer (Cobas e411, Roche Diagnostics, Portugal). Serum levels of leptin were assessed by ELISA (enzyme-

linked immunosorbent assay) by using commercial kits (DIAsource ImmunoAssays, Belgium).

6.3.11. 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 modelled 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 was 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 (Bonafiglia et al., 2018). Statistical significance was set at a two-sided $p<0.05$.

6.4. 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]. Values of body composition, blood biomarkers, and changes between time points are presented in **table 6.1**. No differences were found between groups for baseline variables ($p>0.05$).

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 ($p<0.001$). For the blood biomarkers, insulin decreased for the IG after the 1-year intervention (Estimated difference (ED)=-5.1, [95% CI: -8.7 to -1.5], 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: -6.0 to -1.6], p=0.001) and 12-month (ED=-4.3, [95% CI: -7.0 to -1.7], p=0.002) 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, and FFM), 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 programme, 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).

Table 6.1. Values of body composition and blood biomarkers*

			Control (n=45)	Intervention (n=49)			
Body Composition	*Weight (kg)*	Baseline	91.2 (0.5)	91.1 (0.4)	**Changes †**	**95% CI**	**p-value**
		4months	91.5 (0.5)	86.8 (0.5)‡	-4.7	-6.1, -3.3	<0.001
		12months	92.2 (0.5)	86.8 (0.5)§	-5.3	-6.9, -3.8	<0.001
	BMI (kg/m²)	Baseline	31.0 (0.2)	31.0 (0.2)	**Changes †**	**95% CI**	**p-value**
		4months	31.1 (0.2)	29.5 (0.2)‡	-1.6	-2.1, -1.1	<0.001
		12months	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**
		4months	30.1 (0.4)	26.3 (0.4)‡	-3.8	-5.1, -2.6	<0.001
		12months	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**
		4months	33.3 (0.3)	30.7 (0.3)‡	-2.6	-3.6, -1.7	<0.001
		12months	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**
		4months	59.9 (0.2)	59.3 (0.2)‡	-0.7	-1.5, 0.1	0.118
		12months	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**
		4months	15.1 (0.7)	14.9 (0.7)‡	-2.1	-2.9, -1.3	<0.001
		12months	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**
		4months	29.0 (0.6)	29.0 (0.6)	-0.2	-0.8, 0.4	0.472
		12months	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**
		4months	12.2 (0.5)	11.6 (0.5)‡	-1.5	-2.0, -0.9	<0.001
		12months	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**
		4months	26.6 (0.6)	26.8 (0.6)‡	-0.6	-1.1, -0.1	0.029
		12months	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**
		4months	11.1 (0.8)	9.2 (0.8)‡	-2.9	-5.8, 0.1	0.078
		12months	14.1 (0.9)†	10.2 (0.9)§	-4.9	-8.0, -1.8	0.006
	TSH (µUl/mL)	Baseline	2.1 (0.1)	2.2 (0.1)	**Changes**	**95% CI**	**p-value**
		4months	2.0 (0.1)	2.0 (0.1)	-0.04	-0.32, 0.25	0.802
		12months	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**
		4months	3.2 (0.05)	3.1 (0.05)‡	-0.10	-0.29, 0.10	0.328
		12months	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**
		4months	1.2 (0.02)	1.2 (0.02)‡	-0.02	-0.11, 0.06	0.563
		12months	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**
		4months	24.1 (0.6)	20.8 (0.6)‡	-3.8	-5.9, -1.7	<0.001
		12months	23.2 (0.7)	19.5 (0.7)§	-4.2	-6.5, -2.0	<0.001

Data is presented as estimated means (SE) from linear mixed models.
* 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 months and 12 months, p<0.05.
Changes: Differences in change scores between control and intervention groups e.g., (4 months/12months$_{intervention}$ – baseline$_{intervention}$) - (4 months/12months$_{control}$ – baseline$_{control}$).

The values for REE and AT are presented in **table 6.2.**

Table 6.2. Resting energy expenditure (measured and predicted) and adaptive thermogenesis. Data is presented as estimated means (SE) from linear mixed models, with all models adjusted for sex.

		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
	4months	1605 (40)	1525, 1684	1549 (39)‡	1472, 1625	
	12months	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
	4months	1635 (24)	1587, 1682	1631 (23)‡	1585, 1677	
	12months	1624 (24)	1576, 1671	1629 (23)§	1583, 1675	
mREE – pREE (kcal.d^{-1})	Baseline	-3 (32)	-65, 59	5 (30)	-54, 65	0.001
	4months	-32 (33)	-97, 34	-78 (33)‡	-142, -13	
	12months	98 (35)†	29, 167	-66 (35)	-135, 2	
AT (kcal.d^{-1})	Baseline	NA	NA	NA	NA	0.012
	4months	-26(29)	-87, 28	-85 (29)*	-143, -28	
	12months	88 (31)*†	27, 149	-72 (31)*	-134, -10	

$_{m}$REE – measured resting energy expenditure (indirect calorimetry); $_{p}$REE – predicted resting energy expenditure (predictive equation); AT – adaptive thermogenesis.

* Statistically different from zero (t-test) (only for AT).

‡ Differences within group between baseline and 4months, p<0.05.

§ Differences within group between baseline and 12 months, p<0.05.

† Differences within group between 4months and 12 months, p<0.05.

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 %), Δtrunk (FM and LST), Δappendicular (FM and LST) and blood biomarkers, except for AT and Δtrunk FM (%) at the end of the intervention (12 months) (R=0.294, p=0.031).

Changes in body composition stores (FM and FFM) and in REE (measured and predicted) are displayed in **Figure 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 where 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 6.3.**

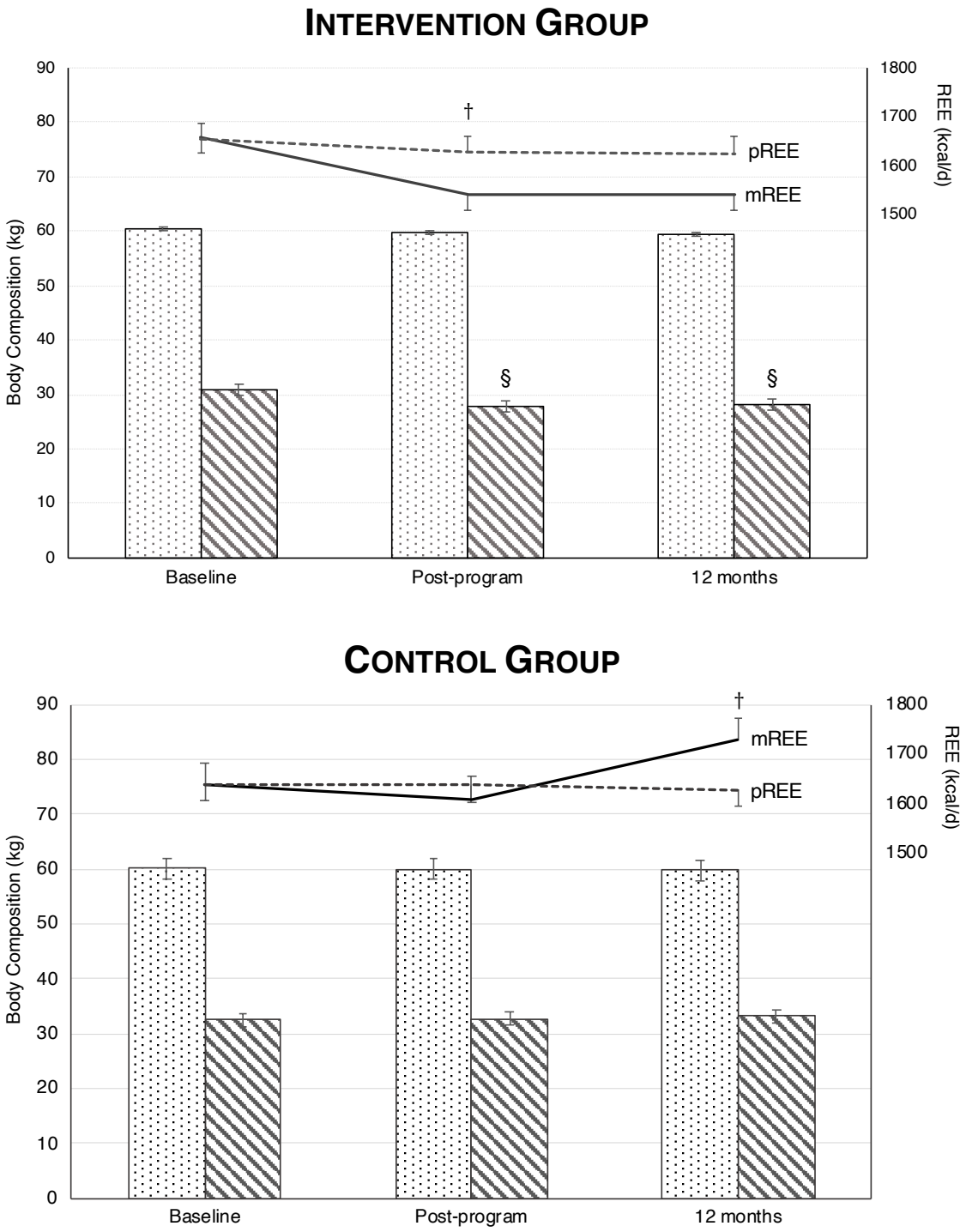

Figure 6.1. Changes in body composition stores (FM and FFM) and Resting Energy Expenditure (mREE and pREE) from mixed model analysis (estimated means (SE), n = 94).

Table 6.3. Comparisons between thrifty and spendthrift individuals from the IG *.

			Thrifty (n=11)	Spendthrift (n=25)			
Body Composition	*Weight (kg)*	Baseline	92.0 (3.2)	91.7 (4.0)	**Changes †**	**95% CI**	**p-value**
		4months	88.5 (3.2)‡	85.3 (4.0)‡	-2.8	-5.4, -0.3	0.032
		12months	88.5 (3.2)§	84.9 (4.0)§	-3.2	-5.9, -0.5	0.020
	BMI (kg/m²)	Baseline	31.0 (0.9)	31.9 (1.1)	**Changes †**	**95% CI**	**p-value**
		4months	29.8 (0.9)‡	29.7 (0.9)‡	-1.0	-1.9, -0.2	0.019
		12months	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)	**Changes †**	**95% CI**	**p-value**
		4months	25.9 (1.5)‡	26.5 (1.8)‡	-2.8	-4.9, -0.6	0.012
		12months	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)	**Changes †**	**95% CI**	**p-value**
		4months	29.8 (1.0)‡	32.0 (1.2)‡	-1.9	-3.7, -0.1	0.036
		12months	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)	**Changes †**	**95% CI**	**p-value**
		4months	61.2 (2.1)	57.7 (2.6)‡	-0.4	-1.7, 0.8	0.475
		12months	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)	**Changes †**	**95% CI**	**p-value**
		4months	14.2 (0.9)‡	14.2 (1.1)‡	-1.4	-2.8, <0.1	0.053
		12months	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)	**Changes †**	**95% CI**	**p-value**
		4months	29.6 (1.0)	28.0 (1.3)‡	0.2	-0.7, 1.1	0.615
		12months	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)	**Changes †**	**95% CI**	**p-value**
		4months	10.7 (0.7)	11.3 (0.8)‡	-1.4	-2.3, -0.4	0.004
		12months	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)	**Changes †**	**95% CI**	**p-value**
		4months	27.6 (1.1)‡	25.6 (1.3)‡	-0.6	-1.5, -0.3	0.187
		12months	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)	**Changes †**	**95% CI**	**p-value**
		4months	11.3 (1.6)‡	7.2 (2.2)	-1.3	-6.7, 4.1	0.624
		12months	11.6 (1.7)	9.0 (2.3)	0.2	-5.5, 5.9	0.943
	TSH (µUl/mL)	Baseline	2.3 (0.2)	2.2 (0.3)	**Changes †**	**95% CI**	**p-value**
		4months	2.2 (0.2)	1.9 (0.3)	-0.2	-0.7, 0.3	0.410
		12months	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)	**Changes †**	**95% CI**	**p-value**
		4months	3.1 (0.1)‡	3.1 (0.1)	0.5	-0.2, 0.3	0.739
		12months	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)	**Changes †**	**95% CI**	**p-value**
		4months	1.2 (0.1)	1.2 (0.1)	0.1	-0.1, 0.3	0.289
		12months	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)	**Changes †**	**95% CI**	**p-value**
		4months	23.4 (2.0)	20.6 (2.5)	-1.0	-4.6, 2.3	0.595
		12months	21.5 (2.0)§	18.9 (2.6)§	-0.7	-4.7, 3.3	0.719

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

* 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.

Changes: Differences in change scores between CG and IG, e.g. (4months/12months$_{intervention}$ – baseline$_{intervention}$) – (4months/12months$_{control}$ – baseline$_{control}$)

Legend: BMI – body mass index, FM – fat mass, LST – lean soft tissue, TSH – thyroid stimulating hormone, T3 – triiodothyronine, T4 – thyroxine.

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 (%) ($p>0.05$).

6.5. 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 (Nunes, Casanova, et al., 2021b). However, the findings are not consistent, as some studies suggest that AT exists and works as a barrier to WL and its maintenance (Martins et al., 2021), while others indicate that AT is not a predictor of weight regain (C. Martins et al., 2020; Catia Martins et al., 2020).

Recently, Martins et al (Catia Martins et al., 2020) found an AT of ~-90kcal.d^{-1} after a 9-week WL period, which halved to ~-38kcal.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 (~800kcal.d^{-1}), which may explain why AT remained significant after this phase (C. Martins et al., 2020). In our study, participants underwent a moderate caloric restriction (300 to 500kcal/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 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 (Silva et al., 2020), such as the regular self-weighting (Painter et al., 2017). 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 (Silva et al., 2021).

Apart from the aforementioned recent manuscripts, few studies have assessed AT after WL and after a period of WL maintenance (Byrne et al., 2018; Fothergill et al., 2016; Karl et al., 2015; Redman et al., 2009). Participants of The Biggest Loser competition (Fothergill et al., 2016), after a massive WL (~-58kg), showed an AT of ~-275kcal.d^{-1}. Additionally, after 6 years of follow-up, AT's magnitude increased to ~-500kcal.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 (Karl et al., 2015) showed similar AT after 12 weeks of a diet intervention (~-54kcal.d^{-1}). However, after 1 year of ad libitum-diet (follow-up periods), some participants regained part of their weight and AT was attenuated (Karl et al., 2015). 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 (Johannsen et al., 2012; McNeil et al., 2015). However, some studies have reported contradictory results (C. Martins et al., 2020; Muller et al., 2016). 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) (Nunes, Casanova, et al., 2021b), considering the surgical interventions, only Tam et al. reported higher values for AT (>300 kcal/d) (Tam et al., 2016). Interestingly, despite their higher amount of WL (~20%), two studies did not report AT (Browning et al., 2017; Coupaye et al., 2005).

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 (Müller et al., 2015), 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 (Johannsen et al., 2012) 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 (Bettini et al., 2018) 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 (Bettini et al., 2018; Johannsen et al., 2012; Müller et al., 2015).

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 were 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 was 4% and ~60 kcal/day, respectively (Silva et al., 2013), where the TEM was similar to our AT values at the end of the intervention (~60-70kcal/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 suggests that AT is unlikely to be a major barrier for WL and its maintenance, specially due to its limited

magnitude (C. Martins et al., 2020). In fact, a recent systematic review showed that AT seems to be attenuated or non-existent after a period of weight stabilization/ neutral EB (Nunes, Casanova, et al., 2021b). Moreover, the role of behavioral compensations as possible barriers to WL are unquestionably more impactful than AT, whereas behavior is 100% of EI and 20-60% of EE (Blundell et al., 2005). 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 (Melby et al., 2017) and thus, long-term success rates for WL maintenance are low, as participants often report weight regain (MacLean et al., 2011). In fact, a decrease in physical activity after a period of caloric restriction has already been showed by Redman et al (Redman et al., 2009). 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 ~10min/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" (Melby et al., 2017). 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 (Melby et al., 2017). 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 (Melby et al., 2017).

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 (Nunes, Casanova, et al., 2021b). Moreover, when participants are measured during a neutral EB, the degree of AT is reduced or even non-significant (de Jonge et al., 2012; C. Martins et al., 2020; Müller et al., 2015). 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 (Swinton et al., 2018).

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 (Nunes, Jesus, et al., 2021). 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. Firstly, 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 life's, they do not seem to have health-related benefits when compared to a non-athletic population (Griffin et al., 2016; Laine et al., 2016). 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 (Dutton et al., 2016). 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 (Dutton et al., 2016). 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 (Laine et al., 2016; Provencher et al., 2018). 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) (Nunes, Casanova, et al., 2021b). Also, tracking changes in body composition by DXA does not

assess the changes in FFM composition (i.e., molecular and anatomical composition) (Müller et al., 2021). 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 was “reflected” to the left upper limb, validated elsewhere (Sherman et al., 2011). Though a small impact was observed in whole-body bone measurement using this approach, no differences were found in assessing soft tissues (Sherman et al., 2011). 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 the 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 (Leibel et al., 1995). 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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CHAPTER 7

INTERINDIVIDUAL VARIABILITY IN METABOLIC ADAPTATION OF NON-EXERCISE ACTIVITY THERMOGENESIS AFTER A 1-YEAR WEIGHT LOSS INTERVENTION IN FORMER ELITE ATHLETES [4]

[4] **Nunes, C. L.,** Rosa, G. B., Jesus, F., Heymsfield, S. B., Minderico, C. S., Martins, P., Sardinha, L. B., & Silva, A. M. (2022, Nov 28). Interindividual variability in metabolic adaptation of non-exercise activity thermogenesis after a 1-year weight loss intervention in former elite athletes. Eur J Sport Sci, 1-10. https://doi.org/10.1080/17461391.2022.2147020

INTERINDIVIDUAL VARIABILITY IN METABOLIC ADAPTATION OF NON-EXERCISE ACTIVITY THERMOGENESIS AFTER A 1-YEAR WEIGHT LOSS INTERVENTION IN FORMER ELITE ATHLETES

Catarina L Nunes, Gil B Rosa, Filipe Jesus, Steven B Heymsfield, Cláudia S Minderico, Paulo Martins, Luis B Sardinha, Analiza M Silva

7.1. ABSTRACT

Lack of efficacy of weight loss(WL) interventions is attributed in-part to low adherence to dietary/physical activity(PA) recommendations. However, some compensation may occur in PA as a response to energy restriction such as a decrease in non-exercise PA(NEPA) or non-exercise activity thermogenesis(NEAT). The current study aim was 1) to investigate whether adaptive thermogenesis(AT) in NEAT occurs after WL, and 2) to understand the associations of these compensations with WL. Ninety-four former athletes [mean±SD, age: 43.0±9.4y, BMI: 31.1±4.3kg/m^2, 34.0% female] were recruited and randomly assigned to intervention or control groups (IG, CG). The IG underwent a one-year lifestyle WL-intervention; no treatments were administered to the CG. PA was measured using accelerometery and NEAT was predicted with a model including sample baseline characteristics. AT was calculated as $_{measured}NEAT^{4mo/12mo}{}_{(kcal/d)} - {}_{predicted}NEAT^{4mo/12mo}{}_{(kcal/d)} - {}_{measured}NEAT^{baseline}{}_{(kcal/d)} - {}_{predicted}NEAT^{baseline}{}_{(kcal/d).}$ Dual-energy x-ray absorptiometry was used to assess fat-free mass and fat mass. No differences were found in the IG for NEAT or NEPA after WL. Considering mean values, AT was not found for either group. The SD of individual response (SD_{IR}) for AT was -2(4-months) and 24(12-months) (smallest worthwhile change=87kcal/d), suggesting that the interindividual variability regarding AT in NEAT is not relevant and the variability in this outcome might reflect a large within-subject variability and/or a large degree of random measurement error. No associations were found between AT in NEAT and changes in

body composition. Further studies are needed to clarify the mechanisms behind the large variability in AT observed in NEAT and related changes in NEPA to better implement lifestyle-induced WL interventions.

Key-words: Behavioural compensation, Energy balance, Exercise energy expenditure, Free-living physical activity, Weight loss.

7.2. INTRODUCTION

When retiring from their sports career, athletes struggle with maintaining their regular exercise habits, reducing drastically their energy expenditure (EE), while energy intake does not always show similar reductions (Stubbs et al., 2004). If this positive energy balance (EB) is maintained, weight gain is to be expected, leading to obesity and obese-related adverse health conditions (Griffin et al., 2016). Despite the increasing number of weight loss (WL) interventions globally, their lack of efficacy (i.e., lower-than-expected WL, weight regain) is still a matter of debate (Aronne et al., 2021). Although these discouraging results are mostly attributed to the lack of adherence to dietary and/or physical activity (PA) recommendations (Heymsfield et al., 2007), metabolic and behavioral adaptations my also occur as a response to a prolonged negative EB (Nunes et al., 2021).

As resting energy expenditure (REE) is the major contributor to total daily energy expenditure (TDEE), most investigations focused on exploring the higher-than-expected decreases in REE (i.e., adaptive thermogenesis – AT) following WL interventions (Nunes et al., 2021). Nevertheless, compensations in other EE components have been highlighted, particularly those related with regular PA habits (Levine et al., 1999).

PA (measured in minutes/day) is defined as “any bodily movement produced by skeletal muscles that results in energy expenditure”, being divided in i) exercise, i.e., a planned and structured PA with a specific aim regarding physical fitness; and 2) daily life

activities, such as fidgeting, posture maintenance and non-specific ambulatory activities, which is considered non-exercise PA (NEPA) (Silva et al., 2018). Following REE, the energy expended in PA [PA-induced EE (PAEE)] is the most significant contributor to TDEE, representing the overall EE during movement activities (measured in kcal/day) (Silva et al., 2018). Similarly to PA, daily PAEE can also be further divided into: i) the energy expended during exercise/sports practice [exercise-induced energy expenditure (EiEE)]; and ii) the energy expended with activities that are not considered exercise (NEPA), defined as non-exercise activity thermogenesis (NEAT).

Therefore, PAEE can potentially play an important role toward the WL and long-term maintenance (Ostendorf et al., 2019). In fact, whereas REE and thermic effect of food provide similar levels of contribution to the TDEE variance, PAEE (specially NEAT) depicts a greater variation in TDEE within and between individuals (accounting for 5 to 50% of TDEE), due to the large variability in NEPA (von Loeffelholz & Birkenfeld, 2000). For this reason, assessing NEPA and/or NEAT in WL interventions may represent a unique opportunity to determine its potential impact on weight management.

Adopting a prolonged caloric restriction may also play an important role regarding the decrease in NEPA, and consequently NEAT (Martin et al., 2011; Redman et al., 2009). Considering these potential marked decreases in NEAT are associated with higher rates of WL, it is expected that such energy imbalances may lead to an increase in energy conservation processes (Silva et al., 2018). Therefore, along with the lack of adherence to the diet and/or exercise recommendations, these compensatory responses may play an important role in weight management, undermining the magnitude of WL and its maintenance.

Despite an increasing research interest in examining the mechanisms underlying the NEPA/NEAT responses to WL interventions, this relationship remains to be fully understood (Silva et al., 2018). Additionally, there is a research gap concerning the effects of a negative EB (through dietary-induced energy restriction) on changes in NEAT and related NEPA and how those changes may affect WL. Therefore, the aims of the

present investigation were 1) to investigate whether adaptive thermogenesis in NEAT occurred after a moderate WL, and 2) to understand how these compensations were associated with the magnitude of WL.

7.3. METHODOLOGY

This investigation is part of the Champ4life project, a lifestyle WL intervention targeting inactive former elite athletes (Silva et al., 2020) and the main results of this program are described in detail elsewhere (Silva et al., 2021). The program comprised of a 1-year lifestyle intervention that consisted of a 4-month WL intervention and an 8-month WL maintenance period. The Champ4life project 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 (World Medical Association, 2008). The trial is registered at www.clinicaltrials.gov (clinicaltrials.gov ID: NCT03031951).

7.3.1. Lifestyle intervention

The IG underwent a self-determination-based intervention, consisting of educational weekly sessions targeting diet, eating behavior, PA, and behavior change domains. Participants were followed throughout the program by a certified dietitian, to adjust their diet and perform a moderate caloric deficit (~300kcal.d^{-1}). Regarding PA habits, the participants were only encouraged to increase their PA levels and to decrease the time spent in sedentary behavior. For the 8-month weight maintenance period, nutritional appointments were held to create a neutral EB.

7.3.2. Body composition

Participants had their weight and height measured to the nearest 0.01 kg and 0.1 cm, using a weight scale and a stadiometer (SECA, Hamburg, Germany), respectively. Body Mass Index (BMI) was calculated as weight (kg) divided by the square of the height (m) and classified according to the World Health Organization (WHO) cutoffs (Weir CB & A., [Updated 2019 Apr 20].). To assess total and regional fat mass (FM) and fat-free mass (FFM), dual-energy X-ray absorptiometry (DXA; Hologic Explorer-W, Waltham, MA, USA) was used, as described elsewhere (Park et al., 2002).

7.3.3. Physical activity (PA)

PA (min/day) was objectively measured using a tri-axial accelerometer (ActiGraph GT3X+, Pensacola, FL). Participants were asked to wear the accelerometer on the right side of the hip for 7 consecutive days and to only remove the sensor during sleep and water-based activities (e.g., bathing and swimming). The accelerometers were initialized on the morning of the assessment day and data were recorded in 15-s epochs and reintegrated into 60-s epochs and using a 100Hz frequency. Periods of at least 60 consecutive minutes of zero counts were considered as non-wear time. A valid day was defined as having ≥600 min of monitor wear per day. Only participants with at least three valid days (with at least one weekend-day) were included in the analysis.

A logbook was given to the participants to record the exercise sessions (type and duration of the activities – start and end time). If participants were not able to use the accelerometer during the exercise session (e.g., water-based activities), this information should be stated in the logbook. The time spent in exercise was removed from the total PA to determine NEPA (PA in daily activities that are not considered exercise, min/day). By contrast, the time excluded for NEPA analysis plus registered information from structured PA in which the participants did not use the accelerometer was used to

determine overall levels of exercise. Participants were also asked to record daily waking and sleeping hours, as well as the timings and reasons for not using the accelerometer.

7.3.4. Energy Expenditure (EE) measures

7.3.4.1. Exercise-induced Energy Expenditure (EiEE) and Non-Exercise Activity Thermogenesis (NEAT)

The caloric expenditure (kcal/d) of both structured (exercise) and unstructured PA (NEPA) was calculated from Freedson Combination' 98 algorithm (Sasaki et al., 2011), which considers the Work-Energy Theorem and the Freedson' 98 equation to calculate EE under 1951 and above 1952 counts, respectively. The energy expended in NEPA, i.e., non-exercise activity thermogenesis (NEAT, kcal/d) was calculated by applying the algorithm over the time spent in non-exercise related activities. On the other hand, the EE of exercise (EiEE) was determined from the combination of the data excluded in the NEAT analysis and additional data of PA participants reported when the accelerometer was not used. The EiEE not recorded with the accelerometer was calculated using specific PA metabolic equivalents (METs) of the 2011 Compendium of Physical Activities (Ainsworth et al., 2011).

7.3.4.2. Resting energy expenditure (REE)

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 ($\dot{V}CO_2$). The flow and volume were measured using a pneumotachograph calibrated with a 3L-syringe (Hans Rudolph, inc.TM). The assessment was performed in the morning, after an overnight fast. Before testing, participants were instructed about all the procedures and asked to relax, breathe normally, and not to sleep or talk during the evaluation. Participants underwent a resting period of ~15 minutes, before the attachment of the calorimeter device to the mask. The

exam duration was ~30min, where the lowest mean of 5 minutes of steady state (i.e., coefficient of variance ≤ 10 % for V̇O2 and V̇CO2), between the 5 and the 25 minutes of REE assessment, with respiratory exchange ratio between 0.7 and 1.0, were considered for analysis.

7.3.4.3. Total Daily Energy Expenditure (TEE)

TDEE was estimated as the sum of REE, NEAT and EiEE, divided by 0.9 (i.e., assuming the thermic effect of food accounts for 10% of TDEE) (Weststrate, 1993).

7.3.5. Statistics

Statistical analysis was performed using IBM SPSS statistics version 27.0 (IBM, Chicago, Illinois, USA). Linear mixed models included randomized group and time as fixed effects, with sex as a covariate, to assess primary and secondary outcomes for the impact of group, time (baseline– 0 months, post-intervention– 4 months, and follow-up– 12 months), and group-by-time interaction. The covariance matrix for repeated measures within subjects over time was modelled as Compound Symmetry. Model residual distributions were examined graphically, and by using the Kolmogorov-Smirnov test, and no data transformations were necessary. Differences-in-differences (DiD) were calculated between the IG and CG throughout time, calculated as the difference between changes for IG and changes for CG. To remove the effect of the hours spent with the accelerometer (usage time), NEPA was adjusted for daily wear time (percentage).

To evaluate the proportion of response in the IG, participants were classified as “responders” and “non responders” according to the typical error (TE) method proposed by Swinton et al (Swinton et al., 2018). TE was assessed by dividing the SD of the changes (difference between 4 or 12 months’ time point and the baseline) for the CG by $\sqrt{2}$. A “responder” is considered an individual who showed beneficial changes that were

greater than TE (Swinton et al., 2018). Chi-square tests were performed to compare the response rates between IG and CG.

Multiple linear regression models were performed with the baseline characteristics of all participants to generate equations to predict NEAT, defined as:

$$\mathbf{NEAT_{(kcal/d)}} = -2149.437 + 7.622 \times FM_{(kg)} + 9.474 \times FFM_{(kg)} + 31.834 \times \text{wear time}_{(percentage)} \ (R^2 = 0.339,\ p < 0.001),$$

Where wear time is considered the amount of time that a participant wore the accelerometer divided by 24h. The generated equations were used to predict values for the aforementioned EE component after 4 months and at the end of the intervention (1-year). Adaptive thermogenesis (AT) was calculated by subtracting measured NEAT (through accelerometry) by predicted NEAT (equation model) and then subtracting the so called residuals (i.e., the difference between the measured and the predicted NEAT at baseline), such as:

$$\mathbf{AT_{(kcal/d)}} = (\text{measured NEAT}^{4mo/12mo}{}_{(kcal/d)} - \text{predicted NEAT}^{4mo/12mo}{}_{(kcal/d)}) - (\text{measured NEAT}^{baseline}{}_{(kcal/d)} - \text{predicted NEAT}^{baseline}{}_{(kcal/d)}),$$

Where negative values indicate a higher-than-expected decrease in NEAT considering the changes in body composition, i.e., the measured NEAT is lower than predicted NEAT, whereas positive values represent a change in NEAT equal to or greater than the predicted NEAT (measured NEAT higher than predicted NEAT). To understand if interindividual differences are present, the SD of individual response (SD_{IR}) was calculated according to Atkinson and Batterham (Atkinson & Batterham, 2015):

$$SD_{IR} = \sqrt{{SD_{IG}}^2 - {SD_{CG}}^2}$$

If the SD_{CG} surpasses the SD_{IG}, the SD_{IR} formula was reversed and the SD_{IR} was reported as a negative value (Bonafiglia et al., 2021). A positive SD_{IR} suggests that there is evidence of interindividual differences in the outcome responses, while a negative SD_{IR}

indicates that these differences are inexistent, suggesting that the reported variability may be due to a large degree of random measurement error and/or within-subject variability (Bonafiglia et al., 2021). These values were compared to the smallest worthwhile change (SWC), calculated by multiplying 0.2 by the SD of the CG at baseline. A SD_{IR} > SWC suggests meaningful interindividual differences, while a SD_{IR} < SWC insinuates that interindividual differences are irrelevant (Atkinson & Batterham, 2015). Ninety-five percent confidence intervals (95%CI) were estimated by using the following equation (Hopkins, 2015):

$$95\%CI = \sqrt{{SD_{IR}}^2 \pm 1.96 \times \sqrt{2 \times \left(\frac{{SD_{IG}}^4}{n_{IG} - 1} + \frac{{SD_{CG}}^4}{n_{CG} - 1}\right)}}$$

All analyses were intention-to-treat including data from all participants who were randomly assigned. Sensitivity analyses were conducted out for analyses of NEAT and NEPA, by using imputation of missing data based on multivariate linear regression to simultaneously predict missing outcomes data from body composition measures and its changes over time. Statistical significance was set at $p<0.05$ (2-tailed).

7.4. RESULTS

The baseline characteristics of the Champ4Life participants are presented elsewhere (Silva et al., 2021). Briefly, 94 participants were included and randomly divided in two groups: intervention [N = 49; mean (SD): BMI = 31.7 (3.9) kg/m^2, age = 42.4 (7.3) y, 35% females] and control group [N = 45; mean (SD): BMI = 30.5 (4.7) kg/m^2, age = 43.6 (11.3) y, 33% females]. At the end, the dropout rate was ~27.7%, being similar between groups (28.6% and 26.7% for the IG and CG, respectively).

After 4 months, participants from the IG achieved a greater WL [estimated difference (ED) from DiD = -4.7kg (95% CI: -6.1 to -3.3; $p<0.001$)] when compared to the CG. Considering body composition stores, the IG lost a greater amount of FM [FM (kg): ED

= -3.8kg (95%CI: -5.1 to -2.6) p<0.001 and FM (%): ED = -2.6% (95%CI: -3.6 to -1.7) p<0.001] and were able to maintain their FFM throughout time. During the follow-up period, weight and FM changes remained significant [weight: ED = -5.3kg (95%CI: -6.9 to -3.8), p<0.001); FM: ED = -4.1kg (95%CI: -5.4 to -2.8) p<0.001 and ED = -3.1% (95%CI: -4.1 to -2.1) p<0.001]. No changes were observed in weight, FM or FFM for the CG (p>0.05 for DiD).

The TE for WL was 1.72kg, corresponding to a 1.88% change in weight. Thirty-one participants from the IG (75.6%) were classified as "responders" for WL, with differences in the proportion of responders in both groups (Chi-square test = 33.47, p<0.001).

Values of the EE components and comparisons between groups and over time (baseline vs 4 months or baseline vs 12 months) are presented in **table 7.1.** The values for REE were already presented and discussed in detail (Nunes et al., 2022).

A time*group interaction was found for EiEE and exercise between groups (p<0.001). Participants from the IG showed an increase on exercise and EiEE at 4 months. However, after the follow-up period, the results were no longer significant. Although the IG achieved a ~5% WL, no differences were found for NEPA nor NEAT over time.

The TE for NEPA was 57.7 min/day, corresponding to a change of 6.9%. Only 9 (18.4%) participants from the IG were classified as responders (i.e., with significant increases in NEPA), with no differences in the proportion of responders in both groups (Chi-square test = 0.548, p=0.459).

Values for AT for NEAT are presented in **table 7.2.**

Table 7.1. Estimated means of energy expenditure components.

		Control	Intervention	Time*group p-value	SD_{IR} (95% CI)	SWC
TDEE (kcal/d)	Baseline	2486 (89)	2420 (87)	**0.010**	-	114
	4months	2323 (97)	2377 (93)		114 (-342, 378)	
	12months	2532 (109)	2197 (106)‡		155 (-419, 473)	
REE (kcal/d)	Baseline	1642 (21)	1645 (20)	**<0.001**	-	59
	4months	1616 (23)†	1527 (22)†		-51 (-127, 146)	
	12months	1722 (25)‡	1533 (25)‡		-8 (-146, 147)	
NEPA (min/day)*	Baseline	853 (11)	830 (11)	0.890	-	14
	4months	858 (13)	843 (12)		3 (-64, 64)	
	12months	838 (16)	824 (14)		-45 (-62, 89)	
NEAT (kcal/d)	Baseline	538 (48)	504 (47)	0.823	-	87
	4months	471 (53)	478 (51)		27 (-235, 238)	
	12months	452 (64)	443 (56)		-166 (-232, 329)	
pNEAT (kcal/d)	Baseline	546 (34)	497 (33)	0.816	-	45
	4months	554 (37)	515 (36)		28 (-159, 164)	
	12months	531 (45)§	457 (52)		-71 (-190, 215)	
Exercise (min/day)	Baseline	5 (3)	8 (3)	**<0.001**	-	2
	4months	6 (3)	23 (3)†		-3 (-20, 20)	
	12months	17 (5)	6 (4)§		-15 (-19, 28)	
EiEE (kcal/d)	Baseline	46 (19)	35 (19)	**<0.001**	-	19
	4months	31 (21)	121 (20)†		9 (-102, 103)	
	12months	89 (26)	45 (23)§		-75 (-99, 145)	
PAEE (kcal/d)	Baseline	584 (51)	539 (50)	0.081	-	86
	4months	502 (56)	599 (54)		28 (-249, 252)	
	12months	541 (68)	489 (59)		-175 (-245, 349)	

TDEE, Total daily energy expenditure. REE, Resting energy expenditure. NEPA, Non-exercise physical activity. NEAT, Non-exercise activity thermogenesis. pNEAT, Predicted NEAT. EiEE, Exercise-induced energy expenditure. AEE, Activity energy expenditure.

* Adjusted for daily wear time (percentage).

† Within-group differences between baseline and 4-months, p<0.05

‡ Within-group differences between baseline and 12-months, p<0.05

§ Within-group differences between 4-months and 12-months, p<0.05

Table 7.2. Adaptive thermogenesis for NEAT

		Control	Intervention	p-value (between groups)	SD_{IR} (95% CI)	SWC
AT	**4mo**	-24 (45)	-41 (45)	0.783	-2 (-209, 209)	87
	12mo	-45 (58)	-56 (56)	0.894	24 (-193, 196)	

Data is presented as estimated mean (SE). AT, Adaptive thermogenesis.
Not statistically different from zero, $p<0.05$ (one-sample t-test)

The IG did not show a higher-than-expected decrease for NEAT. No differences were found between groups. A negative SD_{IR} (-2) was observed for AT in NEAT after 4 months, while a positive but smaller than the SWC value was found at 12 months (SD_{IR} = 24; SWC=87.0). The variability among participants is graphically presented in **figure 1.**

No associations were found (adjusted by group) between changes in NEPA and WL (kg: -0.166, p=0.398; %: -0.245, p=0.210), FM loss (kg and %) (kg: -0.135, p=0.494; %: -0.072, p=0.716) nor EB (kcal/d) (-0.137, p=0.488) at 4-months. After 12 months the associations remained irrelevant (WL(kg): -0.092, p=0.629; WL(%): -0.146, p=0.443; FM loss (kg): -0.101, p=0.596, FM loss (%): -0.136, p=0.475; EB: -0.053, p=0.780).

Similarly, AT in NEAT was not associated with the degree of WL (4 months: kg: -0.060, p=0.762; %: -0.032, p=0.873; 12 months: kg: -0.338, p=0.079, %: -0.338, p=0.079) nor EB (4 months: -0.126, p=0.521, 12 months: -0.281, p=0.148).

After performing single imputation for missing data, the results of sensitivity analyses for NEAT and NEPA were similar and are presented as supplementary file (**table S7.3**).

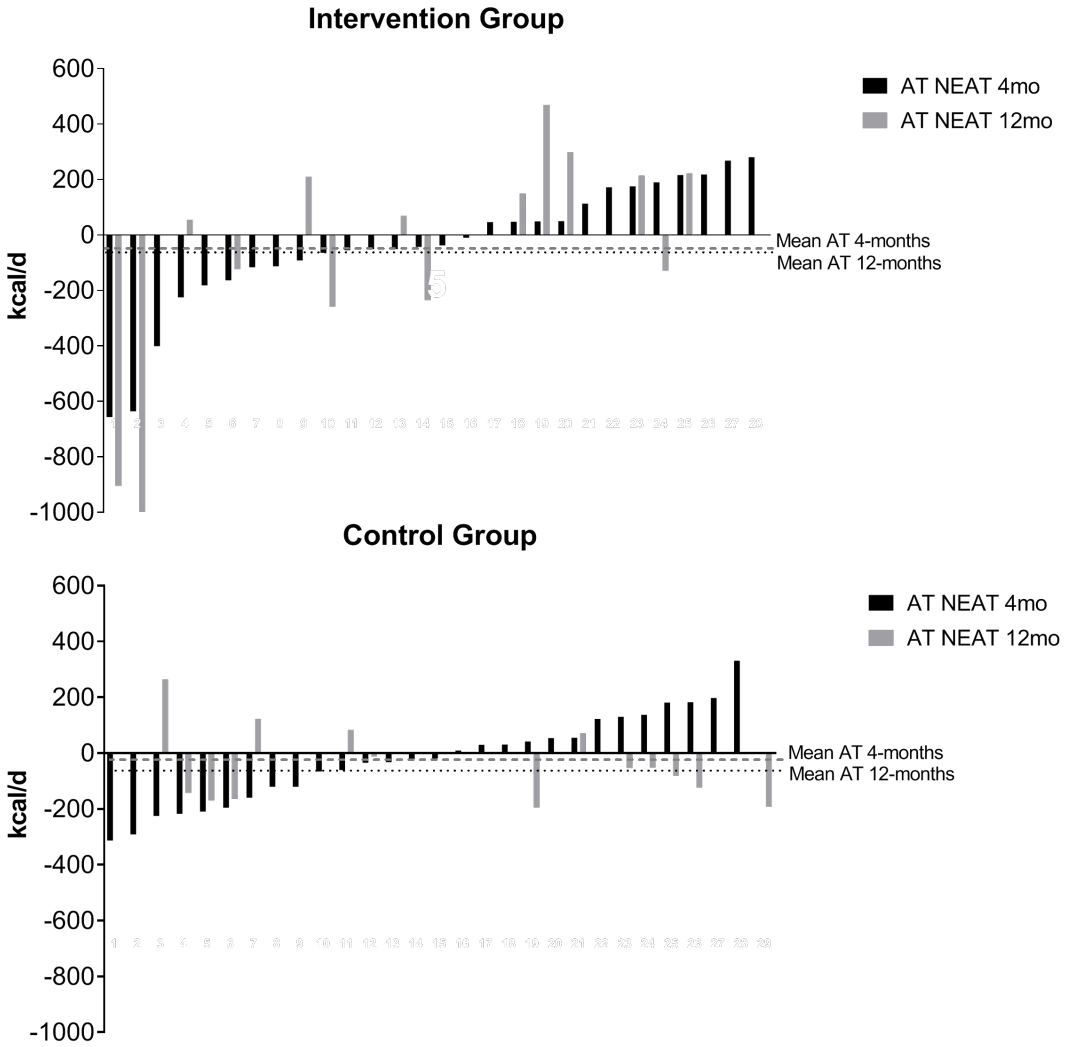

Figure 7.1. Variability of metabolic adaptation on NEAT among participants.

7.5. DISCUSSION

Even though no energy conservation was found in NEAT after the Champ4Life intervention, large variability in this PAEE component was observed among individuals. However, this heterogeneity in observed responses might reflect a large within-subject variability and/or a large degree of random measurement error (Atkinson & Batterham, 2015), as the SD_{IR} was negative at 4 months. After 1 year, although the SD_{IR} was positive, it did not exceed the SWC, suggesting that the interindividual variability regarding AT in NEAT is not relevant. In addition, no associations were found between

the degree of energy conservation (AT) in NEAT and the magnitude of WL or changes in body composition stores.

Along with its well-known health-related benefits, PA seems to play an important role in weight management, potentiating WL and preventing weight regain (Swift et al., 2018). However, a suggestion is that during prolonged negative EB (through a caloric deficit and/or increasing exercise) some behavioral compensations may occur, such as decreases in NEPA (King et al., 2007). While this reduction in NEPA appears not to occur in most exercise-only interventions (Fedewa et al., 2017), some studies involving diet-only interventions reported a compensation in this component (de Groot et al., 1990; Racette et al., 1995). Nevertheless, the effects of a diet and/or an exercise intervention on NEPA/NEAT are still contradictory, as some authors found a decrease in NEPA/NEAT, while others reported no compensations in these components (Silva et al., 2018).

Despite the expected substantial decrease in PAEE due to a lowering in body mass with dieting (Levine et al., 2001; Ostendorf et al., 2019), decreases in NEPA will consequently lead to a decrease in NEAT. Thus, reducing NEPA might lead to a decrease in TDEE, affecting the initially created negative EB and consequently, the ability to lose weight. In our study, NEPA remained stable, even in participants that significantly increased their exercise (Riou et al., 2019) showing that this change did not lead to a decrease in NEPA. Contrary to other studies, the Champ4life program was a Self-Determination Theory intervention, where participants were taught, through educational sessions, the benefits of increasing PA, not only by increasing exercise, but specifically by decreasing their time spent in sedentary behaviors and being more active (Silva et al., 2021). Therefore, in this intervention, we were not focused on delivering exercise sessions nor a personalized exercise plan, but rather giving simple strategies to increase PA and encourage participants to adapt those strategies according to their lives and routines.

Thus, the authors believe that this strategy may have helped on maintaining a similar NEPA not only after WL but also during the follow-up period.

Nevertheless, higher-than-expected reductions in NEAT have been pointed out as a compensatory response to a caloric restriction and/or increasing exercise, undermining negative EB and, consequently, the ability to lose weight (Dhurandhar et al., 2015). The effect of caloric restriction is also known to play an important role in PAEE (i.e., NEAT and EiEE). According to Redman et al., which aimed to examine the metabolic and behavioral compensations in 4 intervention groups (control, 2 groups of diet-only, and a group with combined diet and exercise), NEAT was found to decrease only in the participants from the 2 diet-only groups (Redman et al., 2009). Similarly, the effect of caloric restriction was found to be linked to a substantial decrease in NEAT, independently of sex and age (Martin et al., 2011). These findings are in agreement with previous research demonstrating that caloric restriction may have a negative influence on PAEE, even during moderate caloric restriction interventions (Martin et al., 2011). In our investigation and comparably to NEPA, no differences were found throughout time in NEAT (mean values). The degree of compensation (i.e., AT) in this component was also studied through a predictive equation, similarly to what is usually used to assess AT in REE (Nunes et al., 2021).

Both groups did not show a significant AT for NEAT after 4 months. Also, at the end of the Champ4life program, no differences were found between groups. Nevertheless, a huge variability among participants from both groups was found, emphasizing the importance of analyzing not only the mean responses but also the inter-individual variability in what concerns to outcomes from WL interventions. In fact, despite the Champ4life being well-succeeded on improving body composition (Silva et al., 2021), participants showed a large variability for the amount of WL and FM loss.

In our study, no associations were found between the degree of compensation on NEAT and the magnitude of WL and EB. In contrast, associations between changes in NEAT and body composition changes were reported in other studies (Herrmann et al., 2015;

Martin et al., 2011). In line with this, it is suggested that individuals with larger decreases in NEAT or PAEE are generally those with high rates of weight regain (Herrmann et al., 2015). Even though our participants were well-succeeded in maintaining their weight reduced during the follow up period (Silva et al., 2021), a large variability was observed for changes in body composition. Due to the importance of examining the impact of inter-individual variability when considering the amount of WL after an intervention (Dent et al., 2020), further research on the inter-individual variability on NEAT is needed.

The magnitude of NEAT compensation might be affected by several factors, including either biological and non-biological factors (i.e., the type of study sample and methodology, the duration of the caloric restriction and the magnitude of WL). In terms of non-biological factors, a recent systematic review (Silva et al., 2018) has highlighted that studies that reporting decreases in NEAT were mostly those with higher magnitude of WL. Considering that our participants only lost a moderate amount of weight (~5%), which is a smaller amount when compared with the aforementioned studies, the absence of differences for NEAT throughout the intervention was expectable. Nevertheless, our results go along with other studies with larger WL (~10%) (Leibel et al., 1995; Levine et al., 2005), with no reduction in NEAT after a WL intervention. Such findings may be justified by the preservation of FFM, and consequently skeletal muscle mass, which are known to have a role in mediating the alterations in EE under the occurrence of WL (Leibel et al., 1995).

Another non-biological factor that may explain the discrepancy among investigations concerns to the methodologies used to measure EE, in particular NEAT. While some studies measured EE components with respiratory chambers, others used METs algorithms calculated from accelerometers used under free-living conditions (Silva et al., 2018). Despite respiratory chambers being the current gold-standard for assessing human EE, its use to measure NEAT may compromise the time expended in voluntary PA, underestimating PAEE and, consequently, TDEE (Rosenbaum et al., 1996).

Consequently, a growing number of investigations has been examining accelerometer-derived EE, as it provides more practical and realistic estimation of total PAEE based on free-living conditions. On the other hand, some challenges may arise when estimating NEAT during an intervention, considering that changes in this component may either reflect changes in the muscular efficiency (Rosenbaum et al., 2003) and/or changes in NEPA (time spend and/or intensity) (Levine et al., 2001; Redman et al., 2009). Therefore, further studies are needed to better understand how accelerometers EE prediction is influenced by a caloric restriction intervention.

Despite this interesting discussion, the limitations of this study should be addressed. First, the percentage of dropouts should be considered, as ~30% of participants were lost to follow up that may influence the findings of the study. Second, even though no compensations in NEPA and predictive equation derived NEAT were found, we cannot state that decreases in NEPA or a higher-than-expected decrease in NEAT would still not occur if participants lost larger amounts of weight. Third, as an alternative to respiratory chambers, known as the gold- standard for assessing human PAEE, we used specific METs algorithms calculated from the ActiGraph GT3X+ accelerometer (ActiGraph, Pensacola, FL). Despite PAEE being indirectly estimated through accelerometry, when compared with reference methods, this technique accurately predicts the PAEE over a wide range of PA (Kumahara et al., 2004) and provides a more representative measure of free-living PAEE. Fourth, since EE components were assessed through accelerometry, where participants were asked to remove the device only when sleeping and water-based activities (e.g., bathing and swimming), there may have led to an underestimation of PAEE and TDEE. Even though we were not able to objectively measure EE during these activities, an additional logbook was given to the participants to record the type and duration of activities performed without the accelerometer.

Lastly, since this investigation was based on the Self-Determination Theory, where participants were taught about the importance to increase PA and decrease the time in

sedentary behaviors following the principles of autonomy, competence, and relatedness (Deci & Ryan, 2000), there may have existed different individual responses in terms of the intensity, duration and practice location of PA. However, the research team ensured that all participants had access to the same information throughout the whole intervention.

Therefore, despite no differences at the group level were found for NEAT after a moderate WL, the large variability should be taken into account when studying the potential energy conservation in this component. Therefore, health-related professionals should consider the potential reduction of energy expenditure during free-living PA beyond that expected when implementing lifestyle-induced weight loss interventions.

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Table S7.3. Sensitivity analysis for NEAT and NEPA.

		Control	Intervention	Time*group p-value
NEPA (min/day)	Baseline	838 (9)	839 (9)	0.514
	4months	852 (9)	850 (9)	
	12months	834 (9)	846 (9)	
NEAT (kcal/d)	Baseline	496 (15)	499 (14)	0.514
	4months	521 (15)	516 (14)	
	12months	489 (15)	509 (14)	
AT NEAT	Baseline	NA	NA	0.802
	4months	-12 (41)	-62 (40)	
	12months	-32 (41)‡	-100 (40)	

NEPA, Non-exercise physical activity. NEAT, Non-exercise activity thermogenesis. AT NEAT, Adaptive thermogenesis of NEAT. NA, Not applicable.

‡ Within-group differences between 4-months and 12-months, $p<0.05$

CHAPTER 8

INTERINDIVIDUAL VARIABILITY IN ENERGY INTAKE AND EXPENDITURE DURING A WEIGHT LOSS INTERVENTION[5]

[5] **Nunes C.L.,** Jesus F, Rosa G, Marianito M, Francisco R, Bosy-Westphal A, Minderico C.S., Martins P, Sardinha L.B., Silva A.M.; Interindividual variability in energy intake and expenditure during a weight loss intervention

INTERINDIVIDUAL VARIABILITY IN ENERGY INTAKE AND EXPENDITURE DURING A WEIGHT LOSS INTERVENTION

Catarina L Nunes, Filipe Jesus, Gil B Rosa, Mariana Marianito, Ruben Francisco, Anja Bosy-Westphal, Cláudia S Minderico, Paulo Martins, Luis B Sardinha, Analiza M Silva

8.1. ABSTRACT

Behavioural compensations may occur as a response to a negative energy balance. The aim of this study was to explore the associations between changes in energy intake (EI) and changes in physical activity (PA, in/day and kcal/d) and to understand if interindividual differences occur in EI and energy expenditure (EE). Eighty-one participants [mean(SD): age=42.8(9.4)y, BMI=31.2(4.4)kg/m^2, 37% females] divided in intervention (IG, n=43) and control group (CG, n=38) were included. The IG underwent a moderate ER (300-500kcal/d). EI was measured through the intake-balance method. Non-exercise PA (NEPA) and exercise were measured by accelerometery. The EE in NEPA (NEAT) and in exercise (EiEE) was calculated by applying the Freedson Combination'98 algorithm over the time spent in these activities. To understand if interindividual differences were observed, the SD of individual response (SD_{IR}), as well as the smallest worthwhile change (SWC) were calculated. An interindividual variability was found for EI (SD_{IR}=151.6, SWC=72.3) and EE (SD_{IR}=165, SWC=134). ΔEI(kcal/d) was negatively associated with Δexercise (min/d: r=-0.413, p=0.045; %: r=-0.846, p=0.008) and with ΔEiEE (kcal/d: r=-0.488, p=0.016; %: r=-0.859, p=0.006). A negative correlation was found between Δsedentary time and ΔNEPA (min/d: r=-0.622, p=0.002; %: r=-0.487, p=0.018). No correlations were found between Δexercise and ΔNEPA nor sedentary time (p>0.05). An interindividual variability was found for EI and EE. Decreases in EI were not associated to compensatory responses such as decreases in PA and/or increases in sedentary time. Nevertheless, behavioral compensations and the

interindividual variability should be considered when implementing WL interventions, to increase the likelihood of achieving sustainable results.

(clinicaltrials.gov ID: NCT03031951)

Key-words: Energy restriction, non-exercise physical activity, energy expenditure, exercise.

8.2. INTRODUCTION

A continuous negative energy balance (EB) is needed to achieve weight loss (WL), either by decreasing food intake, increasing energy expenditure (EE), or both (von Loeffelholz C). Though, it is well stated that losing weight is a hard challenge, with most people not being able to maintain a reduced weight state throughout time (Aronne et al., 2021; Fildes et al., 2015). Together with the lack of adherence to dietary and physical activity (PA) recommendations in the long-term (Heymsfield et al., 2007), metabolic and behavioral compensations may also occur as a response to a negative EB, undermining the WL process (Redman et al., 2009). While metabolic adaptations consist of a mass-independent decrease in the EE components, such as resting EE (REE), physical activity EE (PAEE), and thermic effect of food (TEF) (E. J. Dhurandhar et al., 2015), behavioral compensations involve reductions in free-living physical activity (Corby K. Martin, 2012) and compensatory increases in energy intake (EI) (Thomas et al., 2012). Although both metabolic and behavioral compensations may jeopardize WL, one's behavior usually exerts a higher influence (in terms of magnitude) on EB and consequently, on the WL process. For instance, eating a high-density caloric meal and/or undergoing an exercise session will create a higher impact on EB than a higher-than-expected decrease in REE (King et al., 2007). Therefore, when implementing a WL intervention, EI and PAEE are the two major components mainly determined by one's behavior (King et al., 2007) that should be considered.

PA is defined as “any bodily movement produced by skeletal muscles that results in energy expenditure” (Caspersen et al., 1985) and is divided in 1) exercise, i.e., a planned and structured PA; and 2) daily life activities that are not considered exercise, such as fidgeting, posture maintenance and non-specific ambulatory activities - non-exercise PA (NEPA). Similarly,

PAEE can be divided into 1) the EE during exercise/sports practice - exercise activity thermogenesis (EiEE) (MacLean et al.) and 2) the EE in activities that are not considered exercise - non-exercise physical activity (NEAT) (Levine).

Although there is some evidence regarding changes in EI and PAEE (NEAT and EiEE) during a WL intervention, it is not clear how changes in one component (EI, NEPA, exercise) will affect the others, as well as how these interactions may influence the ability to lose weight and maintain it throughout time. For instance, increasing levels of exercise may lead to a compensatory increase in EI as an attempt to counteract the created negative EB (King et al., 2007). Nevertheless, it is unclear whether increasing exercise habits has a positive or negative impact on overall NEPA levels. Even though previous studies suggest that individuals may feel more energetic when exercising, which could motivate them to be more active during the day (Jakicic et al., 2002), others show that increasing regular exercise levels may either boost signs and symptoms of fatigue or lead to a perception of “deserving a reward” perceptions, consequently reducing daily NEPA and increasing sedentary levels (Blundell et al., 2003; King et al., 2007; Westerterp, 2001). Thus, it is important to understand not only how these interactions influence the ability to lose weight and maintain it throughout time, but also which individuals are more prone to experience these behavioral adaptations, in order to develop better individual-centered strategies to increase WL’s success.

Therefore, the aim of this study was to examine the associations between changes in EI with changes in time spent in PA (NEPA and exercise, min/day) and changes in PAEE (divided in NEAT and EiEE, kcal/d), as well as the interindividual variability in EI and EE after a WL intervention. We hypothesize that decreases in EI would be compensated

with decreases in NEPA, as well as in PAEE, attenuating the negative EB and therefore the WL success.

8.3. METHODOLOGY

This is a secondary analysis from the Champ4life project, a WL lifestyle intervention targeting former elite athletes who were living with overweight/obesity and were inactive (Silva et al., 2020). The main results of this program are described in detail elsewhere (Silva et al., 2021). The project 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 (World Medical, 2013). The trial is registered at www.clinicaltrials.gov (clinicaltrials.gov ID: NCT03031951).

The Champ4life project

The program consisted of a 1-year lifestyle intervention that consisted of a 4-month WL intervention and an 8-month WL maintenance period. Ninety-four participants of both sexes were selected and randomly assigned to 1 of the 2 groups: intervention or control group. All of the participants were living with overweight/obesity (BMI $\geq$ 25.0kg/m^2), inactive (<20min/day of vigorous PA intensity for at least 3 days per week or <30 min/day of moderate intensity PA for at least 5 days per week (American College of Sports et al., 2018)), aged 18-65 years and ready to modify their diet in order to achieve a lower body weight. For a more detailed description of inclusion and exclusion criteria, see the study protocol (Silva et al., 2020).

Participants from the IG were followed throughout the program by a certified dietitian, to adjust their diet and perform a moderate caloric deficit (300 - 500kcal/d). Regarding PA habits, the participants were only encouraged to increase their PA levels and to decrease the time spent in sedentary behavior. For the 8-month weight maintenance period,

nutritional appointments were held to create a neutral EB. In parallel, the IG underwent 12 educational weekly sessions targeting diet, eating behavior, PA, and behavior change domains(Silva et al., 2020).

Body composition

Participants had their weight and height measured to the nearest 0.01 kg and 0.1 cm, using a weight scale and stadiometer (SECA, Hamburg, Germany), respectively. BMI was calculated as weight (kg) divided by the square of the height (m) and classified according to the World Health Organization (WHO) cutoffs (Weir CB & A., [Updated 2019 Apr 20].). Dual-energy X-ray absorptiometry (DXA; Hologic Explorer-W, Waltham, MA, USA) was used to assess total and regional fat mass (FM) and fat-free mass (FFM), as described elsewhere (Park et al., 2002).

Physical activity (PA)

PA was objectively measured using a tri-axial accelerometer (ActiGraph GT3X+, Pensacola, FL). Participants were asked to wear the accelerometer on the right side of the hip for 7 consecutive days and to only remove the sensor during sleep and water-based activities (e.g., bathing and swimming). The accelerometers were initialized on the morning of the assessment day and data were recorded in 15-s epochs and reintegrated into 60-s epochs and using a 100Hz frequency (2 minutes spike tolerance). Only participants with at least three valid days (≥600 min/day, with at least one weekend-day) were included in the analysis. Participants were asked to fill a logbook to record daily waking and sleeping hours and exercise routines (when applicable), as well as the timings and reasons for accelerometer removal.

To determine NEPA, the time spent in different levels of PA (excluding exercise) was considered. The time excluded for NEPA analysis plus registered information (logbook) from structured PA in which the participants did not use the accelerometer (e.g., water-based activities) was used to determine overall exercise levels. The Freedson

Combination' 98 algorithm (which includes the Work-Energy Theorem and the Freedson' 98 equation to calculate EE under 1951 and above 1952 counts) (Sasaki et al., 2011) was used to calculate the caloric expenditure from both structured (EiEE, determined from the combination of the data excluded in the NEAT analysis and additional data from logbook) and unstructured PA [energy expended in NEPA, i.e., NEAT (kcal/d)].

The 2011 Compendium of Physical Activities (Ainsworth et al., 2011) was used to calculate the EiEE not recorded with the accelerometer using specific PA metabolic equivalents (METs).

Resting energy expenditure (REE)

The MedGraphics CPX Ultima indirect calorimeter (MedGraphics Corporation, Breezeex Software, Italy) was used to assess the measured REE (mREE), during the morning period (7.00-10.00am), after an overnight fast. The calorimeter was used to measure breath-by-breath oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) using a mask placed in participants' face. A pneumotachograph calibrated with a 3L-syringe (Hans Rudolph, inc.TM) was used to measure the flow and volume. The participates were asked to relax, breath normally and not sleep or talk during the test (Compher et al., 2006).The lowest mean of 5 minutes of steady state (i.e., coefficient of variance ≤10 % for $\dot{V}O_2$ and $\dot{V}CO_2$), between the 5 and the 25 minutes of REE assessment, with respiratory exchange ratio between 0.7 and 1.0, were considered for analysis (Compher et al., 2006). Based on test–retest in 7 participants, the CV for REE was 4.0% (Silva et al., 2013).

Total Daily Energy Expenditure (TDEE)

TDEE was estimated as:

$$\mathrm{TDEE(kcal/d)} = \mathrm{REE(kcal/d)} + \mathrm{NEAT(kcal/d)} + \mathrm{EiEE(kcal/d)} + \mathrm{TEF(kcal/d)},$$

where PAEE (NEAT + EiEE) was assessed by accelerometry and REE measured by indirect calorimetry. TEF accounts for 10% of TDEE (Weststrate, 1993).

Energy intake (EI)

EI was estimated by the intake-balance method (Rosenbaum et al., 1996). This method has been previously validated (Racette et al., 2012; Shook et al., 2018) and has been shown to provide valid estimations of EI through changes in body energy stores, such FM and FFM, together with TDEE. By inverting the EB equation, where energy stores (ES) = EE + EI, the following model was used:

$$\mathrm{EI\ (kcal/d)} = \mathrm{EE\ (kcal/d)} + \mathrm{ES\ (kcal/d)},$$

where ES is calculated using the following equation:

$$\mathrm{ES} = 9500\frac{\Delta FM}{\Delta t} + 1020\frac{\Delta FFM}{\Delta t},$$

with ΔFM, ΔFFM and Δt representing changes in fat mass (kg), fat free mass (kg) and time in days respectively. If FM and FFM are known over a time interval, then ES can be directly calculated and summed with EE to objectively estimate EI (Ravelli & Schoeller, 2021). For the baseline EI, as participants were weight stable during at least 3 months (inclusion criteria), we considered that ES = 0, and therefore EI = EE.

Statistics

For this secondary analysis, only participants that completed the 4-months intervention were included. Statistical analysis was performed using IBM SPSS statistics version 27.0 (IBM, Chicago, Illinois, USA) and statistical significance was set as $p<0.05$ (two-sided). Kolmogorov-Smirnov test was conducted to check normality of variables. Changes over time were analyzed by linear mixed models, included randomized group and time as fixed effects, with sex as a covariate, to assess the impact of group, time (baseline– 0 months, post-intervention– 4 months, and follow-up– 12 months), and group-by-time

interaction. Differences-in-differences (DiD) were calculated between the IG and CG throughout time, calculated as the difference between changes for IG and changes for CG.

Pearson correlations were performed to examine associations between EE components and body composition. Partial correlations (adjusted for group) were conducted to examine the associations between ∆EI, changes in body composition, ∆NEPA, ∆exercise and changes in PAEE (NEAT and EiEE).

The SD of individual response (SD_{IR}) was calculated to understand if interindividual variability occurs, with the following equation:

$$SD_{IR} = \sqrt{{SD_{IG}}^2 - {SD_{CG}}^2}$$ (Atkinson & Batterham, 2015)

When the SD_{CG} > SD_{IG}, the SD_{IR} formula was reversed and the SD_{IR} was reported as a negative value (Bonafiglia et al., 2021). Positive SD_{IR} values were compared to the smallest worthwhile change (SWC), calculated by multiplying 0.2 by the SD of the CG at baseline (Hecksteden et al., 2018). A SD_{IR} > SWC suggests meaningful interindividual differences, while a SD_{IR} < SWC insinuates that interindividual differences are irrelevant (Atkinson & Batterham, 2015). Ninety-five percent confidence intervals (95%CI) were estimated by using the following equation (Hopkins, 2015):

$$95\%CI = \sqrt{{SD_{IR}}^2 \pm 1.96 \times \sqrt{2 \times \left(\frac{{SD_{IG}}^4}{n_{IG} - 1} + \frac{{SD_{CG}}^4}{n_{CG} - 1}\right)}}$$

Data are presented as mean (SD), except for linear mixed models, being presented as estimated marginal means, standard error (SE) and 95% confidence intervals.

The main study was originally powered on changes in total body fat assessed by DXA. A type I error of 5% and a power of 80% were considered (using the software GPower version 3.1.9.2) to detect an effect size of 0.58 for statistically significant differences in total body fat as reported elsewhere (Huseinovic et al., 2016). After considering a dropout rate, 94 participants (47 in each group) were enrolled in the main study.

8.4. RESULTS

For this study, only participants with completed data at baseline for EI, EE components and body composition were included (n = 81, mean (SD): age = 42.8 (9.4)y, BMI = 31.2 (4.4)kg/m^2, 37% females). Participants were divided in intervention (IG, n=43, age = 42.3 (7.8)y, BMI = 31.8 (4.0)kg/m^2, 35% females) and control group (CG, n=38, mean (SD): age = 43.4 (11.0)y, BMI = 30.5 (4.9)kg/m^2, 40% females).

The results of the intervention throughout time for the included participants from baseline to 4 months are presented in **table 8.1**. Overall, the IG participants decreased their weight and FM when compared to the CG [weight: estimated difference (ED) of −4.4 kg (95% CI −6.1 to −2.7; p<0.001); FM: ED =-3.7kg (95% CI -5.2 to -2.3; p<0.001)]. Participants from the IG also decreased their EI [ED =-253 kcal/d (95% CI -466 to -40; p=0.021)] but increased exercise [ED =16min (95% CI 3.6 to 27.4; p=0.012)] and EiEE [ED =107kcal/d (95% CI 43 to 171; p=0.001)].

Table 8.1. Changes in body composition, EI and EE from baseline to 4 months of the included participants.

		Control	Intervention			
Body Composition						
Weight (kg)	Baseline	89.6 (2.4)	92.4 (2.3)	**Changes †**	**95%CI**	**p-value**
	4 months	89.8 (2.4)	88.2 (2.3)‡	-4.4	-6.1 , -2.7	<0.001
BMI (kg/m^2)	Baseline	30.5 (0.7)	31.8 (0.7)	**Changes †**	**95%CI**	**p-value**
	4 months	30.6 (0.7)	30.4 (0.7)	-1.5	-2.1, -0.9	<0.001
FM (kg)	Baseline	29.0 (1.4)	31.0 (1.4)	**Changes †**	**95%CI**	**p-value**
	4 months	30.0 (1.3)	27.7 (1.4)‡	-3.7	-5.2 , -2.3	<0.001
FM (%)	Baseline	32.7 (0.9)	34.3 (0.8)	**Changes †**	**95%CI**	**p-value**
	4 months	33.0 (0.9)	32.0 (0.8)‡	-2.6	-3.7 , -1.5	<0.001
FFM (kg)	Baseline	59.4 (1.4)	60.0 (1.3)	**Changes †**	**95%CI**	**p-value**
	4 months	59.0 (1.4)	59.1 (1.3)	-0.5	-1.4 , 0.5	0.303
Energy Expenditure Components						
$_m$REE (kcal/d)	Baseline	1643 (15)	1645 (15)	**Changes †**	**95%CI**	**p-value**
	4 months	1622 (17)	1526 (17)‡	-97	-161 , -33	0.003
PAEE (kcal/d)	Baseline	615 (59)	519 (56)	**Changes †**	**95%CI**	**p-value**
	4 months	522 (64)	620 (61)	194	31.5 , 357	0.020
NEAT (kcal/d)	Baseline	576 (55)	482 (53)	**Changes †**	**95%CI**	**p-value**
	4 months	497 (60)	489 (57)	87	-66, 239	0.260
EiEE (kcal/d)	Baseline	39 (22)	37 (21)	**Changes †**	**95%CI**	**p-value**
	4 months	26 (24)	131 (23)‡	107	43, 171	0.001
TDEE (kcal/d)	Baseline	2544 (96)	2391 (92)	**Changes †**	**95%CI**	**p-value**
	4 months	2360 (106)‡	2378 (99)	170	-55 , 395	0.136
Sedentary	Baseline	541 (10)	523 (10)	**Changes †**	**95%CI**	**p-value**
time (min/d)	4 months	556 (11)	544 (11)	6	-27, 39	0.706
NEPA (min/d)	Baseline	306 (14)	291 (13)	**Changes †**	**95%CI**	**p-value**
	4 months	302 (14)	302 (14)	14	-20 , 49	0.413
Exercise	Baseline	4 (3)	8 (3)	**Changes †**	**95%CI**	**p-value**
(min/d)	4 months	4 (4)	24 (4)‡	16	3.6 , 27.4	0.012
Energy intake						
EI (kcal/d)	Baseline	2491 (65)	2400 (66)	**Changes †**	**95%CI**	**p-value**
	4 months	2391 (78)	2048 (73)‡	-253	-466, -40	0.021

Data are presented as Estimated Mean (SE).
* All models were adjusted for sex.
Abbreviations:; CI, confidence interval; FM, Fat-mass; FFM, Fat-free mass; EI, energy intake; EiEE, exercise-induced activity thermogenesis; NEAT, non-exercise activity thermogenesis; NEPA, non-exercise physical activity; PAEE, physical activity energy expenditure; REE, resting energy expenditure; TDEE, total daily energy expenditure
‡ Differences within group between baseline and post-programme, p<0.05
† Difference in differences estimated changes
(Post-programme$_{intervention}$ – baseline$_{intervention}$) - (Post-programme$_{control}$ – baseline$_{control}$)

Associations with changes in EI (kcal/d and %)

Correlations between the changes in EI (kcal/d and %) and changes in PA and PAEE are presented in **table 8.2**.

Table 8.2. Correlations between the changes in EI (kcal/d and %) and changes in PA (min/day) and PAEE (kcal/day) (intervention group)

	ΔEI (kcal/d)	**ΔEI (%)**
ΔNEPA (min/day)	r = -0.170 (p = 0.474)	r = -0.164 (p = 0.489)
ΔNEPA (%)	r = -0.056 (p=0.813)	-0.064 (p=0.788)
ΔNEAT (kcal/day)	r = 0.165 (p=0.441)	r = 0.104 (p=0.629)
ΔNEAT (%)	r = 0.181 (p=0.396)	r = 0.154 (p=0.474)
ΔSedentary (kcal/day)	r = 0.344 (p=0.138)	r = 0.276 (p=0.239)
ΔSedentary (%)	r = 0.433 (p=0.057)	r = 0.368 (p=0.110)
ΔExercise (min/day)	**r = -0.413 (p=0.045)**	**r = -0.423 (p=0.039)**
ΔExercise (%)	**r = -0.846 (p=0.008)**	**r = -0.831 (p=0.011)**
ΔEiEE (kcal/day)	**r = -0.488 (p=0.016)**	**r = -0.494 (p=0.014)**
ΔEiEE (%)	**r = -0.859 (p=0.006)**	**r = -0.846 (p=0.008)**

Abbreviations; CI, confidence interval; FM, Fat-mass; FFM, Fat-free mass; EI, energy intake; EiEE, exercise activity thermogenesis; NEAT, non-exercise activity thermogenesis; NEPA, non-exercise physical activity; PAEE, physical activity energy expenditure.

Changes in EI (kcal/d) were negatively associated with changes in exercise (min/d: r = -0.413, p=0.045; %: r=-0.846, p = 0.008), i.e., larger decreases in EI were associated with larger increases in exercise, and with EiEE (kcal/d: r = -0.488, p=0.016; %: r = -0.859, p=0.006). The degree of caloric restriction (%) was negatively correlated with exercise (min/d: r = -0.423, p=0.039; %: r = -0.831, p=0.011) and EiEE (kcal/d: r = -0.494, p=0.014; %: r = -0.846, p=0.008).

Associations with exercise, NEPA and sedentary behavior

A negative correlation was found between changes in sedentary time and NEPA (min/d, %), i.e., showing that those who increased NEPA were also those who showed larger decreases in sedentary time (min/d: r=-0.622, p=0.002: %: r=-0.487, p=0.018). No correlations were found between changes in exercise and changes in NEPA nor sedentary time (p>0.05).

Interindividual variability in EI and EE

An interindividual variability among participants was found for both EI, (SD_{IR} = 151.6, with a SWC = 72.3) and EE (SD_{IR}= 165, with a SWC = 134). This large variability in changes in EI and EE, as well as the corresponding EB are graphically represented in **Figure 1**, where 4 situations were highlighted:

A - Decreases in EI that were accompanied by a decrease in EE, attenuating the negative EB;

B – Decreases in EI and an increase in EE, increasing the magnitude of a negative EB;

C – A negative EB caused by an increase in EE;

D – Increases in EI and a decrease in EE, leading to a positive EB.

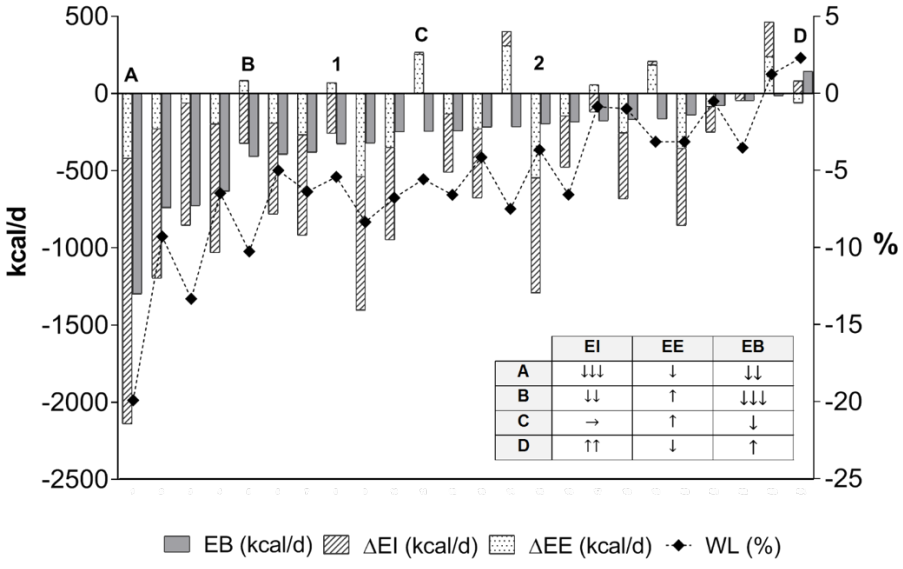

Figure 8.1. Interindividual variability in changes in EI, EE and the corresponding EB.

Most participants from the IG decrease their EI and, despite decreasing EE, they were able to achieve a negative EB (**situation A**). It is also observed that, although participant 2 showed a larger decrease in EI when compared to participant 1, changes in EE were the opposite, as participant 2 decrease and participant 1 increase their EE. Despite participant 2 showed a larger energy restriction, participant 1 ended with a larger negative EB and, consequently with a higher WL.

8.5. DISCUSSION

This study highlighted the occurrence of a meaningful interindividual variability for both EI and EE. Decreases in EI were not associated to compensatory responses such as decreases in PA and/or increases in sedentary time. Nevertheless, decreases in EI were associated with increases in time spent in exercise and EiEE. A negative correlation was also found between changes in sedentary time and changes in NEPA.

A wide range of observed responses in body composition after a WL intervention is expected and documented in the literature (Dent et al., 2020). However, having a large variability of individual responses does not mean that interindividual variability exists, as this variability may reflect a large random measurement error and/or a within subject variability (Bonafiglia et al., 2021). According to Atkinson et al. the use of SD_{IR} is an adequate approach to understand if truly interindividual differences occurs for a certain outcome (Atkinson & Batterham, 2015). In our study, both EI and EE showed a positive SD_{IR} that surpassed the SWC, suggesting the existence of significant interindividual differences for these outcomes.

Together with different degrees of compliance with the intervention, metabolic and behavioral compensations may occur as a response to a disturbance in the EB, affecting the WL process. While metabolic compensations are widely debated, especially the higher-than-expected decrease in REE (i.e., adaptive thermogenesis) (Nunes et al., 2022), little is known regarding the relation between changes in EI and EE components.

In fact, the existence of behavioral compensations as a response to a negative EB was suggested in 1980 by Epstein and Wing, as “Exercise may stimulate the appetite so that persons who exercise increase their eating and do not lose as much weight as expected” and “a person who exercises in the early evening may go to sleep earlier or require more rest in the evening” (Epstein & Wing, 1980). More recently, King et al. underlined the behavioral and metabolic adaptations that occur as a response to exercise-induced WL (King et al., 2007), where changes in EI, exercise and NEPA were highlighted as behavioral responses that varies among individuals.

Although the large variability in changes in EI and EE was well demonstrated in this study, decreases in EI were mostly accompanied by a decrease in total EE, attenuating the EB. Given that EE is composed by REE, TEF and PAEE, changes in this parameter can be derived from several combinations of changes in each component. More specifically, when analyzing total EE (without considering each component separately), we cannot assure if decreases in overall EE were due to decreases in REE, PAEE or a combination of both. Plus, as PAEE is related to NEPA and exercise, decreases in this component may be due to decreases in PA (behavioral compensation) rather than an increase in muscular efficiency (metabolic compensation), which is known to account for approximately 35% of change in PAEE during weight regain (Rosenbaum et al., 2003). In fact, previous studies showed that maintaining high levels of PAEE during WL maintenance is a good strategy to maintain the reduced weight state (Ostendorf et al., 2019).

Although participants from the Champ4life project lost a significant amount of weight, their NEPA levels remained similar after 4 months. The effects of a WL intervention in NEPA are still contradictory, as some authors found a decrease in NEPA/NEAT, while others reported no compensations in these components (Silva et al., 2018). In the Herrmann et al. study (Herrmann et al., 2015), where participants underwent an exercise-intervention targeting WL, NEPA decreased for the non-responders group (WL<5%) but increased for the responders (WL≥5%), suggesting that the decrease in

NEPA (and consequently NEAT) was sufficient to compensate the increase in PA due to exercise, failing at achieving a negative EB. Similarly, the effect of energy restriction through diet has been found to be linked to a substantial decrease in NEAT, independently of sex and age (Martin et al., 2011), which is in agreement with previous research demonstrating that energy restriction may have a negative influence on PAEE, even during moderate energy restriction interventions (Martin et al., 2011). Along with the fact that losing weight leads to a higher self-awareness regarding one's actions (e.g., knowing the importance of being active, choose more adequate and nutritionally-dense meals), a sensation of feeling more energetic may occur, which might motivate them to be more active during the day (Jakicic et al., 2002). Yet, this small increase may not be enough to maintain the PAEE, as the related metabolic demand may not offset the reduction in PAEE due to WL. Moreover, in our study, decreases in EI did not lead to compensatory changes in NEPA. These results are similar to the Weinsier et al. study, where PA levels did not change after a WL (Weinsier et al., 2000) and no differences were found regarding the levels of NEPA after a moderate WL. These findings are in line with our initial expectations considering that, due to the nature of the Champ4life project (self-determination theory-based intervention), where participants were taught, through educational sessions, the benefits of increasing PA, not only by increasing exercise, but specifically by decreasing their time spent in sedentary behaviors and being more active (Silva et al., 2021). Therefore, it was expected that NEPA was at least maintained during the active WL phase.

Despite the different results, the importance of increasing and maintaining adequate levels of PAEE during WL maintenance are well stated in most studies (Bonomi et al., 2013; Martin et al., 2011; Weinsier et al., 2000). Losing weight is often accompanied by metabolic and behavioral adaptations such as decreases in EE components (specially REE) (Nunes et al., 2021). These compensations may promote a change toward a positive EB, weakening the benefits of losing weight and potentiating weight regain. Therefore, to maintain a reduced-weight state, people need to change their behavior

permanently, whether by increasing PA and/or decreasing EI (Ostendorf et al., 2019). Nevertheless, relying only on an energy restriction, although considered as an effective strategy to WL (Cioffi et al., 2018; Wei et al., 2022), may not work as well as a tool to WL maintenance (Benton & Young, 2017). Then, evidence suggests that PA should be further considered in long-term WL interventions, since high levels of PA are positively associated with WL maintenance's success (Jakicic et al., 2002; Jeffery et al., 2003; Ostendorf et al., 2019). Even though our study did not find associations between levels of PAEE and the WL maintenance's success (data not shown), we expect that maintaining high levels of PA may work as a good strategy to compensate the "more-than-expected" reduction in TDEE, and therefore to remain in a neutral EB, without decreasing their EI (Ostendorf et al., 2019). Additionally, as it seems that individuals who fail to lose weight by an exercise-intervention show increases in EI and decreases in NEAT (Herrmann et al., 2015), highlighting the importance of inducing behavioral counseling along with this type of interventions to attenuate any behavioral compensation that may occur.

Despite the interesting findings of this work, limitations should be addressed. First, EI and EE assessments were not performed with gold-standard methods, which may change the interpretation of our results, as well as the magnitude of the changes throughout time and its contribution to WL. Moreover, the impact of exercise on EI was only studied in terms of total EI. Nevertheless, it is known that increasing exercise may influence EI by changing macronutrients preferences, frequency of eating and/or by increasing meals' energy density (King et al., 2007). Furthermore, although 3-days food diaries were included in our project, due to its well-known degree of underreporting (N. V. Dhurandhar et al., 2015), the authors decided to assess EI through the intake-balance method, which is known to be an accurate and precise method (Ravelli & Schoeller, 2021) and focused only on the daily EI. Also, as the sample was comprised by former elite athletes, a highly specific group with specific characteristics, the results must be interpreted carefully when considering a non-athletic population. Finally, as this study is

a secondary analysis of the Champ4life intervention, the sample size was powered for detecting changes in FM rather than changes in EI or EE components.

In sum, changes in EI and EE as a response to the Champ4life intervention varied among participants, as interindividual variability occurred for both variables. Additionally, despite behavioral compensations had not been found in this study, they should be considered when implementing a WL intervention. Health professional/researchers should take into consideration that an "one size fits all" approach may not work, and more individual strategies should be considered to increase the likelihood of achieving the expected results not only during the active WL phase but also in a long-term.

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Conflicts of interest

The authors reported no conflicts of interest.

Author Contributions: The Champ4Life project led by Primary Investigator A.M.S. obtained funding for the research. C.L.N conceptualized and designed the study. C.L.N, F.J, R.F and G.B.R acquired the data. C.L.N. performed the data analysis and interpretation. C.L.N and M.M. wrote the first draft of the manuscript. All authors revised the manuscript critically and contributed to the final approval of the version to be submitted.

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CHAPTER 9

CHANGES IN FOOD REWARD AND INTUITIVE EATING AFTER WEIGHT LOSS AND MAINTENANCE IN FORMER ATHLETES WITH OVERWEIGHT OR OBESITY[6]

[5]**Nunes, C. L.,** Carraca, E. V., Jesus, F., Finlayson, G., Francisco, R., Silva, M. N., Santos, I., Bosy-Westphal, A., Martins, P., Minderico, C., Sardinha, L. B., & Silva, A. M. (2022, May). Changes in food reward and intuitive eating after weight loss and maintenance in former athletes with overweight or obesity. Obesity (Silver Spring), 30(5), 1004-1014. https://doi.org/10.1002/oby.23407

CHAPTER 9

Changes in food reward and intuitive eating after weight loss and maintenance in former athletes with overweight or obesity.

CHANGES IN FOOD REWARD AND INTUITIVE EATING AFTER WEIGHT LOSS AND MAINTENANCE IN FORMER ATHLETES WITH OVERWEIGHT OR OBESITY

Catarina L Nunes, Eliana V Carraça, Filipe Jesus, Graham Finlayson, Rúben Francisco, Marlene N Silva, Inês Santos, Anja Bosy-Westphal, Paulo Martins, Cláudia Minderico, Luís B Sardinha, Analiza M Silva

9.1. ABSTRACT

We aimed to explore 1)the impact of Champ4Life's intervention on intuitive eating (IE) and food reward (FR) and 2)associations between changes in eating behavior and changes in body composition. Ninety-four former athletes[BMI=31.1(4.3)kg/m^2, age=43.0(9.4)y, 34% females], assigned to intervention(IG,N=49) and control groups(CG,N=45), underwent 4-months of an active weight loss (WL) followed by 8-months of WL maintenance. IE and FR were assessed by the Intuitive Eating Scale and the Leeds Food Preference Questionnaire, respectively. The WL was -4.8(4.9)% and 0.3(2.6)% for the IG and CG, respectively. Participants reported a decrease in fat bias for explicit/implicit wanting and explicit liking after 4 months and 1 year. For intuitive eating, the unconditional permission to eat(UPE) decreased after 4 months and the body–food choice congruence(BFCC) increased after 1-year. Changes in UPE and in BFCC were positively and negatively associated with both ΔWeight and with ΔFM, respectively. Changes in explicit wanting for fat and taste bias were associated with ΔWeight. FR decreased after a moderate WL intervention. Participants successfully maintained their reduced weight and most of the changes in eating behavior remained significant at the end of the follow-up period. Lifestyle interventions aiming at WL should also consider IE and FR.

Key-words: Food reward, Intuitive eating, Motivation, Weight loss, Weight maintenance

9.2. INTRODUCTION

For an athlete, the transition to post-career is often perceived as a difficult challenge (Carapinheira et al., 2018), as there is a need to adopt new strategies to ensure they do not exceed their lower energy requirements. There is a lack of support for former athletes when transitioning to post-career, which increases susceptibility to develop obesity and other obesity-related diseases (Pomeroy & White, 1958). In fact, the prevalence of overweight/obesity in former elite athletes is ~50% (Batista & Soares, 2013), and it is known that a higher body mass index (BMI) increases the risk of developing several diseases such as cardiovascular diseases, dyslipidemia and elevated fasting plasma glucose (Miller et al., 2008; Tucker et al., 2009). Therefore, there is a need to implement lifestyle interventions targeting former athletes to increase healthy lifestyle behaviors and sustain them over time.

Although literature is full of interventions aimed at weight loss (WL) (Zaghloul et al., 2021), difficulties in sustaining changes in health behaviors in populations at risk of developing obesity-related diseases are well recognized (Greaves et al., 2017). During WL, metabolic and behavioral adaptations may occur, jeopardizing the ability of losing weight and maintaining it (Johannsen et al., 2012; Tremblay et al., 2013). Although these difficulties are considered a possible barrier to WL (Nunes et al., 2021), difficulties in losing weight and maintain it are mainly due to the lack of long-term adherence to dietary and physical activity (PA) recommendations (Gurevich-Panigrahi et al., 2009). Also, these compensatory responses regarding exercise and dietary habits may be influenced by psychological mechanisms, namely the type of motivations that guide these behaviors (Carraca et al., 2019). Literature based on Self-Determination Theory (SDT) has shown that when a behavior is endorsed by an autonomous motivation rather than more external ones (i.e., to obtain others' approval), it tends to be maintained over time (Ng et al., 2012; Ryan et al., 2007). Thus, SDT-based lifestyle interventions may be helpful not only to achieve WL but also to avoid weight regain during WL maintenance.

It is known that food intake is regulated by homeostatic (eating when metabolically hungry) and hedonic (eating for pleasure, reward) pathways (Lutter & Nestler, 2009). The high abundance of highly palatable food, typical in the current obesogenic environment, activates the brain reward circuits, by stimulating the hypothalamic hunger signals and inhibiting satiety mediators (Monteleone et al., 2012). As a result, the hedonic pathway can override the homeostatic pathway by increasing the desire to consume highly palatable foods. This consequently puts larger demands on the cognitive, less intuitive, regulation of eating behavior (Espel-Huynh et al., 2018), directly influencing an individual's food choices and consumption (Berthoud, 2012). Furthermore, being under a caloric deficit leads to increased psychological distress (Tylka et al., 2015), potentially creating a compensatory drive to overeat (Birch et al., 2003; Cameron et al., 2014), which might endanger the maintenance of a reduced weight. Therefore, components of eating behavior such as food reward and intuitive eating have started to be studied in WL interventions (Cameron et al., 2014; Finlayson et al., 2011; Oustric et al., 2021).

Intuitive eating, i.e., the action of eating based on physiological hunger and satiety cues, rather than situational and emotional cues (Tylka & Diest, 2013), has been described as a flexible and adaptive eating behavior (Tribole & Resch, 2012; Tylka et al., 2015). Higher levels of intuitive eating are associated with improved well-being, greater levels of enjoyment and positive associations with food choices, decreasing eating-related distress (Smith & Hawks, 2006). However, people with overweight/obesity often use emotional cues to guide their eating behaviors rather than physiological and satiety cues (Tylka, 2006), reporting lower levels of intuitive eating (Camilleri et al., 2016; Carraça et al., 2020; Gast et al., 2015; Mata et al., 2009).

Based on the behavioral operationalization of liking and wanting, food reward can be defined as a process that contributes to the pleasure and motivation/drive to obtain food (Cameron et al., 2014), being divided in 2 sub-components: liking, i.e., subjective pleasure from food, and wanting, i.e., desire for a specific food. Wanting can be assessed as an "implicit" (the automatic, unconscious, drive to eat a specific food) or "explicit" (the

cognitive, conscious, desire to eat) (Berridge, 2009) response, and both liking and wanting play a role in eating behavior, influencing WL and its maintenance (Oustric et al., 2018). Sensibility to reward has been related to overconsumption and weight regain (Davis et al., 2004), emphasizing its role in the development of obesity.

Understanding how one's eating behavior changes during WL and its maintenance is paramount for developing strategies that improve the likelihood of participants' success. This study is a secondary analysis of the Champ4Life project, a 1-year SDT-based lifestyle intervention directed to inactive former elite athletes who presented overweight/obesity. The project was divided into 4 months of active WL followed by 8 months of follow-up (Silva et al., 2020). Therefore, we aimed to explore: 1) the impact of a 1-year lifestyle intervention (4 months of WL followed by 8 months follow up) on intuitive eating and food reward outcomes (vs. control group) and 2) if there is a relation between changes in eating behavior components and changes in body composition outcomes. We hypothesized that the SDT-based Champ4Life intervention would lead to sustainable improvements in participants' eating patterns and habits, by fulfilling participants' basic psychological needs and promoting autonomous motivations to regulate eating behavior (mechanisms not explored herein but supported in previous literature (Carraca et al., 2019; Mata et al., 2009)). These improvements in eating behavior were hypothesized to be associated with successful weight loss and maintenance.

9.3. METHODOLOGY

9.3.1. Study design

This study is part of the Champ4Life project, a 1-year randomized controlled trial targeting former elite athletes with overweight/obesity. A detailed description of the study protocol, including the recruitment procedures, exclusion and inclusion criteria, randomization process, and methods, as well the results of the intervention are published

elsewhere (Silva et al., 2021; Silva et al., 2020). All assessments took place in the Faculty of Human Kinetics, University of Lisbon and were performed at the three time points: baseline, after 4 months and after 12 months.

The trial was registered at www.clinicaltrials.gov (clinicaltrials.gov ID: NCT03031951). This 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 (World Medical Association, 2008).

9.3.2. The Champ4Life intervention

For the active WL, the intervention group (IG) underwent an educational/motivational SDT-based program (Ng et al., 2012; Ryan et al., 2007) aimed at promoting behavioral changes possible to be integrated in participants' daily lives and contexts. Initially, an individual 1-hour nutrition appointment with a certified dietitian was provided to each participant from the IG to discuss the participant's eating pattern and create a personalized dietary strategy to promote a moderate caloric deficit (~300-500kcal/d), according to each participant's energy requirements and preferences. Also, 12 educational sessions were given during the intervention (4 months, 1 per week), including educational content and practical application of in-class exercises in the areas of physical activity (PA) and exercise, diet and eating behavior, as well as behavior modification (Michie et al., 2009).

During sessions, strategies to support the three basic psychological needs (autonomy, competence, and relatedness), to promote autonomous motivations were included, such as: i) encouragement of self-selected relevant goals (for weight, PA and eating); ii) encouragement of volitional (not compulsory), regular self-weighting, and self-monitoring of PA and eating behaviors. Participants had their weight tracked weekly, as well as their daily steps (with the auxilium of a pedometer).

For the follow-up period (8 months), the aim was to understand if participants were able to maintain the new healthy habits that they acquired during the intervention. Thus, after the 4-months WL phase, a nutrition appointment was given to each participant to adjust their caloric intake to create a neutral energy balance. During the follow-up period, if the participants were struggling with maintaining their reduced weight state, they were allowed to contact our team members to clarify any rising doubts, ask for advice and, if necessary, to readjust their maintenance diet. However, their body composition was not tracked.

Participants from the control group 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.

9.3.3. Body Composition

Participants had their weight and height measured with a weight scale (Seca 799, Hamburg, Germany) and a stadiometer (Seca, Hamburg, Germany), respectively.

Dual energy X-ray absorptiometry (DXA; Hologic Explorer-W, Waltham, USA) was performed to assess the body composition stores, such as total fat mass (FM) and fat-free mass (FFM), as described previously (Silva et al., 2020).

9.3.4. Eating behavior

9.3.4.1. Food reward

The Leeds Food Preference Questionnaire (LFPQ) (Finlayson et al., 2008; Finlayson et al., 2007) is a computer procedure that provides measures of food preference and food reward, including explicit liking/wanting and implicit wanting. A ‘forced choice’ reaction time task is used as a measure of implicit wanting in addition to explicit subjective measures of liking and wanting for visual food stimuli varying in fat content (high fat or low fat) and taste (sweet or savory). The LFPQ consists of two sub-tasks that are

counterbalanced within the test, namely 1) an explicit evaluation of food images randomly presented from an array of pre-validated photographs using VAS and 2) a rapid choice to be made between paired combinations of the food images from different categories (Oustric et al., 2020). Participants were able to practice the two tasks before starting the questionnaire. Food images that best represented the Portuguese food culture were selected from the original food picture database with the support of a certified dietitian. To verify if the selected food images are accurately recognized, frequently eaten, enjoyed, correctly perceived as sweet/savory, low- or high-fat, and appropriate for the intended time of day, an online questionnaire was applied to a sample of 367 individuals (mean (SD): age = 43.3(12.6) years, BMI = 24.6 (4.2) kg/m^2, 75% females). From that, 139 reported having overweight/obesity (age = 45.6 (12.8) years, BMI = 28.7 (3.3) kg/m^2, 60% females) and 208 reported a BMI < 25 kg/m2 (age = 41.8(12.9) years, BMI = 21.8 (1.8) kg/m^2, 82% females). This is an additional procedure that was added after the termination of the Champ4Life program, following the recommendations for cross-cultural adaptation of the LFPQ that were published in 2020 (Oustric et al., 2020), and data is currently being analyzed.

Implicit wanting was measured by requiring participants to choose between pairs of food images by asking “Which food do you want to eat now?”. Participants were not aware that their reaction times are being recorded and were instructed to work as “quickly as possible” in the task, limiting the opportunity for reflective processes to affect the outcome. There was no verbalization or linguistic reasoning required to complete the trials. The required speed and repetition of responding in the task prevents an intentional pattern of responses that diverges from the participant’s true preferences. The speed with which one category of stimuli was chosen relative to alternative categories provided a quantifiable measure of implicit wanting for each food category in the procedure.

Explicit liking and wanting measures were obtained by rating the same stimuli. Subjects were presented with single food images and were required to rate them according to the statements ‘‘How pleasant would it be to experience a mouthful of this food now?’’ for

explicit liking and ‘‘How much do you want some of this food now?’’ for explicit wanting. For both scales, the anchor “Not at all” was used on the left side of the scale and “Extremely” on the right side, where higher scores represent a greater explicit liking or wanting for a specific food. Questions were presented intermittently and in a random order. The results were computed by category and interpreted as the absolute explicit liking or wanting for each category (Oustric et al., 2020).

Two composite scores – Fat Bias and Taste Bias – were calculated for each food reward component (explicit liking and wanting and implicit wanting). Fat Bias score was calculated by subtracting the mean for low-fat scores from the mean for high-fat scores, while Taste Bias was calculated by subtracting mean savory values from mean sweet values. For both outcomes, a higher value means that the person shows a high preference for high fat/sweet foods over low fat/savory foods, respectively (Oustric et al., 2020).

9.3.4.2. Intuitive eating – IES-2 questionnaire

Intuitive eating was assessed using the Intuitive Eating Scale – 2 (IES-2) (Tylka & Diest, 2013). IES-2 is a 23-item questionnaire that measures the degree to which one eats in response to physiological eating cues, comprising 4 subscales: eating for physical rather than emotional reasons (Cronbach’s α =0.92), unconditional permission to eat (Cronbach’s α=0.81), reliance on hunger and satiety cues (Cronbach’s α=0.85), and body-food choice congruence (Cronbach’s α =0.83) (Tylka & Diest, 2013). Participants respond to the questionnaire “For each item, please check the answer that best characterizes your eating attitudes or behaviors” on a 5-point Likert scale ranging from 1 (“strongly disagree”) to 5 (“strongly agree”). The IES-2 was performed in a sub-sample of the Champ4Life project (66 out of 94 included participants).

9.3.5. Statistics

Statistical analyses were performed using IBM SPSS statistics version 27.0 (IBM, Chicago, Illinois, USA). All analyses were intention-to-treat, including data from all participants who were randomly assigned. Due to the repeated structure of our data and to better deal with missing data (dropouts during the intervention), Linear Mixed Models (LMM) were performed. LMM were used to assess differences in food reward and intuitive eating outcomes during the Champ4Life project. All the assessments included the group (intervention vs control), time (baseline – 0 months, post-intervention – 4 months, and follow-up – 12 months) and the interaction intervention*time as fixed factors. The variables sex and baseline values were added as covariates, as differences between sexes for body composition (Wu & O'Sullivan, 2011), WL rates (Williams et al., 2015), intuitive eating (Schaefer & Magnuson, 2014) and sensibility to food reward (Arganini et al., 2012) are well documented in the literature. Differences-in-differences (DiD) were performed to assess differences between the IG and CG throughout time (Time1 – Baseline, Time2 – 4 months, Time3 – 12 months), calculated as the difference between changes for IG (Difference_IG = Time2/3 -Time1) and changes for CG (Difference_CG = Time2/3 – Time1): DiD = (Difference_IG) – (Difference_CG). The covariance matrix for repeated measures within subjects over time was modelled as Compound Symmetry. Model residual distributions were examined graphically and using the Kolmogorov-Smirnov test, and no data transformations were necessary. To test associations between changes in food reward/intuitive eating domains and changes in body composition outcomes [weight (kg), FM (kg and %), FFM (kg)], Pearson's correlations were performed. Statistical significance was set at $p<0.05$ (2-tailed).

9.4. RESULTS

Ninety-four participants [mean (SD): BMI = 31.1 (4.3)kg/m^2, age = 43.0 (9.4)y, 34% females] were included in this program and were randomly assigned into intervention [N = 49; mean (SD): BMI = 31.7 (3.9)kg/m^2, age = 42.4 (7.3)y, 35% females] and control

groups [N = 45; mean (SD): BMI = 30.5 (4.7)kg/m^2, age = 43.6 (11.3)y, 33% females]. The drop-out rate was ~27.7% and was similar between groups (28.6% and 26.7% for the IG and CG, respectively).

The baseline characteristics for intervention and control group are presented in **table 9.1.**

Table 9.1. Baseline characteristics of participants in the Champ4life program allocated to the intervention and control groups.

	Control (n=45)	**Intervention (n=49)**
Age (years)	43.6 (11.3)	42.4 (7.3)
%Female	15 (33.3%)	17 (34.7%)
Body Composition		
Weight (kg)	90.4 (17.1)	93.2 (15.4)
BMI (kg/m^2)	30.5 (4.7)	31.7 (3.9)
Fat mass (kg)	29.0 (9.5)	31.0 (8.0)
Fat mass (%)	32.4 (7.5)	34.1 (8.2)
FFM (kg)	60.1 (12.1)	60.6 (13.3)

Data are presented as mean (SD) or n (%).
No differences were found between groups, p>0.05.

9.4.1. Body Composition

The results for changes in body composition have been published in detail elsewhere (Silva et al., 2021). After 4 months, the IG had a greater WL [estimated difference from DiD (ED) = -4.7kg (95% CI: -6.1 to -3.3; p<0.001)] and FM loss [ED = -3.8kg (95%CI: -5.1 to -2.6) p<0.001 and ED=-2.6% (95%CI: -3.6 to -1.7) p<0.001] when compared to the CG. These alterations remained significant at the end of the follow-up (1-year) [weight: ED=-5.3kg (95%CI: -6.9 to -3.8), p<0.001); FM: ED=-4.1kg (95%CI: -5.4 to -2.8) p<0.001 and ED=-3.1% (95%CI: -4.1 to -2.1) p<0.001].

9.4.2. Intuitive eating

The results for intuitive eating (IES-2 domains) are presented in **Table 9.2**.

Table 9.2. Changes in intuitive eating outcomes (IES-2 domains) at program's end (4 months) and at follow-up's end (12 months)*.

		Control (n=45)	Intervention (n=49)			
IES – Global Score	Baseline	73.3 (1.3)	74.5 (1.3)	**Changes †**	**95% CI**	**p-value**
	Post-program	75.7 (1.3)	74.7 (1.3)	-2.2	-7.0 , 2.5	0.357
	12 months	75.7 (1.5)	75.0 (1.7)	-1.8	-7.2 , 3.6	0.503
RHSC	Baseline	17.5 (0.6)	17.8 (0.5)	**Changes †**	**95% CI**	**p-value**
	Post-program	17.8 (0.6)	18.6 (0.6)	0.5	-1.6 , 2.7	0.620
	12 months	18.8 (0.7)	19.2 (0.8)	0.1	-2.3 , 2.5	0.953
EPR	Baseline	26.1 (0.6)	26.2 (0.5)	**Changes †**	**95% CI**	**p-value**
	Post-program	27.3 (0.6)	27.8 (0.6)	0.4	-1.9 , 2.6	0.753
	12 months	26.9 (0.7)	27.5 (0.8)	0.4	-2.1 , 2.8	0.775
UPE	Baseline	20.7 (0.4)	20.5 (0.4)	**Changes †**	**95% CI**	**p-value**
	Post-program	20.5 (0.5)	17.0 (0.5)‡	-3.4	-5.0 , -1.7	<0.001
	12 months	20.1 (0.5)	18.0 (0.6)§	-1.9	-3.8 , -0.1	0.042
BFCC	Baseline	10.6 (0.3)	10.6 (0.3)	**Changes †**	**95% CI**	**p-value**
	Post-program	11.0 (0.3)	11.7 (0.3)‡	0.6	-0.5 , 1.7	0.274
	12 months	10.6 (0.4)	11.9 (0.4)§	1.3	<0.1 , 2.5	0.049

Data are presented as estimated mean (SE) from linear mixed models.
Abbreviations: IES, Intuitive Eating Scale Global Score; RHSC, Reliance on Hunger and Satiety Cues; EPR, Eating for Physical Rather Than Emotional Reasons; UPE, Unconditional Permission to Eat; BFCC, Body–Food Choice Congruence.
* All models were adjusted for baseline values and sex.
‡ Differences within group between baseline and post-program, p<0.05.
§ Differences within group between baseline and 12 months, p<0.05.
† Difference in differences estimated changes
(Post-program/12months$_{intervention}$ – baseline$_{intervention}$) - (Post-program/12months$_{control}$ – baseline$_{control}$).

When divided by sexes, females reported lower baseline values for IES global score and for eating for physiological and satiety cues [Estimated mean from DiD (SE): 68.7 (11.7) vs 77.0 (10.7), p=0.007; 23.0 (7.1) vs 28.3 (6.5), p=0.001, respectively].

The unconditional permission to eat (UPE) domain decreased in the IG compared with the CG after 4 months (ED=-3.4 [95% CI: -5.0 to -1.7] p<0.001) and after 1 year (ED=-

1.9 [95% CI: -3.8 to -0.1], p=0.042). At the end of follow-up (1 year), the mean score for the body–food choice congruence (BFCC) domain increased in the IG (ED=1.3 [95% CI: <0.1 to 2.5] p=0.049).

9.4.3. Food reward

Changes in food reward (explicit liking/wanting and implicit wanting) after 4 and 12-months, adjusted for baseline values and sex, are presented in **Table 9.3**. No differences were found between sexes for any food reward outcomes.

Concerning explicit wanting, significant changes were found for fat bias, i.e., preference for high fat relatively to low fat foods, after 4 months (ED=-7.5 [95% CI: -13.2 to -1.8] p=0.010) and from baseline to 12 months (ED=-9.1 [95% CI: -15.4 to -2.8] p=0.005). The IG also showed significant decreases in implicit wanting fat bias (post-program: ED=-27.2 [95% CI: -40.3 to -14.1] p<0.001; 12 months: ED=-33.7 [95% CI: -48.1 to -19.3] p<0.001) and for taste bias (post-program: ED=-9.4 [95%CI: -17.8 to -1.0] p<0.001) and explicit liking fat bias (4 months: ED=-7.3 [95% CI: -13.1 to -1.4] p=0.016); 12 months: ED=-10.6 [95% CI: -17.0 to -4.1] p=0.001).

Table 9.3. Changes in explicit wanting, implicit wanting, and explicit liking at the post-program time point (4 months) and at follow-up (12 months)*.

		Control (n=45)	Intervention (n=49)			
Explicit Wanting						
Fat bias	Baseline	-5.6 (2.8)	-4.3 (2.7)	**Changes †**	**95% CI**	**p-value**
	Post-program	-4.7 (2.7)	-11.4 (2.7)‡	-7.5	-13.2 , -1.8	0.010
	12 months	-2.3 (2.6)	-10.6 (2.4)§	-9.1	-15.4 , -2.8	0.005
Taste bias	Baseline	5.8 (1.4)	5.6 (1.4)	**Changes †**	**95% CI**	**p-value**
	Post-program	5.9 (1.5)	1.5 (1.5)	-4.2	-9.6 , 1.3	0.131
	12 months	5.7 (1.8)	4.3 (1.7)	-1.3	-7.3 , 4.7	0.669
Implicit Wanting						
Fat bias	Baseline	-9.6 (3.5)	-6.9 (3.3)	**Changes †**	**95% CI**	**p-value**
	Post-program	-3.0 (3.7)	-27.4 (3.7)‡	-27.2	-40.3 , -14.1	<0.001
	12 months	4.0 (4.4)§	-26.9 (4.1)§	-33.7	-48.1 , -19.3	<0.001
Taste bias	Baseline	12.8 (2.3)	12.6 (2.2)	**Changes †**	**95% CI**	**p-value**
	Post-program	12.6 (2.4)	3.0 (2.4)‡	-9.4	-17.8 , -1.0	0.028
	12 months	13.1 (2.9)	5.1 (2.7)	-7.8	-17.1 , 1.4	0.096
Explicit Liking						
Fat bias	Baseline	-4.6 (1.6)	-4.3 (1.5)	**Changes †**	**95% CI**	**p-value**
	Post-program	-4.7 (1.6)	-11.7 (1.7)‡	-7.3	-13.1 , -1.4	0.016
	12 months	-1.8 (2.0)	-12.1 (1.8)§	-10.6	-17.0 , -4.1	0.001
Taste bias	Baseline	6.0 (1.5)	5.8 (1.5)	**Changes †**	**95% CI**	**p-value**
	Post-program	5.7 (1.6)	0.8 (1.6)‡	-4.7	-10.4 , 1.1	0.109
	12 months	6.6 (2.0)	3.0 (1.8)	-3.3	-9.6 , 3.0	0.301

Data are presented as estimated means (SE).

* All models were adjusted for baseline values and sex.

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

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

† Difference in differences estimated changes

$(\text{Post-program/12months}_{\text{intervention}} - \text{baseline}_{\text{intervention}}) - (\text{Post-program/12months}_{\text{control}} - \text{baseline}_{\text{control}})$.

An illustration that summarizes the results for LFPQ domains is displayed in **Figure 1.**

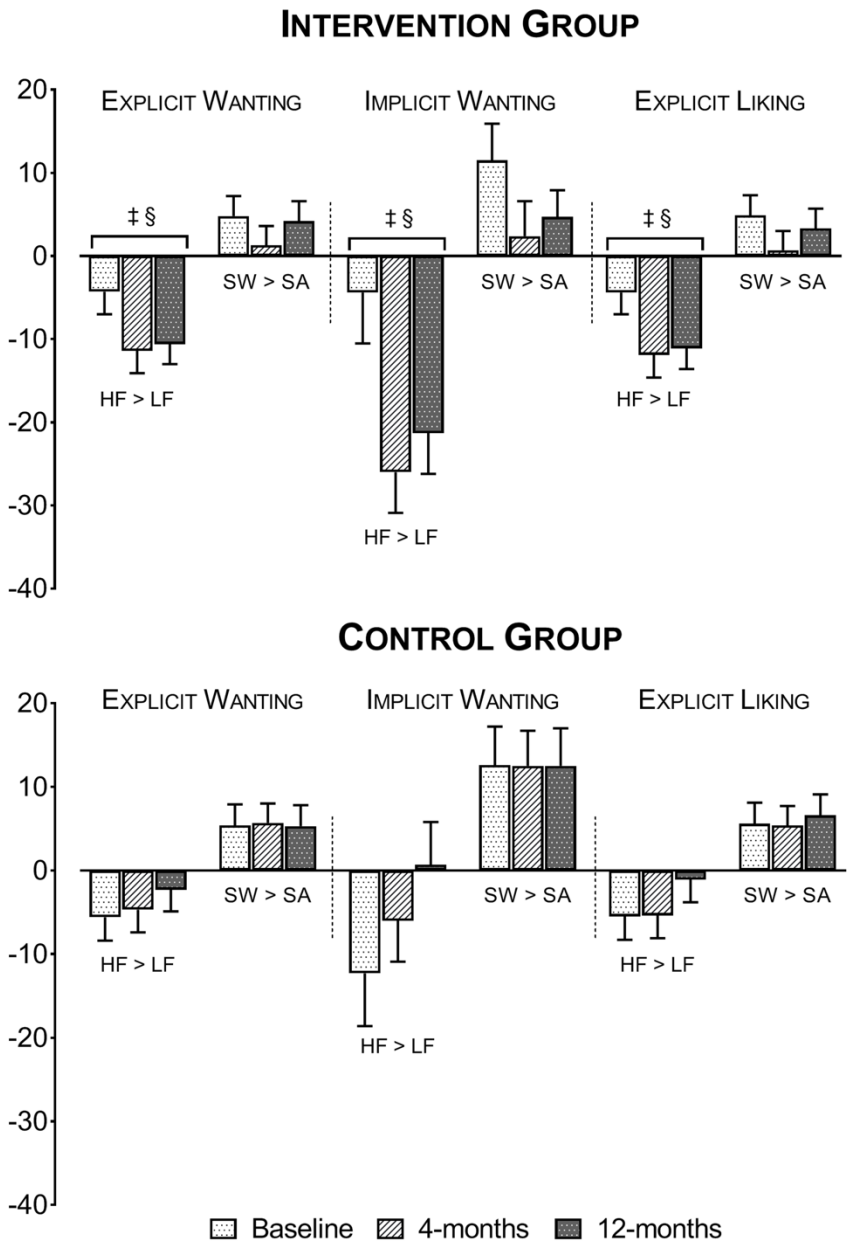

Figure 9.1. Results from the Leeds food Preference Questionnaire for Explicit wanting, Implicit wanting and Explicit liking.

HF > LF: Preference for high-fat food versus low-fat food; SW > SA: Preference for sweet food versus savory food.

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

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

9.4.4. Associations between changes in eating behavior components and changes in body composition outcomes

Associations between food reward/intuitive eating outcomes and body composition are displayed in **table 9.4.**

Table 9.4. Pearson's correlations between food reward/intuitive eating and body composition.

			ΔWeight (kg)	ΔWeight (%)	ΔFM (kg)	ΔFM (%)	ΔFFM (kg)
INTUITIVE EATING	**4 months**	**ΔIES**	-0.110	-0.155	-0.013	-0.040	-0.084
		ΔRHSC	-0.194	-0.231	-0.018	-0.048	-0.223
		ΔEPR	-0.149	-0.175	-0.164	-0.180	0.027
		ΔUPE	**0.399****	**0.380****	**0.406****	**0.375****	0.108
		ΔBFCC	**-0.298***	**-0.309***	-0.229	-0.198	-0.139
	12months	**ΔIES**	-0.119	-0.152	-0.181	-0.200	0.071
		ΔRHSC	-0.168	-0.168	-0.242	-0.237	0.071
		ΔEPR	-0.121	-0.155	-0.210	-0.230	0.183
		ΔUPE	**0.448****	**0.440****	**0.470****	**0.391****	0.101
		ΔBFCC	**-0.548****	**-0.578****	**-0.495****	**-0.467****	-0.271
FOOD REWARD	**4 months**	**ΔEW - Fat bias**	**0.268***	**0.293****	0.207	0.197	0.212
		ΔEW – Taste bias	**0.256***	**0.258***	0.219	0.210	0.140
		ΔIW - Fat bias	0.219	**0.243***	0.153	0.130	0.223
		ΔIW – Taste bias	0.217	0.220	**0.238***	**0.228***	0.082
		ΔEL - Fat bias	**0.289****	**0.311****	**0.233***	0.199	**0.233***
		ΔEL – Taste bias	0.207	0.208	0.187	0.193	0.133
	12 months	**ΔEW - Fat bias**	**0.292***	**0.309***	0.215	0.211	0.209
		ΔEW – Taste bias	**0.296***	**0.306***	**0.301***	**0.329***	0.049
		ΔIW - Fat bias	0.157	0.166	0.152	0.143	0.081
		ΔIW – Taste bias	0.093	0.106	0.078	0.019	0.077
		ΔEL - Fat bias	0.160	0.170	0.125	0.106	0.165
		ΔEL – Taste bias	0.038	0.055	-0.001	-0.038	0.055

* P<0.05; ** p<0.01

Abbreviations: IES, Intuitive Eating Scale Global Score; RHSC, Reliance on Hunger and Satiety Cues; EPR, Eating for Physical Rather Than Emotional Reasons; UPE, Unconditional Permission to Eat; BFCC, Body–Food Choice Congruence; EW – Explicit Wanting; IW – Implicit Wanting; EL – Explicit Liking.

Changes in unconditional permission to eat (ΔUPE) were positively associated with ΔWeight (kg and %) and with ΔFM(kg and %) after 4 and 12 months. Changes in body-food choice congruence (ΔBFCC) were negatively associated with ΔWeight (kg and %) and with ΔFM(kg and %), i.e., people who lost more weight and FM reported a higher increase for BFCC.

Changes in explicit wanting for fat and taste bias were associated with ΔWeight (kg and %) after 4 and 12 months, i.e., people that lost a large amount of weight were also those who reported a decrease in their preferences for high-fat/sweet food relative to low-fat/savory food, respectively. After 4 months, changes in implicit wanting for fat and taste bias were associated with ΔWeight (%) and with ΔFM (kg and %), respectively, meaning that the participants who had a higher percentage of WL showed a higher decrease in their implicit wanting for fat bias, i.e., they decreased their unconscious preference for high-fat food comparing with low-fat food, and participants who showed a higher decrease in FM also reported a higher decrease in their implicit wanting for taste bias, i.e., decreased their desire to eat sweet foods. Explicit liking for fat bias showed a positive correlation with ΔWeight (kg and %), ΔFM(kg) and with ΔFFM(kg).

9.5. DISCUSSION

Overall, participants showed improvements in several components of food reward after 4 months of active WL, which remained significant after 8 months of WL maintenance. Intuitive eating results revealed a reduction in unconditional permission to eat at program's end, which was no longer significant at follow-up's end, and also a long-term (at 12 months) improvement in body-food choice congruence.

Traditional programs that only focus on WL often fail to succeed in the long-term (Dombrowski et al., 2014). Despite weight being an important indicator of health, creating a more health-centered approach, considering intuitive eating and food reward

components, may help participants to lose weight and to maintain it in the long-term (Schaefer & Magnuson, 2014).

Intuitive eating encompasses eating in accordance with physiologic hunger and satiety cues, as well as enjoying a wide variety of foods, rather than eating in accordance with strict diet rules or cognitive deliberations (Tribole & Resch, 2012; Tylka et al., 2015; Tylka & Diest, 2013). Trusting in one's internal eating cues to determine when and how much to eat and making food choices that contribute to one's health and body functioning are associated with improvements in physiologic (e.g., blood lipids, blood pressure), psychological (e.g., body image, self-esteem), and behavioral outcomes (e.g., dietary quality, physical activity) (Bruce & Ricciardelli, 2016; Clifford et al., 2015; Schaefer & Magnuson, 2014). In line with this research, at the end of the follow-up, participants in the IG reported making more body-congruent food choices, which might entail selecting foods that were more nutritious and that improved their body composition and cardiovascular risk markers. This might also have resulted from the therapeutic effect of participating in the program (e.g., group dynamic effects, an autonomy supportive climate, and social support).

Traditional WL interventions often rely on external rules aimed to lose weight, defining portion sizes, scheduling mealtimes, and avoiding some food groups (often categorizing food as "bad" or "good") (Schaefer & Magnuson, 2014). These interventions are often related with poorer scores for intuitive eating (Camilleri et al., 2016; Gast et al., 2015), compromising an individual's food choices and their eating behavior (Berthoud, 2012). Although the IG also reported a decrease in unconditional permission to eat (i.e., willingness to allow themselves to eat when hungry and whatever food is desired), this may be since the Champ4Life project did not explicitly reinforce this style of eating, following instead a more traditional cognitive-behavioral approach to weight management. During the intervention, participants were asked to create small-term goals, receiving positive feedback and praise when achieving them, which might have increased their levels of confidence and excitement about their WL process, creating

fruitful relationships and stimulating a "healthy" competition among them (Roberts; & Treasure, 2012). Also, in our study, decreases in UPE were associated with greater WL. It is known that a certain degree of dietary restraint might lead to better WL outcomes (JaKa et al., 2015; Schaumberg et al., 2016). As a part of a WL intervention, a sustained negative energy balance leads to some compensatory adaptations that may increase hunger (Casanova et al., 2019; Martin et al., 2007). Therefore, along with knowledge acquired during the educational sessions, participants were able to make better food choices to counteract that increased hunger and to promote satiety, avoiding eating certain types of food. Thus, although the global score did not change after 1-year, these findings can be considered encouraging from an intervention perspective.

Our findings suggest that those who lost more weight and FM (kg or %) reported a higher increase for BFCC. The BFCC reflects the choice of food that matches their physical needs and has been negatively associated with BMI (Ruzanska & Warschburger, 2019). As dieting is associated with a higher food preoccupation (Tylka et al., 2015), poorer body image (Sharpe et al., 2018), increased hunger (Cameron et al., 2014) and episodes of binge eating (Birch et al., 2003), the use of a health-centered approach, focusing on one's personally relevant behaviors (towards eating or exercise), might have led to a more successful WL management, together with an improvement in one's overall well-being and mental health (Carraca et al., 2019; Schaefer & Magnuson, 2014).

An increase in the reward value of food, as a consequence of a caloric deficit, is thought to be a relevant factor in passive overconsumption and obesity (Blundell & Gillett, 2001). However, according to Anton et al (Anton et al., 2012), participants decreased their food cravings for high-fat and sweet foods after 6, 12 and 24 months of dieting. As a result, these authors suggested that the association between consuming this type of foods and the emotional relief was decreased after a prolonged period where these foods are restricted, decreasing the preference for "unhealthy" foods throughout time. In our study, the IG increased their preference for low-fat relative to high-fat foods after 4 and 12

months, by showing reductions in both liking and wanting fat appeal biases. These findings are in line with a recent systematic review, which suggested that food reward appears to decrease rather than increase during weight management interventions (Oustric et al., 2018). The authors argued that a shift in reward from high-energy foods to low-energy foods might derive from the gradual internalization of WL goals throughout the intervention, reflecting a greater matching between cognition and eating behavior (Oustric et al., 2018).

There are few studies exploring changes in food reward after WL and during its maintenance. Recently, Oustric et al (Oustric et al., 2021) studied the effects on food reward after WL (≥5%) and after a WL maintenance period, in women with overweight/obesity. After a period of follow-up, participants regained part of their lost weight, and no differences were found on food reward between baseline and after 1-year. In this study, despite liking decreasing from baseline to post WL, no differences were found between baseline and WL maintenance, which might had contributed to weight regain. Also, as wanting did not change during the intervention, the authors suggested that changes in this component may be necessary to maintain the reduced weight. In our study, together with a decrease in wanting, participants maintained their reduced weight successfully, which goes along with that suggestion. Andriessen et al (Andriessen et al., 2018), which explored the alterations in food reward during 2 months and showed that liking decreased after a diet-induced WL, suggested that these improvements may suffer alterations during the WL maintenance, influencing weight regain.

In our study, improvements in both liking and wanting for fat bias were maintained during the follow-up period. We also found a decrease in implicit wanting for taste bias (preference for sweet rather savory foods) after 4 months. However, this reduction did not remain significant after the follow-up period. Andriessen et al (Andriessen et al., 2018) also reported a decrease in taste bias as a response to a low-calorie diet (LCD, ~750kcal/d). Contrary to this study, participants from the Champ4Life were asked to

make small changes in their dietary intake, creating a moderate caloric deficit (Silva et al., 2020), without restraining any particular type of food and/or macronutrients. As the association between consuming a certain type of foods and its consequent emotional relief decreases after a period of restriction for that type of foods (Anton et al., 2012), the reason why the reductions in fat and/or taste bias were not that drastic at the end of our project can be explained due to the fact that our participants were not fully restrained to any type of foods and/or macronutrients when compared to Andriessen's study (Andriessen et al., 2018).

During the intervention, several strategies were developed that may influence intuitive eating and food reward. First, the nutritional appointments aimed not only to create a moderate caloric deficit, but also to increase awareness of each individual's eating pattern and how it was contributing to their excess weight. Plus, some of our educational sessions were focused on eating behavior and behavior modification, focusing on strategies to distinguish real from "emotional" hunger and on emotional eating. Self-regulatory skills and behavior change techniques were also implemented, such as i) encouragement of self-selected relevant goals; ii) self-monitoring of weight, PA and eating habits and iii) providing basic knowledge allowing informed decisions and choices. Together with the educational/motivational sessions, participants learnt how to create healthy and sustainable eating habits and acquired specific strategies that helped them to pursue their health-related goals. These acquired "healthier" habits were maintained after the WL intervention and, therefore, the reduced weight was successfully maintained as well, not changing the improvements made in food reward during the follow up period. Similar findings were reported by Morin et al (Morin et al., 2018), with cognitive dietary restraint (CDR), where people were weighed weekly, were conscious of the caloric restriction that they underwent and were taught the importance of losing weight. Therefore, people were engaged in cognitive control over the food they were eating and were more aware regarding the choices they made.

Most studies regarding intuitive eating or food reward are performed mainly in women with overweight/obesity (Oustric et al., 2018; Schaefer & Magnuson, 2014). In our study, women reported lower values for IES-2 global score and for eating due to physiological hunger and satiety cues rather than emotional cues when compared with men. Women are usually more prone to suffer with body image issues (Striegel-Moore et al., 2009), experiencing highly-restricted diets, unsustainable long-term ("yo-yo" diets). Consequently, they do not allow themselves to eat some food groups, reducing food quantity and sometimes having a strict schedule for eating (Schaefer & Magnuson, 2014). Nevertheless, there is a need to create more evidence regarding the effects of an intuitive eating approach in men.

Despite the several strengths of our study, some limitations should be addressed. Regarding the LFPQ validation, the additional procedure (i.e., an online questionnaire) to verify if the selected food images are well-representative of the Portuguese food culture is still undergoing and currently being analyzed, which calls for some caution in the interpretation of these findings. Nevertheless, we do not expect substantial differences in the cultural food environment, given that the entrance of Portugal in the Central European space has accelerated changes in eating habits along with the cultural globalization of food market (da Silva et al., 2009) and has reduced the adherence to the once traditional Mediterranean diet pattern (Lopes et al., 2017). Also, the heterogeneity of our sample needs to be considered, as several modalities were included (weight-sensitive sports vs non-weight-sensitive sports). On the other hand, despite having an acceptable drop-out rate, it would be interesting to understand the reason why some participants did not complete the program. Lastly, the direction of the relationship between WL and changes in intuitive eating/food reward needs to be understood: Is it the WL per se that leads to changes in eating behavior or are the changes in eating behavior causing the WL?

In conclusion, a motivational intervention such as the Champ4Life was successful in improving former athletes' eating behavior, decreasing several disrupting eating

patterns. Hence, lifestyle interventions aiming at WL should focused not only on dietary restriction and/or PA but also in changing components of eating behavior such as intuitive eating and food reward, as these have been shown to coexist with WL maintenance.

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CHAPTER 10

DISCUSSION

10. DISCUSSION

10.1. OVERVIEW

Despite literature being full of interventions aimed to WL, including bariatric surgeries, pharmacotherapies and lifestyle interventions, a successful WL is almost impossible to achieve. Moreover, it seems that maintaining a weight reduced state is even harder than simply losing weight, with weight regain frequently occurring (Greaves et al., 2017; Wadden et al., 2011). Alongside with the decreasing adherence to dietary and PA recommendations that is often reported during the WL maintenance (Heymsfield et al., 2007), the existence of compensatory responses has been proposed (Doucet & Cameron, 2007; Leibel et al., 1995; Racette et al., 1995; Weigle, 1988).

Although AT has been widely discussed in REE, literature involving the other EE components are still scarce. Moreover, the results are not consistent, as some authors found a higher-than-expected decrease in REE (Bosy-Westphal et al., 2009; Bosy-Westphal et al., 2013; Byrne et al., 2018; Camps et al., 2015; Karl et al., 2015; Martins et al., 2020; Müller et al., 2015; Nymo et al., 2018; Rosenbaum & Leibel, 2016), but others did not (Doucet et al., 2001; Gomez-Arbelaez et al., 2018; Pourhassan et al., 2014). These inconsistencies might be explained by several factors, such as the participants' characteristics, intervention's type, magnitude of WL, methodologies used to predict REE and/or assess AT, and others. Though numerous narrative reviews that explore the AT existence have been already published, and most of them focused specifically on REE (Casanova et al., 2019; Dulloo et al., 2012; Major et al., 2007; Müller & Bosy-Westphal, 2013; Muller et al., 2016; Rosenbaum & Leibel, 2010; Tremblay et al., 2007; Tremblay et al., 2013; Trexler et al., 2014) and no systematic reviews were conducted covering this topic. Therefore, the first study was a systematic review aimed to understand the existence of AT not only in REE, but also in SEE and TDEE.

Together with compiling all the available evidence regarding this topic, the first study also pointed out some issues that needed to be looked further. It is already known that the

results about AT existence in REE are truly discrepant between and within studies. However, even when considering the same population and a similar intervention's type, AT values widely varied from minimal to extreme values, emphasizing the substantial impact of the chosen methodology to predict REE and/or assess AT. As one of the major problems raised in study 1 was the lack of standardization among methodologies, study 2 sought to compare 13 different approaches to assess AT, varying in how REE is predicted and/or AT is assessed. Likewise, this study also aimed to understand if AT occurs in a moderate WL, as most studies reported a >10% WL, which is not representative of the modest results that occur in most studies aimed to WL by changing diet and/or PA patterns.

Apart from the methodological issues that were raised, most studies measured their participants immediately after the WL intervention, whereas studies comprising a period of follow up are scarce. As some authors showed that, after a period of weight stabilization, AT attenuates or even disappear (Gomez-Arbelaez et al., 2018; Marlatt et al., 2017; Martins et al., 2020; Novaes Ravelli et al., 2019; Wolfe et al., 2018), there is a need to include more studies involving a period of follow up to understand the role of AT under a neutral EB as well as its influence on the ability of maintaining a reduced weight state. Plus, it is uncertain if changes in some appetite-related hormones are somehow associated with the degree of AT and/or its existence after WL. Hence, study 3 aimed to understand if AT occurred not only after 4 months of a moderate WL (which was already explored in study 2 through different methodologies) but also after 8 months of WL maintenance. Additionally, associations between appetite-related hormones and changes in body composition with AT were also considered.

As REE is the major contributor of TDEE, it is easy to understand why most researchers studied AT in this EE component after a WL intervention, as explained by our first study. Despite the interesting findings of the previous studies, the existence of AT in other EE components such as PAEE was still a matter of debate. Indeed, understanding if some compensations occur in this component is important, as it can potentially play an

important role toward the WL and long-term maintenance (Ostendorf et al., 2019). Moreover, PAEE is the most variable component of the TDEE, depicting a great variation within and between individuals (accounting for 5 to 50% of TDEE), explained by the large variability in NEPA and NEAT (von Loeffelholz & Birkenfeld, 2000). Therefore, study 4 aimed to understand if AT occurs in NEAT, a PAEE component. Thus, study 4 contributed to the evidence already available about AT in other components rather than REE. Moreover, the interindividual variability was also addressed in this study, as a large variability among individuals was already found in previous studies exploring changes in REE and AT after WL (Browning et al., 2017; Carrasco et al., 2007; Hopkins et al., 2014; Thom et al., 2020).

As more attention was given to metabolic compensations, and since the magnitude of a behavioral compensation is likely to be higher than a higher-than-expected decrease in any EE component, addressing the role of these behavioral compensatory responses is crucial to understand its influence on the ability to lose weight and to maintain a reduced weight state. Therefore, study 5 aimed to evaluate the interindividual variability in EI and EE after a WL intervention and to understand how changes in EI are associated to changes in PA duration and energy expenditure (PAEE). The relation between appetite-related hormones and its role on the hedonic system has been proposed, where the control of food intake and body weight is guided by a “cognitive and emotional brain”, based upon the reward value of the food (Yu et al., 2015). Indeed, with the current obesogenic environment, characterized by a high abundance of highly palatable food and a strong pressure to increase the time spent in sedentary behavior, people no longer eat only when they are hungry. Additionally, it is known that eating behavior is not only influenced by metabolic but also by hedonic drives (Berthoud, 2011). While no relevant associations were found for the homeostatic system in this dissertation, the role of hedonic system was not considered thus far. Therefore, the 6th and last study aimed to explore the impact of the Champ4life intervention on intuitive eating and food reward

outcomes and if there is a relation between changes in eating behavior components and changes in body composition.

Figure 10.1. depicts and summarizes the interconnection and organization of the 6 studies that were included in this dissertation.

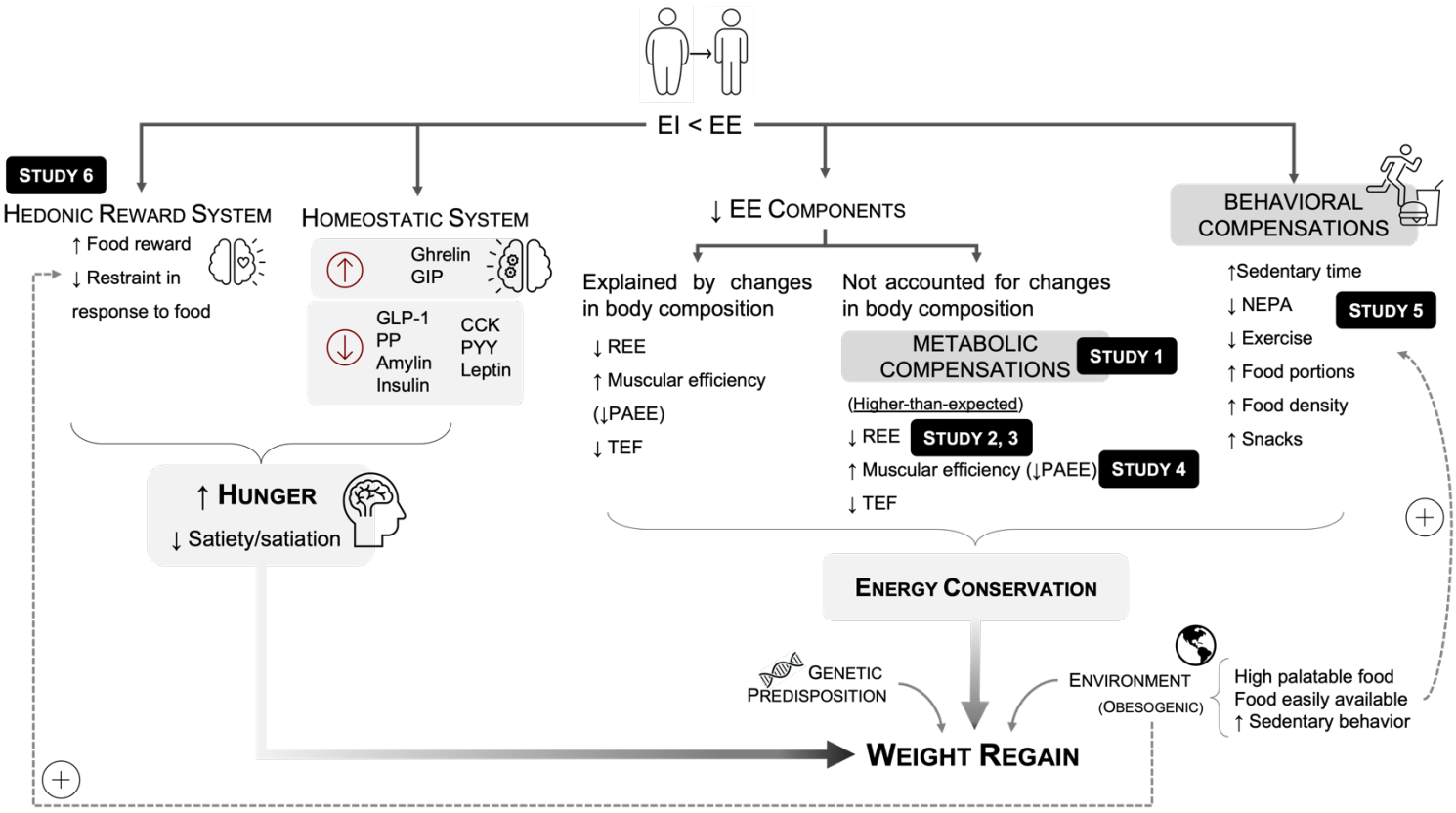

Figure 10.1. Interconnection among the 6 studies that were included in this dissertation.

Legend: EI – energy intake, EE – energy expenditure, GIP – Gastric inhibitory polypeptide/ glucose-dependent insulinotropic polypeptide, GLP-1 – glucagon-like peptide 1, PP – pancreatic polypeptide, CCK – cholecystokinin, PYY – peptide YY, REE – resting energy expenditure, PAEE – physical activity energy expenditure, TEF – thermic effect of feeding, NEPA – Non exercise physical activity.

In summary, this dissertation contributed to the evidence accumulated to date regarding the existence of metabolic and behavioral compensatory responses to WL and its influence on WL management. More specifically, the present thesis explored: 1) The

current evidence concerning the existence of AT not only in REE but also in SEE and TDEE; 2) the methodological issues in AT assessment, by comparing 13 different approaches; 3) if AT still occurs after a moderate WL and after a period of weight stabilization; 4) the impact of WL on hedonic components, namely food reward and intuitive eating; and 5) associations among changes in appetite-related hormones, WL magnitude, changes in EI and PA patterns and AT.

This chapter aimed to gather the contributions of the studies included in this dissertation, by summarizing the main results and to discuss them. A detailed discussion of each individual study is presented at the end of each correspondent chapter. Additionally, recommendations for future research and practical applications will be also discussed throughout this chapter, as well as limitations.

10.2. MAIN RESEARCH FINDINGS

As more evidence has been developed about AT, i.e., the lower-than-expected decrease in EE components (specially in REE), the first study aimed to compile all the evidence of AT in EE components during and after WL. This was particularly important for the development of this work, as it allowed the identification of some issues regarding this phenomenon. Firstly, it is important to state that most studies addressed compensatory responses in REE, underlining the lack of evidence regarding the other EE components. Although AT was found in at least one EE component in most studies, the lack of standardization on the used methodologies was the major problem that was pointed out. The included studies varied in how body fat stores were assessed, how the EE component was predicted and how AT is assessed. Considering body composition measurements, the multiple methods are based on different properties and assumptions about body components, and consequently, their results should not be interchangeable. Also, AT calculations varied among studies, being important to consider baseline residuals (the difference between measured and predicted REE at baseline), as it allows

to calculate more accurately the existence of AT by "removing" the initial baseline error (if residuals were already statistically different from zero at baseline, indicating that the predicted REE was initially different from the measured REE). Therefore, comparisons among studies should be taken carefully, as the accuracy of their measurements vary according to the used methodologies.

Moreover, most of the available literature did not include a follow-up period, where participants remained weight stable. In fact, this systematic review showed that most studies who reported a minimal or even nonexistent AT had their measurements taken under a neutral EB, suggesting an association between the existence of AT and the EB state. Therefore, the state of EB at the time of the measurements must be considered when studying this phenomenon.

Furthermore, most studies encompassed in this systematic review reported a >10% WL, which is not representative of the modest results that occur in most WL intervention studies. Therefore, when considering moderate WL, it is still unclear if AT exists and, more important, if it can jeopardize the WL management. Lastly, the methodological quality of each included study needs to be considered, as those who were considered well-designed studies reported lower or non-statistically significant values for AT. Also worth-nothing, as most studies lacked a control group, the existence of AT after WL cannot be accurately studied as it is not possible to understand if AT was also present in a group where WL did not occur, i.e., it is not possible to understand if AT occurred due to WL rather than to other factors. Thus, more high-quality studies are warranted, not only to disclose the existence of AT in each EE component, but also to comprehend its clinical relevance on weight management outcomes.

To sum up, the issues that were identified are stated below:

- It is still unknown if AT occurs in other EE components rather than REE;
- The impact of a negative vs neutral EB on AT;

- If AT still occurs in moderate WL (<10%);
- Lack of standardization among methodologies, namely:
    - How body composition stores (FM and FFM) are assessed;
    - How REE is predicted;
    - How AT is calculated;
- Lack of good design studies (e.g., RCT).

The following studies included in this dissertation aimed to contribute to the scientific progress regarding the existence of AT, by analyzing the issues that were raised in study 1 and helping in the understanding of this topic. These studies were conducted in former elite athletes during the Champ4life intervention, an effective RCT in reducing weight [i.e., WL was greater in the IG than in the CG (-4.7kg; 95% CI: -6.3 to -3.1; $p<0.001$)] and also FM (-3.8kg; 95% CI: -5.2 to -2.4; $p<0.001$), while preserving FFM after 4 months of WL (Silva et al., 2021). Participants were able to maintain a reduced weight state after 8 months of follow-up (weight: -5.5kg; 95% CI: -7.3 to -3.7; $p<0.001$, FM: -4.0kg; 95% CI: -5.5 to -2.5; $p<0.001$) and improved cardiovascular risk markers and quality-of-life.

The methodological issues were addressed in study 2, where 13 different approaches were included, based on the studies that study 1 encompassed. The clear discrepancy among methodologies, with values varying from ~-70 to -220kcal/day for the intervention group, emphasizes the lack of standardization among methodologies (which leads to discordant results) that was pointed out in study 1. Considering only the IG, all approaches lead to a negative and statistically significant value for AT ($p<0.05$, different from zero), suggesting that AT occurs after a moderate WL. Nevertheless, only 2 approaches presented different values for IG and CG, while the others did not, which emphasizes the importance of implementing good-design studies, namely the inclusion of a control group, to explore the real impact of WL on AT.

A large variability within participants was also found for every approach, which could be explained by the high variability seen in body weight responses to the intervention

(Casanova et al., 2019). Nevertheless, when plotting the AT and the WL (%) (for each approach), we can see that there is no association between these two variables, as people who had higher WL were not necessarily those with higher values for AT. Although this interindividual variability in changes in REE can be explain by the existence of two phenotypes (thrifty vs spendthrift) (Piaggi et al., 2018), some methodological issues can also contribute to this phenomenon. As using a predictive equation to assess REE (and therefore compare it with the measured REE), if the equation should not provide a good fit for the observations, some individuals will have a large different between predicted and measured REE even at the baseline. This can be easily explained by comparing the approach which baseline residuals were considered vs those which did not, as the AT magnitude decreased in most individuals when subtracting the baseline residuals, meaning that some individuals have already a large difference between measured and predicted REE at baseline and this discrepancy remained after 4 months of WL.

Despite all the interesting findings from the previous studies, most researchers cannot assure that both baseline and after WL measurements were taken under the same EB. In fact, two issues were pointed out regarding the state of EB, namely 1) Most studies did not assure that the baseline measurements were taken under a neutral EB, and 2) most studies performed their measurements immediately after WL, where participants were still under a negative EB. Although participants of the Champ4life study did not undergo a period of weight maintenance before entering the study (more details in the limitations' section), this lifestyle intervention comprised an 8-months follow-up period, where participants successfully maintain their WL (Silva et al., 2021). Therefore, as some studies found that AT was attenuated or even disappeared after a follow-up period (Karl et al., 2015; Martins et al., 2020), the study 3 aimed to understand if AT not only exists after a moderate WL but also if persists after a period of WL maintenance. Therefore, AT was measured immediately after 4 months of WL (under a negative EB) and after 8

months of follow up (under a neutral EB). To calculate AT, and considering the recommendations that were given in study 2, the best approach from the previous 13 was chosen. This study also aimed 1) to analyze the weight-related hormones, such as leptin, insulin and thyroid panel; and 2) to understand if interindividual differences occur in AT.

Thus, AT occurred after 4 months of WL, where participants lost ~5% of their initial weight and remained significant after a successful WL maintenance. Nevertheless, despite these values were statistically significant, it is worth noting that its magnitude was considered small and consequently, its clinical significance should be considered, i.e., if these mild values can exert a significant impact on body weight regulation, undermining the WL and its maintenance. When it comes to the appetite-related hormones, a reduction in leptin was found for the IG, which was expected as they lost a significant amount of FM. Nevertheless, no association was found between changes in this hormone and AT, which goes along with the findings from other authors (Bettini et al., 2018; Johannsen et al., 2012; Müller et al., 2015). Similar to our study, Muller et al also reported a moderate WL (~8%), which can explain the lack of association between AT and changes in leptin (Müller et al., 2015). Nevertheless, studies with massive WL also failed to find an association, as participants from the Johannsen et al study lost ~40% after 30 weeks (Johannsen et al., 2012) and Bettini et al showed a ~30% of WL (Bettini et al., 2018). Nevertheless, participants from Bettini's study underwent a sleeve gastrectomy and therefore caution is needed when comparing their findings with studies comprising lifestyle interventions. On the other hand, thyroid hormones did not change throughout the WL intervention.

Following REE, PAEE is the second major contributor to TDEE, accounting for 5 to 50% of TDEE. In this sense, understanding the changes in PAEE as a response to a WL intervention are crucial to achieve a successful WL. The main findings from study 4, which aimed to understand if AT occurs in NEAT, revealed that although an energy

conservation was not found in this EE component after WL, the large variability among participants should be considered. In turn, this emphasizes the need of analyzing not only the mean values but also the individual responses regarding to WL outcomes.

Similar to REE, it is expectable that PAEE decreases after losing weight (Levine et al., 2001; Ostendorf et al., 2019). However, together with this expected decrease, additional compensations may occur, which can be defined as metabolic (e.g. muscular efficiency) or behavioral (decreases in PA – NEPA and/or exercise).

Increases in muscular efficiency as a response to a WL intervention were reported in some studies (Amati et al., 2008; Coutinho, Halset, et al., 2018; Coutinho, With, et al., 2018; Goldsmith et al., 2010; Nymo et al., 2018; Rosenbaum et al., 2003), suggesting that these changes in skeletal muscle towards a more "economical" body may undermine the WL and its maintenance. Nevertheless, it is important to state that these studies differed from what was done in study 4. In these studies, muscular efficiency was mainly measured by cycle ergometry. Together with this, few authors also included other techniques such as nuclear magnetic resonance spectroscopy - that examines the muscle energy consumption excluding the effects of any possible artifacts that are not directly involved in the prescribed exercise - and/or nuclear magnetic resonance – which provides a direct measurement of the ATP cost per muscle contraction (Goldsmith et al., 2010; Rosenbaum et al., 2003). In study 4, a predictive equation was created based on changes in body composition (FM and FFM) to calculate a predictive value for NEAT. Therefore, this value was compared to the measured value (through accelerometry) at each time point. The R^2 for this predictive model was ~34%, meaning that 34% of the variance in NEAT was explained by the body composition stores. This measure of fit was significantly lower when compared to the REE (~57%) in study 3, meaning that this model does not fit the real observations accurately as the model developed to predict REE, which might compromise our interpretation.

Nevertheless, changes in NEAT could have been due to changes in the intensity or/and time spent on PA (i.e., by being more sedentary). Indeed, it is known that an energy

deficit has found to be associated with a substantial decrease in NEAT, independently of sex and age (Martin et al., 2011). However, no differences were found throughout time in NEAT (mean values) in this study, which can be explained by the fact that the Champ4life was a SDT-based intervention, where participants were taught, through educational sessions, the benefits of having adequate PA and eating patterns. Moreover, participants were encouraged not only to increase exercise but also to reduce their time spent in sedentary behavior (being more active). Although it can be assumed that changes in NEAT were not due to changes in NEPA (as changes in NEPA did not occur), once again, the variability in both outcomes should be considered and their interpretation should go beyond than simply looking at mean values.

The findings of the study 4 brought to attention a topic that should be further explored, namely the large variability that occurs in some outcomes as a response to a WL intervention (such as NEPA). More specifically, when undergoing a lifestyle intervention aimed to lose weight, each participant will behave differently regarding eating and PA patterns. Hence, it is important to understand if behavior adaptations occurred as a response to a negative EB, as it has been hypothesized that decreases in EI can be compensated with decreases in NEPA, as well as in PAEE (King et al., 2007). To this end, study 5 demonstrates perfectly the variability in EI and PA patterns that was previously addressed, as even undergoing the same WL intervention, 4 observations occurred in the IG, namely: 1) Decreases in EI that were accompanied by a decrease in EE, attenuating the negative EB; 2) Decreases in EI and an increase in EE, potentiating the negative EB; 3) A negative EB caused by an increase in EE; 4) Increases in EI and a decrease in EE, leading to a positive EB. This large variability of individual responses is already documented in the literature (Dent et al., 2020) but may reflect a large random measurement error rather than a within subject variability (Bonafiglia et al., 2021). However, as both EI and EE showed a positive SD_{IR} (which is an adequate approach to understand if truly interindividual differences occurs for a certain outcome (Atkinson &

Batterham, 2015)) that surpassed the SWC, we can state that this large variability reflects the existence of significant interindividual differences.

This study also allowed the comparison between the magnitude of changes in EI and PAEE (divided in NEAT an EiEE) with the AT that was reported in previous studies. It is important to understand that the impact of decreasing PAEE (due to changes in duration and/or intensity of PA) due to a decrease in EI, as well as increasing EI as a response to an increase in exercise and/or NEPA is significantly higher than any metabolic compensation that might occur (i.e. higher-than-expected decrease in REE). Moreover, behavioral compensations are usually associated to a "choice", as it can be (at least partially) controlled by our actions (whereas metabolic compensations are inevitable). Hence, these different degrees of compliance with the intervention emphasize the importance of implementing more individual strategies when WL is aimed to increase the likelihood of achieving the expected results and therefore avoiding the "one size fits all" approach. The same logic is applied to the existence of behavioral adaptations as a response to WL, as although decreases in EI were not associated to decreases in PA nor increases in sedentary time, most individuals who decrease their EI also showed a decrease in total EE, which can be derived from several combinations of changes in TEF, REE and/or PAEE.

The last papers brought to attention the large variability that occur among individuals for both EI and EE (total and its components). Therefore, it is important to understand why some individuals can successfully lose weight and maintain it throughout time, while others are not able to achieve the expected results, even when undergoing the exact WL intervention, to better implement adequate and successful WL strategies. Moreover, the role of appetite-related hormones was also considered, as efforts were made to find any association between hormones such as leptin, insulin and/or thyroid panel with changes in WL, FM, FFM and AT. To complement this thesis, the 6th and last study aimed to explore the role of the hedonic system, focusing on intuitive eating and food reward

outcomes, as well as the relation between changes in eating behavior components and changes in body composition.

Participants from the IG reported a lower unconditional permission to eat (UPE) – defined as the willingness to allow themselves to eat when hungry and whatever food is desired -, after 4 months and at the end of follow up (1 year). As a certain degree of dietary restraint is associated to better WL outcomes (JaKa et al., 2015; Schaumberg et al., 2016), this decrease was expected as participants were trying to lose weight. Moreover, as participants were asked to create small-term goals and receive positive feedback and recognition upon achieving them, it is possible that their levels of confidence and excitement about their WL process increased, which might had fostered fruitful relationships and stimulates a "healthy" competition among them (Roberts; & Treasure, 2012). Plus, the body-food choice congruence (BFCC) increased after 1 year. The Champ4life intervention was based on the SDT employing education sessions to increase participants' knowledge regarding nutrition and PA. Therefore, participants might be more prone to choose foods that were more nutritious and related to an improvement of their body composition.

As a response to an energy restriction, an increase in the reward value of food was expected, which may undermine the WL process (Blundell & Gillett, 2001). In this study, participants decreased their preference for high-fat vs low-fat foods after 4 and 12 months, by showing reductions in both liking and wanting fat appeal biases. Similar results were found in a systematic review, suggesting that food reward appears to decrease rather than increase during weight management interventions (Oustric et al., 2018). This may be explained due to the gradual internalization of WL goals throughout the WL process, leading to a shift in reward from high- to low-energy foods.

Hence, the impact of this type of WL intervention on intuitive eating and food reward outcomes must be considered. Although WL was the main goal of the Champ4life project, efforts were made to create a moderate energy deficit without restraining any particular type of food and/or macronutrients. Consequently, the fact that participants

were not fully restricted to any type of foods might explain why the reductions in fat and/or taste bias were not that drastic when compared to other studies (Oustric et al., 2018).

10.3. GENERAL LIMITATIONS

Although a detailed description of the specific limitations of each study was addressed in each correspondent chapter, general limitations should be addressed. Firstly, most studies involved a specific population with particular characteristics, namely former elite athletes who developed overweight/obesity and were considered inactive. While a non-athletic population with obesity may have been sedentary all their life's, when it comes to athletes, they generally experienced weight gain and a transition to a sedentary state throughout adulthood. Nevertheless, and as the evidence suggests, athletes are not protected against any risk factors or have health-related benefits when compared to a non-athletic population if they do not maintain their sport career's diet and PA patterns (Griffin et al., 2016; Laine et al., 2016). Moreover, it has been showed that the weight gain observed after athletic retirement was of a similar magnitude to what was observed in non-athletic population (Dutton et al., 2016). In this sense, choosing individuals who did not have a history of overweight/obesity during their child and adulthood and only gained weight when changed their diet and PA patterns assures that weight gain was a consequence of changes in PA patterns and an inadequate diet rather than genetic and hormonal effects, thus minimizing the influence of any possible confounding factors.

Another important limitation is the fact that EI and EE assessments were not performed with gold-standard methods, which may change the interpretation of our results, as well as the magnitude of the changes throughout time and its contribution to WL. The DLW method is the gold standard for measuring EE (Speakman et al., 2021; Westerterp, 2017) and indirectly EI (through the intake-method balance) (Ravelli & Schoeller, 2021). However, as DLW is expensive and requires specialized technicians (Poslusna et al., 2009), there was a need to find an alternative to measure EE. Therefore, the use of

accelerometry-based wearable motion devices also provides a valid estimate of EE and therefore can be used as a valid alternative to the reference method (Shook et al., 2018). Consequently, and despite participants filled a 3-days food diary, EI was also estimated through the intake-balance method, considered more accurate and precise when compared to food records (Ravelli & Schoeller, 2021). With this approach, it was not possible to study changes in macronutrients preferences, frequency of eating and/or meals density throughout the Champ4life intervention, as only the total EI was calculated.

When it comes to AT assessment, although previous weight stability was an inclusion criterion to undergo the Champ4life intervention, it was not assured a neutral EB at the beginning of the intervention. Similarly, the post-intervention assessments (after 4 months) might not have happened under a neutral EB, as they were measured immediately after the WL intervention.

Lastly, changes in the FFM composition due to WL were not considered, as DXA does not assess changes in the main FFM components (water and protein)(Müller et al., 2021). This would have been an interesting additional focus as it is known that decreases in FFM after WL might lead to a decline in REE (Bosy-Westphal et al., 2009; Bosy-Westphal et al., 2013), undermining the ability to maintain the WL. In fact, decreases in FFM might contribute to weight regain by increasing EI in an attempt to restore the baseline values (collateral fattening) (Dulloo et al., 2017). Moreover, when predicting REE, and consequently AT, FFM composition should be considered rather than merely relying on changes in body composition stores.

10.4. CONCLUSIONS

This dissertation contributes substantially to the available literature considering metabolic and behavioral compensations that may occur as a response to an energy restriction. This thesis included an initial compilation of all papers comprising AT in some

EE components, pointing out some important questions that needed to be explored. Regarding methodological issues, the study 2 showed that there is a lack of standardization among methodologies to assess AT, which lead to different results (in terms of magnitude). Therefore, comparisons among studies with different methodologies must be avoided, emphasizing the need of providing an accurate methodological approach to assess AT.

The study 3 showed that although AT occurred after a moderate WL and remain statistically significant after a period of follow up (under a neutral EB), its clinical relevance, i.e., its impact on WL and its maintenance, is debatable. Moreover, a large variability among individuals was found. Thus, more studies are needed to better clarify the large variability observed in AT. Despite compensations in other EE components, namely NEAT, were not observed, the variability in this outcome might be due to a large degree of random measurement error. No associations were found between changes in weight nor body composition with AT in REE or NEAT, suggesting that these compensations are susceptible to other factors and not only to the magnitude of weight and/or fat loss.

Considering behavioral compensations, study 5 showed that although decreases in EI were not associated to compensatory responses such as decreases in PA and/or increases in sedentary time, an interindividual variability was found for EI and EE. Moreover, the last study found that food reward decreased after a moderate WL, as well as a decrease in willingness to allow themselves to eat whatever food is desired when hungry and an increase in better food choices (in terms of matching one's physical needs). Nevertheless, the impact that a behavioral compensation may cause on EB and undermine WL success is undebatable higher when compared to any metabolic adaptation. Therefore, it would be interesting to understand the effects of changes in EE (namely in PA) on eating patterns (macronutrients composition, meals' density, and frequency of eating) rather than only total EI.

Hence, more studies should be conducted comprising metabolic and behavioral compensations in WL, focusing on the variability among individuals to understand why some people are able to lose weight without higher-than-expected decreases in some EE components and/or behavioral compensations and others do not. Understanding the role of these compensations is paramount to better implement WL interventions that will lead to a successful WL and its maintenance at a long-term.

10.5. PRACTICAL IMPLICATIONS AND FUTURE DIRECTIONS

Lastly, this section encompasses the practical findings from the 6 included studies to the implementation of WL treatment in order to increase the likelihood of a successful WL, which includes its maintenance at a long-term.

These practical implications will be divided in two sections: 1) Recommendations to assess AT and 2) Recommendations on how researchers and health professionals should deal with metabolic and behavioral compensations when managing body weight

10.5.1. Recommendations when assessing AT:

Practical recommendations concerning the AT assessment derived from the studies are summarized below:

- State of EB:
    - A neutral EB should be assured before the measurements (e.g., by including a 2-weeks period of weight maintenance).
- To assess body composition stores:
    - As the reference method is expensive and time-consuming, DXA is a reliable option to assess FM and FFM. Other methodologies should be

avoided due to their different assumptions that might compromise the accuracy of the measurements.

- To predict REE:
    - The baseline characteristics of the participants should be used to generate the predictive equation (the use of equations developed for other populations should be avoided);
    - The predictive equation should provide a good fit for the observations;
    - Consider the inclusion of other variables such as sex and age;
    - Consider not only changes in FM and FFM but also the changes in FFM composition.
- To calculate AT:
    - The residuals (i.e., differences between measured and predicted REE) should be considered when assessing AT;
    - The variability within individuals should also be explored;
- Study design:
    - The inclusion of a control group is crucial to understand the real effects of AT on weight management.

10.5.2. How health professionals should deal with metabolic and behavioral compensations when managing body weight.

- **Metabolic vs behavioral compensations:** Although research focused mainly on AT, behavioral compensations are more likely to seriously undermine the WL process due to their magnitude. Therefore, health professionals should focus on these compensatory responses that occur through behavior changes, namely changes in EI as a response to an increase in PA/exercise and/or changes in PA (usually NEPA) to tackle decreases in EI. For instance, when implementing a

diet-only intervention, health professionals should monitor the PA patterns and implement realistic goals to avoid decreases in PA levels;

- **Interindividual variability:** Similar to what usually occurs in WL outcomes after a WL intervention, a large interindividual variability was found for metabolic and behavior compensatory responses. Therefore, it should be avoided "one size fits all" interventions, implementing tailored interventions that consider individual's characteristics, such as diet preferences, PA levels and medical history;
- **Encourage the increase of PA levels:** Although no associations were found between levels of PAEE and the WL maintenance's success in this dissertation, it is known that high levels of PA are positively associated with a successful WL maintenance (Jakicic et al., 2002; Jeffery et al., 2003; Ostendorf et al., 2019). Moreover, increasing PA may mitigate the metabolic compensatory responses that occur in the other EE components as a response to WL.
- **Focus on WL maintenance:** Health professionals should consider not only the active WL phase but also the WL maintenance, providing an adequate follow-up after achieving the WL goals in order to avoid weight regain.

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