# WHY WEIGHT LOSS PROGRAMS ARE NOT THE NEAT WAY TO LOSE WEIGHT

## The activitystat

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# Abstract

Obesity is a worldwide problem and its prevalence continues to grow. In order to fight obesity, programs have been designed to promote weight loss, which are often based on increasing physical activity through exercise. Exercise is thought to increase energy expenditure, thereby inducing negative energy balance and enhancing weight loss. However, exercise programs often do not result in the expected amount of weight loss. One of the reasons might be activitystat: a compensatory mechanism in physical activity (PA) in order to remain energy balance and prevent weight loss. It was found that exercise programs do not increase total daily energy expenditure (TDEE) nor reduce basal metabolic rate (BMR), suggesting that compensation takes place in PA. PA can be divided into exercise (voluntary PA) and non-exercise activity (involuntary PA, also referred to as NEAT). Studies suggest that exercise reduces NEAT, however, not much is known on the effects of activitystat on energy balance and weight loss programs. Therefore, this essay describes how activitystat can be the reason of less-than-expected weight loss during weight loss programs based on exercise, and attempts to explain through which mechanisms it would exert these effects.

# 1. The weight loss problem

Obesity is a worldwide problem and its prevalence continues to grow. The World Health Organization (WHO) defines obesity as an abnormal or excessive fat accumulation with a body mass index (BMI) greater or equal to 30. According to the WHO (2018), about 39% of the world's population was overweight or obese in 2016, which is more than every 1 in 3 people. The prevalence of obesity has nearly tripled since 1975 and at this current pace, researchers estimate that half of the world's adult population will be affected by obesity in 2030 (WHO, 2018). This is a major problem, for not only is obesity related to a number of diseases, including heart disease, high blood pressure, stroke and diabetes (source), it also affects a person's mental health, the ability to work or participate in the society, ultimately affect ting the economy (WHO, 2018). For example, obesity alone is responsible for about 2 trillion dollars of health care costs per year worldwide (Dobbs *et al.*, 2014). This clearly shows there is an urgent need to find a solution for this obesity 'epidemic'.

Trying to fight the problem of obesity, programs have been designed in order to promote weight loss in overweight or obese individuals. These programs focus on diet and physical activity, the two factors that are widely accepted for managing body weight. A weight loss program, therefore, often consists of a great amount of exercise alone or in combination with a strict diet, limiting calorie intake. This is actually the most common weight loss strategy, employed by about 63% of people that are trying to lose weight (Martin *et al.*, 2018).

However, a problem with these weight loss interventions is that they have no or only a small effect on body weight (Williams *et al.*, 2015; Harris *et al.*, 2009). In many interventions, the mean weight loss observed is far less than expected. The individual responses also vary widely, with some individuals losing a substantial amount of weight, others maintaining weight, and a few actually gaining weight (Boutcher & Dunn, 2009). For example, in a study from Jacqmain *et al.* (2001), a woman involved in a weight loss program followed a strict diet, limiting her calorie intake by almost a quarter. After 15 weeks in the program, not only did she not lose weight, she even gained several pounds. The explanation for this unexpected result was that her body made up for the loss of calories: it was burning less calories, in order to maintain body weight. This illustrates that weight loss programs might not be effective, because there are potential compensatory mechanisms of the body in place that protect against weight loss.

However, is this the only mechanism that occurs during weight loss programs, disabling participants to lose weight, or is another factor contributing to less-than-expected weight loss, which is now overlooked? If compensation occurs as a response to alterations in diet, one could suggest that compensation also might take place in the other aspect of weight loss programs: physical activity. It was Rowland who in 1998 first suggested that the amount of physical activity in humans is regulated

and set to a certain level, called 'activitystat'. Due to activitystat, an increase in exercise might be compensated by a reduction in overall physical activity: when people are performing more physical activity at a certain moment, they will compensate this by moving less at another moment. This might explain why weight loss programs are not always effective, leading to the following question: does activitystat contribute to less-than-expected weight loss during weight loss programs due to compensation in physical activity?

# 2. How is body weight regulated?

In order to find out if activity stat could interfere with the effectiveness of weight loss programs, an understanding of how body weight is regulated is needed.

## 2.1 Energy balance

Body weight is controlled very closely by the body. This is seen in the fact that body weight remains quite stable over longer periods of time, in spite of variations in food intake and exercise. Maintaining a constant body weight, provided it lies within healthy ranges, is important for optimal performance of the body for maintenance, growth and reproduction, and for prevention of diseases, such as cancer, diabetes type 2 and heart disease (Westerterp, 2010).

The most important way body weight is maintained is by a strict, dynamic balance between energy intake (EI) and energy expenditure (EE), called energy balance (Schoeller, 2009). It can be considered a homeostatic system, since constant monitoring is involved and adjustments are made when energy values differ from a certain set-point. Energy intake and expenditure are expressed in calories: the amount of energy (heat) that is needed to raise 1 g of water by 1°C (Roehrig *et al.*, 2013). The effect of energy balance on body weight can be explained by the first law of thermodynamics. According to this law, energy can be transformed, but it can neither be created nor destroyed (Clausius, 1879). In simpler words: energy has to go somewhere. Applied to humans, this means that when

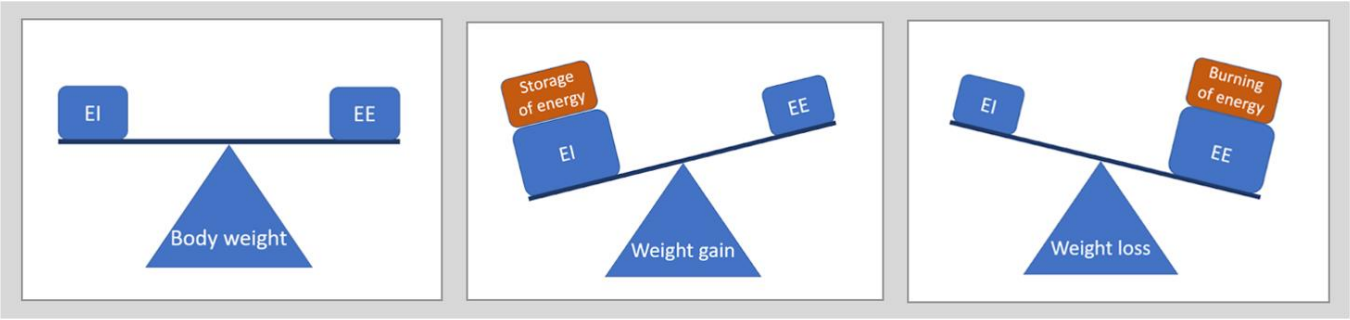


*Figure 1*. Effects of energy balance on body weight.

energy is taken in, the energy has to go somewhere. In order to remain a balance between energy intake and energy expenditure, the energy has to be burned (expended), which can be achieved by physical activity or by burning calories to fuel bodily functions (Schoeller, 2009). When a person fails to do so, an imbalance between energy intake and energy expenditure occurs, which has consequences for body weight. Namely, when energy intake exceeds energy expenditure, the excess energy has to go somewhere, and will therefore be stored inside the body in fat tissue or glycogen (muscles or liver). This results in body weight gain (Schoeller, 2009) (figure 2A). The quantity of energy stored by the human body is impressive; lean individuals store at least two to three months of their energy needs in adipose tissue, whereas obese individuals can carry one year's worth of their energy needs (Levine, 2003). The other way around, when energy expenditure exceeds energy intake, this results in a negative energy balance. In this case, energy from storage in fat or glycogen has to be burned to provide energy for the body, resulting in body weight loss (Schoeller, 2009) (figure 2B).

### 2.1.1 Energy intake

Energy intake is determined by the consumption of food. It is the total amount of calories that are provided by carbohydrates (4 kcal/g), fat (9 kcal/g) and protein (4 kcal/g) (figure 3). Energy intake is influenced by feelings of hunger and satiety, as will be explained later.

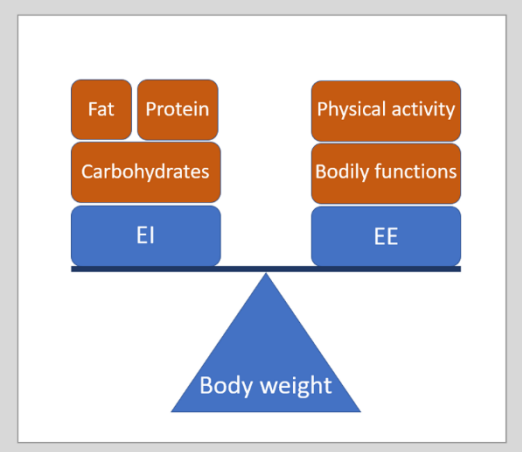


*Figure 2*. Components of energy intake and energy expenditure in regard to energy balance and body weight.

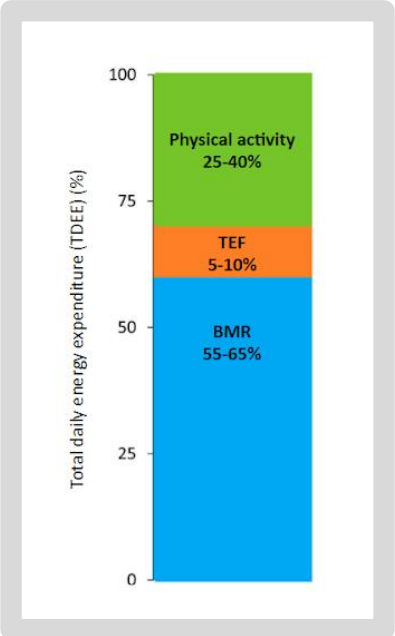


*Figure 3*. Components of energy expenditure.

### 2.1.2 Energy expenditure

The other side of the balance, energy expenditure, is the amount of energy that humans expend during physical functions, including basic cellular maintenance and repair, digestion, thermoregulation, locomotion, growth and reproduction (Garland *et al.*, 2011). The total number of calories burned by an individual in one day is the total daily energy expenditure (TDEE). Since energy is needed for different processes and functions of the body, energy expenditure can be categorized into three main components: basal metabolic rate (BMR), thermic effect of food (TEF) and energy expenditure from physical activity (figure 4) (Levine, 2003).

BMR is the amount of energy that is needed to maintain minimal bodily functions at complete rest (in the morning, laying down, in a neutral temperature, after active meal digestion). It accounts for 55-65% of the total daily energy expenditure (TDEE) (figure 4). TEF refers to the heat produced in response to and following the consumption of a meal, due to the metabolic costs of digestion, absorption, metabolism, and storage of nutrients. TEF is thought to only contribute for 5-10% to TDEE. The remaining 25-40% of daily energy expenditure is ascribed to physical activity, which is defined as all movement during the day associated with normal day-to-day living, not just planned and structured exercise (Garland *et al.*, 2011; Levine, 2003; Münzberg *et al.*, 2015; Schoeller, 2009).

## 2.2 Energy balance and the brain

### 2.2.1 Hypothalamus

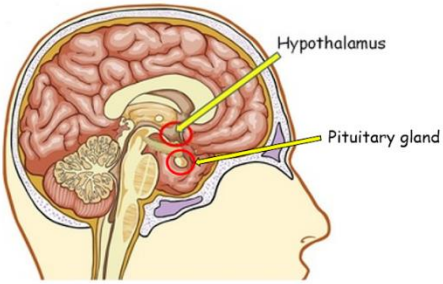


*Figure 4.* Locations of the hypothalamus and pituitary gland in the brain. Image retrieved from voedingsadviesrotterdam.nl

One of the main components in body weight regulation is the hypothalamus in the central nervous system (CNS). The hypothalamus is located immediately below the thalamus at the centre of the brain and is connected with other central areas of the brain stem and peripheral tissues. It controls many autonomic functions of the body, such as blood pressure, body temperature, and fluid and electrolyte balance. Its primary function is to maintain these functions within a restricted range of values, the set-point, and thereby regulates the balances within the body. This is called homeostasis. The hypothalamus receives neural input from several brain areas, as well as from circulating hormones. In response to those signals, it synthesizes and secretes certain neurohormones, called releasing hormones. These hormones stimulate or inhibit the secretion of hormones from the pituitary gland, which in turn affects downstream pathways in order to restore the body's balances (Benedini, 2009).

In addition to the examples mentioned above, the hypothalamus is involved in energy homeostasis and therefore body weight regulation. It has been found to play a central role in the control of appetite and satiety (Prodam *et al.*, 2006). It reacts to nutritional information, including peripheral and central neuronal input and metabolic signals from circulation, such as glucose or fatty acids (Roh & Kim, 2016). Depending on nutritional status, the hypothalamus elicits appropriate behavioural and metabolic responses to counterbalance any changes in energy balance, thereby maintaining energy balance and body weight.

### 2.2.2 Neuroendocrine regulation of energy intake

The hypothalamus exists of different nuclei, which each have their own function. One of the areas that is involved in the regulation of energy balance is the arcuate nucleus (ARC) (Roh & Kim, 2016). It is located near a brain area with a relatively porous blood-brain barrier, providing the ARC free access to circulating nutrients and hormones, making it the primary nutrient-sensing centre of the hypothalamus (Roh & Kim, 2016). ARC contains two distinct neuronal populations: neurons that express neuropeptide Y (NPY) and agouti-related peptide (AgRP) and neurons that express proopiomelanocortin (POMC) (figure 5). When NPY/AgRP neurons are activated, they stimulate a feeling of hunger. Activation of POMC neurons, on the other hand, stimulates feelings of satiety. In conditions where nutritional status (the level of nutrients, such as glucose, in the body) is high, such as in the case of a positive energy balance, POMC neurons are activated. These neurons produce alpha-melanocyte stimulating hormone (αMSH), a neuropeptide derived from the precursor protein POMC, which increases feelings of satiety and reduces hunger, thereby inhibiting food intake (Shipp *et al.,* 2016). In nutrient-deprived conditions (negative energy balance), NPY/AgRP neurons are activated, causing an increase in hunger and a decrease in satiety, thereby stimulating food intake.

In addition to circulating nutrients, there are multiple other signals that suppress or increase appetite and feeding behaviour via the hypothalamus. One of these is leptin, a hormone that is synthesized by adipocytes (fat cells). Leptin receptors are present in the cell membranes of a lot of different cell types, but the main site of action is the hypothalamus. Concentrations of leptin are higher with increasing fat mass, and blood levels rise during a positive energy balance, so when more energy is taken in than there is being expended (Benedini, 2009). When leptin reaches the hypothalamus via the blood-brain barrier, it exerts an inhibitory effect on NPY/AgRP expression, thereby inhibiting hunger, while simultaneously promoting POMC expression and thus feelings of satiety (Belgardt & Brüning, 2010). As a result, food intake will be inhibited and energy balance will be restored (Benedini, 2009; Van Swieten *et al.*, 2014).

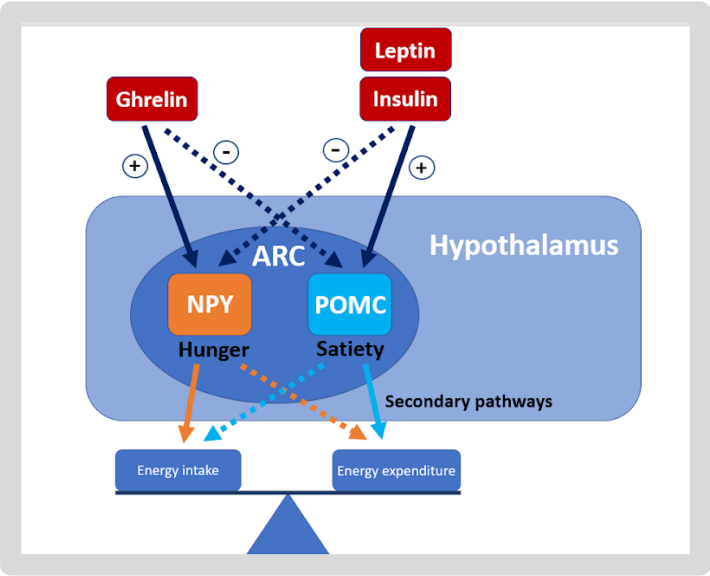


*Figure 5.* Neural regulation of hunger and satiety and its relation to energy balance.

Another factor that has the same mechanism of action is insulin. When food is ingested, blood glucose levels rise and as a response, insulin is secreted from β-cells in the pancreas. Activation of

insulin receptors on NPY/AgRP and POMC neurons in the hypothalamus lead to stimulation of satiety and inhibition of appetite and therefore reduce energy intake again (Loh *et al.*, 2017).

One more signal known to influence energy balance on a hypothalamic level is ghrelin, a hormone that is produced by cells of the gastrointestinal tract, especially the stomach. It is called a "hunger hormone", because it increases food intake. Before a meal, when nutrient levels are low, blood ghrelin levels are highest. When ghrelin reaches the hypothalamus, it activates the NPY/AgRP pathway, thereby stimulating food intake. The presence of food in the stomach inhibits the production of ghrelin, after which the stimulation of food intake is reduced and energy balance is restored (Abizaid *et al.*, 2012; Serrenho *et al.*, 2019).

When a negative energy balance occurs, levels of leptin and insulin will decrease and ghrelin will increase, with an opposite effect as a result.

More signals are involved in regulating energy intake, however, since this paper focuses on energy expenditure, only the most prominent signals have been discussed.

### 2.2.3 Neuroendocrine regulation of energy expenditure

Next to energy intake, the hypothalamus seems to regulate energy expenditure. Less is known about the exact mechanisms behind the hypothalamic regulation of energy expenditure, but the same nuclei and neuropeptides seem to be involved. When POMC neurons are activated, they increase energy expenditure (Enriori *et al.*, 2011), while activation of NPY/AgRP neurons decreases energy expenditure (Shi *et al.*, 2013). Thus, following a change in energy balance, depending on the type of neurons that is activated, either an increase or decrease in energy expenditure will occur, resulting in restoration of energy balance.

One of the mechanisms through which this is thought to occur, is through regulation of brown adipose tissue (BAT) thermogenesis (Timper *et al.*, 2017). In adults, BAT is mainly located between the shoulder blades, surrounding the kidneys, the neck and along the spinal cord (Sacks & Symonds, 2013). It is known to play an important role in adaptive thermogenesis. So, in situations where the body needs extra heat, such as during cold temperatures, BAT is activated and promotes the generation of heat: a process that requires the burning of calories, and therefore increases energy expenditure (Pandit *et al.,* 2017).

In addition, BAT thermogenesis is found to be affected by leptin and insulin. Following food intake, resulting in a positive energy balance, higher levels of leptin and insulin will activate POMC neurons and inhibit NPY/AgRP neurons (Pandit *et al.*, 2017). This has been shown to increase BAT thermogenesis, and thus higher energy expenditure, thereby restoring energy balance. Since BAT thermogenesis is affected by changes in energy balance and it is an autonomic process, it can be

considered being part of the BMR component of energy expenditure (Marlatt & Ravussin, 2017; Hibi *et al.*, 2016; Scheele *et al.*, 2017).

In addition, higher levels of ghrelin following a negative energy balance, will decrease energy expenditure in order to prevent energy imbalance. In contrast to leptin and insulin, ghrelin is thought to inhibit BAT thermogenesis through the activation of the NPY/AgRP pathway (Nogueiras *et al.*, 2010).

In summary, the net effect of leptin and insulin within the hypothalamus is to inhibit food intake and to increase energy expenditure following a positive energy balance. Following a negative energy balance, increased levels of ghrelin result in an increase of energy intake and a decrease of energy expenditure to restore energy balance. How is the regulation of energy balance related to the efficacy of weight loss programs?

# 3. Weight loss programs and energy (im)balance

As explained in the previous chapter, a negative balance needs to be evoked in order to lose weight. This is why weight loss programs focus on either decreasing energy intake by dieting, increasing energy expenditure by intensive exercise, or a combination of both. However, when an imbalance in energy like this occurs, the hypothalamus will try to restore energy balance in order to maintain body weight. To do so, it has two options: it can either 1) increase energy intake or 2) decrease energy expenditure.

## 3.1 Negative energy balance and homeostasis

### 3.1.1 Reduced energy intake

The first method to evoke a negative energy balance, which is also the most common method for weight loss, is reducing caloric intake. However, as mentioned before, the expected weight loss based on the energy deficit that has been created by dieting is not always achieved (Saquib *et al.,* 2008; Foster *et al.,* 2003; Doucet *et al.,* 2018; Heymsfield *et al.,* 2007). Because of the reduction in energy intake, the hypothalamus will sense a decrease in nutritional status, whereas other (hunger) signals, such as ghrelin, will be increased and stimulate the hypothalamus to increase food intake, in order to prevent an energy imbalance. However, when an individual is dieting and therefore will not consume any more food, the body fails to increase energy intake. As a result, the only other option to restore energy balance is by reducing energy expenditure. Studies show that this is achieved by a reduction in basal metabolic rate, which might be a consequence of reduced BAT thermogenesis (Fox *et al.,* 2019; Fricker *et al.,* 1991; Dulloo & Jacquet, 1998). This restoration in energy balance would result in no or less-than-expected weight loss.

### 3.1.2 Increased energy expenditure

Since a negative energy balance as a result of reduced food intake evokes compensatory mechanisms, one might assume that a same kind of mechanism happens using the other way to evoke a negative energy balance: increasing energy expenditure (Donnelly *et al.,* 2003). The only option for an individual to do so is by physical activity: a person cannot voluntarily increase BMR subsequently in order to increase energy expenditure, for it is an autonomic process. Therefore, exercise is implemented in the participant's lifestyles during a weight loss program, during which the intended physical activity, such as sports and fitness exercises, is higher than the general exercise recommendations for health. The addition of structured exercise should theoretically result in a negative energy balance and subsequently weight loss. However, exercise-based weight loss programs do not always lead to weight loss or do not match the expected amount of lost weight (Swift *et al.,* 2014; Dhurandhar *et al.,* 2015; Donnelly *et al.,* 2003; Thomas *et al.,* 2012; Riou *et al.,* 2019). For example, Donnelly *et al.* (2003) investigated the effect of aerobic exercise for 16 months in 74 young overweight or obese men and women. According to calculations based on DLW measurements, this should result in an increase in energy expenditure by 668±116 kcal/ day in men and 439±88 kcal/day in women. However, at the end of the study the men had only lost 5.2±4.7 kg, which was significantly less than predicted, and the women did not even lose any significant weight. Since the program is not effective, it suggests that there is no negative energy balance resulting in weight loss. There are two options that may clarify this phenomenon: 1) individuals compensate for exercise by increasing their energy intake, or 2) the body compensates for exercise by reducing energy expenditure.

Regarding the first option, a negative energy balance would be compensated through stimulation of energy intake by the hypothalamus. The interesting thing is, though, that participants do not always tend to increase their food intake. For example, Woo and colleagues studied the effect of a 57-moderate physical intervention on food intake in obese women (1982). By adding exercise, the women had increased their energy expenditure with 551 kcal per day. However, it was found that not only did the women not lose weight, they also did not increase their food intake. Similar results were found in the study from Donnelly *et al.* (2003) and Riou *et al.* (2019), and numerous other studies have found that food intake did not increase during various types of exercise programs in normal-weight participants (Ebrahimi *et al.,* 2013; Donnelly *et al.,* 2014; Stubbs *et al.,* 2002; Woo *et al.,* 1982; Shamlan *et al.,* 2017), suggesting that increased energy expenditure is not or only partially compensated by increased energy intake. This suggests that compensation in energy balance is taking place on the level of energy expenditure and not in energy intake.

If a negative energy balance would be compensated by reducing energy expenditure - which is the only other option in order to restore energy balance - this would be achieved by reducing BAT activity, resulting in lower TEF and BMR, as discussed before. However, studies show that BMR and

TEF do not decrease significantly during exercise programs (Woo *et al.,* 1982; Riou *et al.,* 2019; Morio *et al.,* 1998; Santa-Clara *et al.,* 2005). In addition, even TDEE does not always increase, as would be expected when adding exercise to energy expenditure (Drenowatz *et al.,* 2015; Byrne & Hills, 2018; Donnelly *et al.,* 2003; Riou *et al.,* 2019; Morio *et al.,* 1998; Goran *et al.,* 1992), confirming that compensation takes place in energy expenditure. Riou et al*.,* for example, examined the effect of a 3-month exercise trial on resting metabolic rate (RMR) and total energy expenditure in 21 overweight or obese women, and found that both RMR and total EE did not alter throughout the program. These results confirm that compensation for negative energy balance as a consequence of exercise is taking place in the energy expenditure part of energy balance, but not in BMR or TEF. This indicates that there must be a decrease in another component of energy expenditure. Interestingly, the only component of energy expenditure that is left is physical activity, which paradoxically, already should be increased as a result of exercise. This raises the question whether there might be a factor in physical activity which is now overlooked, which is compensating for changes in energy balance, thereby contributing to less-than-expected weight loss during exercise programs.

# 4. Compensation in physical activity

## 4.1 Activitystat

How is it possible that despite an increase in physical activity through exercise, TDEE is not always found to be increased, without the other two components of energy expenditure – TEF and BMR – to decreasing? It suggests that a compensatory mechanism for physical activity is taking place. This was first suggested by Rowland in 1998. He called it an 'activitystat': a hypothetical control centre, maintaining energy expenditure at a particular set-point via regulatory changes in physical activity. He proposed that when exercise is increased in an individual, other physical activity may decrease during the rest of the day, as compensatory mechanism for the increase in energy expenditure.

One of the studies that supports this hypothesis is that of Frémeaux and colleagues (2011) (figure 6). In this study, the amount of total physical activity during three weeks of school children from three different schools were compared, using accelerometry. The schools differed in level of physical education

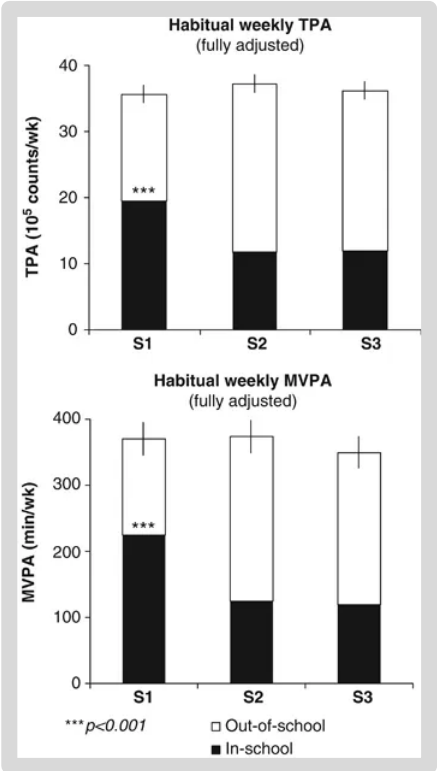


*Figure 6.* Weekly total physical activity (TPA) and moderate-and-vigorous physical activity (MVPA), divided into out-of-school physical activity and in-school physical activity, of school children from 3 different schools (Frémeaux *et al.,* 2011).

(PE): children from school 1 had significantly more hours of PE than those from schools 2 and 3. Frémeaux found that even though children in school 1 had significantly higher levels of physical activity in-school, their total physical activity did not differ from the children in the other schools. In other words, children from school 1 seemed to compensate the exercise during school time by a decrease in physical activity on their own time, suggesting a regulation of total physical activity, and thus supports the existence of an activitystat. How does this work?

## 4.2 Exercise versus NEAT

### 4.2.1 Definitions

First, it is of importance to understand the definition of physical activity. Physical activity is defined as any locomotion or movement that is the result of skeletal muscle contraction. It can be divided into two types of activity: exercise and non-exercise physical activity. Exercise refers to voluntary, planned activity, such as playing sports, whereas non-exercise activity involves spontaneous, involuntary activity, including the activities of daily living, walking, fidgeting, spontaneous muscle contractions, and maintaining posture when not recumbent (sitting, standing), but excluding sleeping and eating (Levine, 2004; Levine *et al*., 1999). The latter form of physical activity is often expressed as the energy expended during those activities, called non-exercise activity thermogenesis (NEAT), and therefore this term will be used during the remainder of this essay.

### 4.2.2 Studies regarding exercise and NEAT

Numerous studies have assessed the effect of exercise on NEAT, and thus indirectly investigated activitystat, which are presented in table 1 (appendix). Studies were performed in various types of people: obese, lean, elderly, young, men, women, etc. One of the studies is that from Colley et al. (2010), who investigated the effect of aerobic exercise for a period of 8 weeks on NEAT in obese women, using heart rate monitors, accelerometry and indirect calorimetry. They found that NEAT was significantly reduced compared to that of the control group. The same results were recently found by Riou et al. (2019), after 3 months of exercise in obese women. These studies support the theory of activitystat: the addition of exercise results in a decrease in non-exercise physical activity and NEAT.

However, there are also studies rejecting the activitystat. Willis and colleagues, for example, did not find any significant reductions in non-exercise activity in obese men and women after 10 months of exercise compared to baseline, measured by pedometry (2014). Also, Rangan et al. (2011) did not find a change in off-exercise physical activity energy expenditure during an 8-month exercise program, suggesting no decrease in NEAT.

| Study | Participants | | | | Type of exercise | Duration/intensity of exercise | Training period | Conditions (controlled? Etc.) | Increase in TDEE? | Effects on NEAT | When NEAT measured? | Method of measurement |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | Gender | Age | BMI | | | | | | | | |
| Stubbs *et al.,* 2002 | 6 | Male | 31 +- 5 yrs | Lean | Aerobic | 2-3 sessions/day, 40 min | 7-10 days | Supervised, ad lib diet | Yes | N.A. | Baseline, middle, after | HR monitors |
| Stubbs *et al.,* 2002 | 6 | Female | 23 +- 1 yrs | Lean | Aerobic | 2-3 sessions/day, 40 min | 16 days | Supervised, ad lib diet | Yes | N.A. | Baseline, middle, after | DLW |
| Donnely *et al.,* 2003 | 74 | Both | Young | OW/obese | Aerobic | 4-5 days/week, 20-45 min/session | 16 months | Supervised | No | N.A. | Baseline and 16 months | DLW |
| Colley *et al.,* 2010 | 13 | Female | 18-60 yrs | Obese | Aerobic | Not mentioned | 8 weeks | Supervised | No | Decrease | Baseline and 8 wks | HR monitors, accelerometry and indirect calorimetry |
| Goran *et al.,* 1992 | 11 | Male | 56-78 yrs | Lean | Aerobic | 3 days/week, 150-300 kcal/session | 8 weeks | Supervised | No | Decrease | Baseline and 8 wks | EE calculations, DLW, indirect calorimetry |
| Drenowatz *et al.,* 2015 | 9 | Male | 27 +- 3 yrs | Lean | Aerobic or resistance | 3 days/week | 16 weeks | Supervised | No (aerobic), yes (resistance) | Decrease (aerobic), increase (resistance) | Baseline, 8 wks, 16 wks | Accelerometry |
| Morio *et al.,* 1998 | 13 | Both | 63 +- 2 yrs | OW | Aerobic | 3 days/week, 20-40 min | 14 weeks | Supervised | No | Decrease | Baseline, 7 wks and 14 wks | Indirect calorimetry, 7 days activity records |
| Meijer *et al.,* 1999 | 15 | Both | 59 +- 4 yrs | Unknown | Aerobic and resistance | 2 days/week, 60-90 min | 12 weeks | Supervised | N.A. | Decrease | Baseline, 6 wks and 12 wks | Accelerometry |
| Riou *et al.,* 2019 | 21 | Female | 31 +- 4 yrs | OW/obese | Aerobic | 5 days/week, 300 kcal/session | 3 months | 3 supervised, 2 unsupervised | No | Decrease | Baseline, 1 wk, 2 wks and 3 months | HR monitor, indirect calorimetry, DLW, accelerometry |
| Rangan *et al.,* 2011 | 82 | Both | 18-70 yrs | OW/obese | Aerobic, resistance or both | 3 days/week 3 sets, or 12 miles/week or combination | 8 months | Majority supervised | N.A. | No change | Baseline and 8 months | Indirect calorimetry, accelerometry |
| Alahmadi *et al.,* 2011 | 16 | Male | Young | OW/obese | Aerobic | Acute bouts of moderate-continuous (60 min) and high-intensity interval (60 min) | 2 x 1 day | Supervised | N.A. | Increase after 2 days | Baseline, on day of intervention and 3 days after | Accelerometry |
| Mutrie *et al.,* 2012 | 41 | Both | >65 yrs | Unknown | Aerobic | 2 days/week, 30 min | 12 weeks | Supervised | N.A. | Increase | Baseline, 12 wks, 24 wks | Pedometry |
| Willis *et al.,* 2014 | 92 | Both | 18-30 yrs | OW/obese | Aerobic | 5 days/week, 400-600 kcal/session | 10 months | Supervised | No | No change | Baseline and 10 months | DLW, accelerometry |

*Table 1.* Overview of various studies regarding exercise and NEAT.

In conclusion, although studies regarding exercise and NEAT find conflicting results, there is emerging evidence to suggest that activitystat exists. This might be one of the reasons why weight loss programs based on exercise have no or only little effect on weight loss. In order to understand how activitystat interferes with the effect of these programs, un understanding of the mechanisms behind exercise and NEAT is needed.

### 4.2.3 Mechanisms of exercise

During exercise (voluntary physical activity), motor neurons stimulate skeletal muscle fibres in order to promote locomotion. The mechanical work associated with muscle contractions requires energy. For the first 1-2 hours of exercise, the main source of energy is glycogen, but with ongoing physical activity, fat storages need to be addressed (Burton *et al.,* 2004). As a result of the associated loss of energy as heat during muscular contraction, the energetic capacity of working muscles is about 25% (Li *et al.,* 2009). Therefore, physical exercise will increase energy expenditure above the basal energy expenditure, which, theoretically, results in a negative energy balance. Recently, it has also been proposed that exercise promotes the browning of white adipose tissue (WAT), which is the type of adipose tissue in which energy is stored as fatty acids (see chapter 2), resulting in BAT (Dewal *et al.,* 2019; Aldiss *et al.,* 2018). As mentioned earlier, BAT thermogenesis has been associated with energy expenditure. So, WAT browning might be another way through which exercise stimulates energy expenditure. Next to these effects on energy balance, it was found that exercise decreases the amount of adipose tissue, thereby improving body composition, which is associated with lower leptin concentrations (Donnely *et al.,* 2003). In addition, studies show that exercise decreases insulin levels (Marliss & Vranic, 2002; Karacabay, 2009). These decreases in leptin and insulin in turn decrease feelings of satiety and thus stimulate food intake. On the other hand, exercise was also found to decrease levels of ghrelin – the 'hunger hormone'-, which is in contrast with the previously mentioned observations, and unexpected according to energy balance (Vantansever-Ozet *et al.,* 2011). The mechanisms behind this remain unknown. However, the overall effect of exercise on these satiety signals and the subsequent effects on energy balance seems to be an inhibition of energy intake, as was mentioned in chapter 3.

So, exercise exerts its effect on energy expenditure through several ways. However, the exact neural mechanisms of exercise are still unclear. Because of the extra work load for muscles and the increased energy need, exercise is a metabolic challenge that disrupts homeostasis and this requires the rapid use and mobilisation of energy substrates. One of the brain areas that has been proposed to be involved in metabolic adaptations to exercise is the ventromedial hypothalamus (VMH). It has been demonstrated that VMH neurones contribute to the regulation of metabolism during exercise through

the partitioning of energy substrates, energy expenditure and heat dissipation (Fujikama *et al.,* 2018). The VMH can sense circulating glucose levels (De Vries *et al.,* 2003), and it appears to be activated or inhibited by other nutrients, including fatty acids, ketone bodies and lactate, all of which levels are increased after exercise (Fujikama *et al.,* 2018). So, an exercise-induced negative energy balance would be sensed by VMH neurons, which in turn stimulate metabolic changes in order to supply in the energy need that is required for muscular contraction. The mechanism by which the VMH does this, remains unclear but it is thought to improve glucose uptake, which is why exercise has been proven to have many beneficial health effects (Fujiwaka *et al.,* 2018). For example, it has been shown that regular physical activity helps in the prevention of several chronic diseases, such as cardiovascular disease, diabetes, cancer, hypertension, obesity, depression and osteoporosis, and premature death (Warburton *et al.,* 2006).

#### 4.2.4 Mechanisms of NEAT

Just like exercise is non-exercise physical activity, and therefore requires energy for muscle contractions. The difference, however, is that this type of physical activity is seen as involuntarily. Not many studies have reported on the neural mechanisms behind NEAT in humans. However, animal studies suggest several brain areas to be involved in non-exercise activity. One of these areas is the lateral hypothalamus (LH) (Perez-Leighton *et al.,* 2017). It synthesizes orexin, which is a neuropeptide that affects multiple brain sites. Injection of orexin in this area in rats, has been found to increase spontaneous activity, which could be compared to NEAT in humans. Orexin is proposed to increase the craving for food (Kotz *et al.,* 2018), so it might be that in response to a negative energy balance, which would be the case after increased exercise, the hypothalamus would release orexin, and as a consequence, NEAT would increase. However, this is not what is seen in activitystat. So, how would activitystat be regulated?

# 5. How does activitystat work?

## 5.1 Neuroendocrine regulation

### 5.1.1 Links between exercise and NEAT: orexin and dopamine

Because activitystat regulates physical activity in a homeostatic way, the control centre would be located in or near the hypothalamus. However, no literature on the neural regulation of activitystat is available. The effect of exercise on NEAT in humans has been extensively studied, as well as the effect of exercise on metabolism and various peripheral tissues, including WAT and BAT. However, a combination of both in order to investigate the neural mechanisms behind the effects of exercise on

NEAT could not be found. Nonetheless, a deduction can be made from the information mentioned above regarding mechanisms involved in exercise, NEAT and energy balance. According to activitystat, exercise influences NEAT. So, how are these factors related to each other?

As mentioned in the previous chapter, exercise was found to result in WAT browning, accompanied by decreases in circulating satiety signals, such as leptin and insulin. NEAT, on the other hand, was found to be associated with orexin. Interestingly, Chieffi et al. (2017) mention that reductions in leptin and insulin are associated with higher levels of orexin. And indeed, after exercise, it appears that orexin concentrations are also increased (Messina *et al.,* 2014; Messina *et al.,* 2016). In addition, the VMH was found to have direct projections to orexin neurons in the LH, indicating that VMH activity regulates orexin release, which in turn appeared to regulate BAT activity and thus energy expenditure (Chieffi *et al.,* 2017). From this, it can be deduced that exercise reduces WAT and satiety signals, and stimulates VMH neurons, resulting in an increase in orexin levels (figure 7).

Another aspect that has been associated with higher orexin activity, was an increase in dopamine levels (Calipari & España, 2012). Dopamine is a hormone and neurotransmitter that is associated with locomotion and reward. One of the areas that contains dopamine neurons and is associated with reward, is the ventral tegmental area (VTA) in the hindbrain (Dodson *et al.,* 2016). The VTA was found to receive direct projections from orexin neurons from the LH (Baimel *et al.,* 2017), suggesting orexin's role in dopamine release. With regards to NEAT, Dodson et al. (2016) showed that shortly before spontaneous physical activity was performed in rats, firing of dopaminergic neurons changed, indicating that dopamine is involved in the induction of spontaneous movement and NEAT. From an evolutionary point of view, this makes sense: thousands of years ago, it was rewarding for humans to move and search for food in order to survive. Next to this, dopamine is found to play a role in BAT thermogenesis (Folgueira *et al.,* 2019). So, this implicates that orexin, which is released by exercise, increases NEAT and BAT thermogenesis through dopamine, thereby increasing energy expenditure. However, as mentioned, according to this pathway, the amount of NEAT should increase, but this is not the case in activitystat.

### 5.1.2 Negative feedback on NEAT

Studies from Linehan et al. (2019) and Alberto et al. (2006) suggest that dopamine provides feedback to orexin: high levels of dopamine inhibit the release of orexin. This would mean that high levels of dopamine induced by exercise (and elevated levels of orexin) suppress the amount of orexin released and thus decrease orexin levels. This would in turn decrease NEAT. However, the idea of activitystat is that exercise directly influences the amount of NEAT, and the pathway described above is an indirect effect of exercise on NEAT. Because, if this were the case, would this not also be the case during food

restriction? Namely, as a result of reduced energy intake, inducing a negative energy balance, a decrease in leptin and insulin takes place, which should theoretically result in an increase in orexin. This, in turn, would increase NEAT as a mechanism to stimulate food foraging. So, this would mean that both a negative energy balance as result of food restriction and exercise work through the same mechanism. Unfortunately, no studies reporting on orexin release during fasting could be found, nor is there evidence for an increase in NEAT after food restriction. Thus, it cannot be determined whether the effects of negative energy balance through exercise and reduced energy intake operate through the same mechanisms and whether they both affect physical activity in the same way. However, since exercise seems to be compensated in NEAT, whereas food restriction often affects BMR, it suggests that they work through different pathways. This would make sense, since there is a large difference between the negative energy balance retrieved from exercise and the negative energy balance as a consequence of food restriction. Namely, during exercise, energy expenditure is increased through involvement of muscle contractions, which is not the case during food restriction. But how would this influence activitystat?

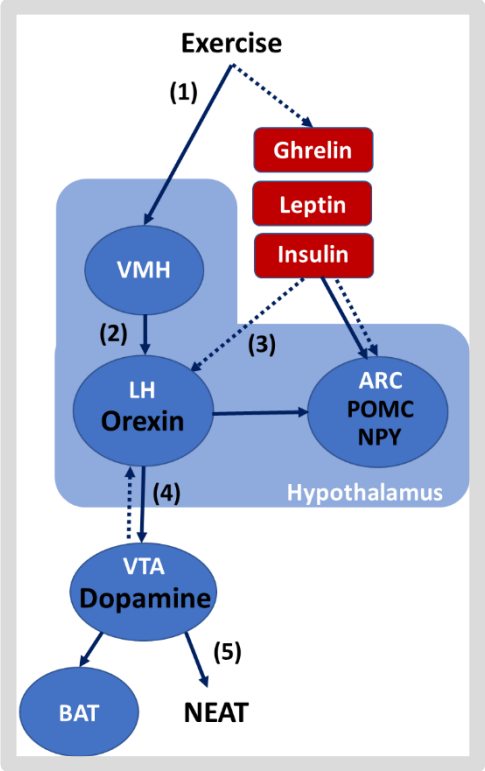


*Figure 7.* Schematic representation of neuroendocrine mechanisms behind activitystat. 1) Exercise induces decreases in ghrelin, leptin and insulin levels, and stimulates the VMH. 2) VMH stimulates orexin neurons in the LH. 3) Reductions in ghrelin, leptin and insulin stimulate orexin neurons in the LH. 4) Orexin stimulates dopamine release in VTA, dopamine inhibits orexin. 5) Dopamine increases BAT activity and NEAT.

## 5.2 Function of activitystat

### 5.2.1 Protective mechanism

This might be explained by another thought regarding activitystat, which is: activitystat is not only a mechanism to maintain energy balance, but also a protective mechanism to prevent the muscles from becoming overloaded. If a human keeps on exercising, the body and muscles might be overworked and will be harmed. Also, TDEE will continue to increase. If exercise would be compensated by a decrease in BMR, it would be suboptimal for health, and thus it would be more beneficial to decrease physical activity in NEAT first. Therefore, Pontzer et al. suggested there is a limit to how much a human can be physically active: it can only increase this much. They concluded from a comparative analysis of TDEE and physical activity data, that TDEE increases with physical activity at low activity levels but plateaus

with higher activity levels. They suggested a model of constrained TDEE with metabolic adaptations to physical activity. As activity energy expenditure 1 (AAE1, which could be seen as exercise) increases, AEE2 (which could be seen as NEAT) decreases, while RMR and TEF remain equal with increasing exercise levels (figure 8). This suggests that there is indeed a protective mechanism in place, which results in activitystat. But what factor causes this?

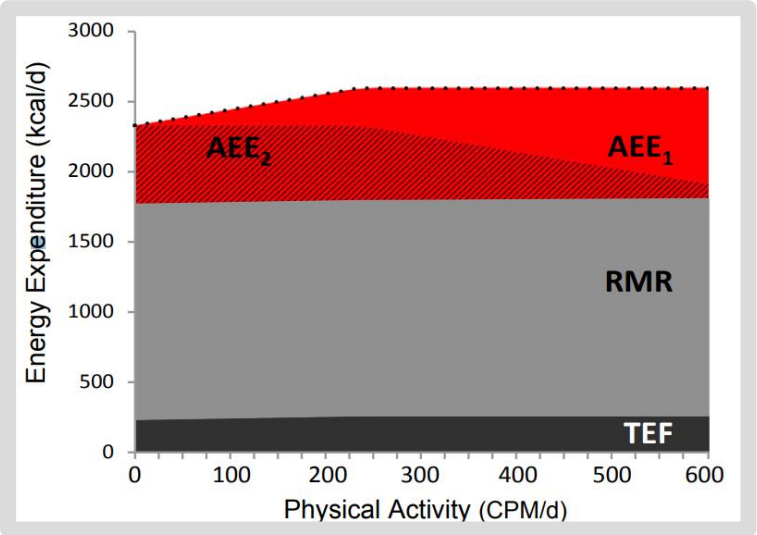


*Figure 8.* Energy expenditure during different intensities of physical activity. AEE2 is comparable to NEAT, AEE1 to exercise. RMR: resting metabolic rate, TEF: thermogenic effect of food. Pontzer *et al.,* 2016.

### 5.2.2 Myokines

Recently, it has been demonstrated that skeletal muscle is an endocrine organ: during muscle contraction, humoral factors are being produced and released, so-called myokines (Pedersen, 2011). Receptors for myokines, such as IL-6, IL-10, and IL-1, are found on muscle, fat, liver, pancreas, bone, heart, immune, and brain cells, which reflects the fact that myokines have multiple functions. Foremost, they are involved in exercise-associated metabolic changes, as well as in the metabolic changes following training adaptation (Pedersen, 2011).

One of the myokines that has recently gained interest is irisin, for its alleged role in weight loss, due to its thermogenic effect on fat cells and its role in the browning of WAT (Boström *et al.,* 2012). Boström et al. reported a two-fold increase of circulating irisin in healthy humans after 10 weeks endurance training, an observation that was further supported by other studies in rodents (Silva-Magosso *et al.,* 2017; Wrann *et al.,* 2013) and in some cases in human subjects (Norheim *et al.,* 2014; Lecker *et al.,* 2012). Interestingly, Ferrante et al. (2016) showed that intra-hypothalamic injection of irisin in rats decreased both orexin and dopamine levels in the hypothalamus. This would indicate that exercise-induced increases in irisin reduce orexin levels, thereby decreasing dopamine and thus resulting in a decrease in NEAT (figure 9). Therefore, irisin might be the direct link between exercise and NEAT, and thus a mechanism through which activitystat is regulated.

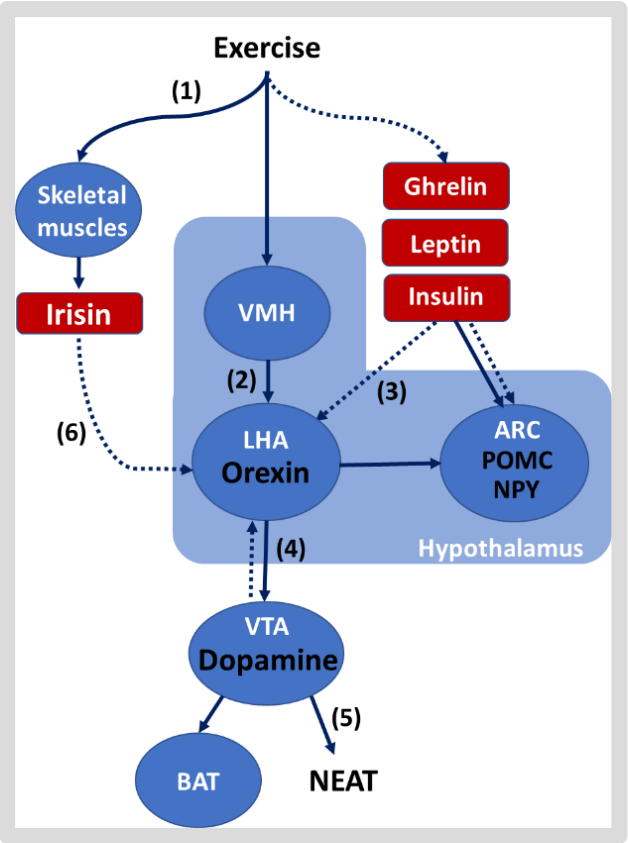


*Figure 9.* Schematic representation of neuroendocrine mechanisms behind activitystat. 1) Exercise stimulates skeletal muscles to produce irisin, induces decreases in ghrelin, leptin and insulin levels, and stimulates the VMH. 2) VMH stimulates orexin neurons in the LH. 3) Reductions in ghrelin, leptin and insulin stimulate orexin neurons in the LH. 4) Orexin stimulates dopamine release in VTA, dopamine inhibits orexin. 5) Dopamine increases BAT activity and NEAT. 6) Irisin inhibits release of orexin, thereby reducing dopamine release and thus NEAT. Orexin was also found to stimulate POMC neurons (Ferrante *et al.,* 2016), which in turn stimulates satiety. This might explain why no increases in energy intake were found after exercise interventions.

# 6. Discussion

## 6.1 Activitystat and weight loss interventions

Activitystat might be one of the reasons why weight loss interventions based on exercise have no or only little effect. Exercise is universally cited as means of weight control. However, the contribution of exercise to TDEE is found to be only small, whereas NEAT is found to substantially contribute to TDEE, namely about 15–50% (Münzberg *et al.,* 2008). Therefore, NEAT might often be overlooked in weight loss programs. Namely, if exercise leads to a decrease in NEAT through irisin and/or other unknown mechanisms, weight loss programs based on exercise might not be a good way to lose weight. With respect to the obesity epidemic mentioned in the first chapter, NEAT might offer some insights and even solutions. When taking part in an exercise-based weight loss program, the compensation in NEAT by activitystat needs to be taken into mind. For successful weight loss, it is of importance to prevent a decrease in non-exercise activity when performing exercise. Even better, an increase in NEAT needs to be promoted in order to evoke an even larger energy deficit. Since exercise only contributes little to TDEE, it can be encouraged to not implement exercise in a weight loss program at all, but instead increase non-exercise activity, in order to avoid compensation via activitystat. However, whether this is applicable to people's every day's life is one of the challenges to face. People who have very

scheduled and sedentary lifestyle - for example, office work from nine till five - and have to schedule their physical activity, might have more trouble increasing NEAT. However, small changes have been found to increase NEAT: taking the stairs instead of the elevator, going by bike instead of by car, take a walk during lunch hours, or standing up instead of sitting (Levine, 2003). This is why, for example, standing desks are becoming more and more popular: the energy expenditure in an upright position is larger compared to that of sitting, and so NEAT increases.

However, despite the small effect on body weight, exercise has been proven to have many other beneficial effects on health (Warburton *et al.,* 2006). Therefore, exercise should be implemented in daily life, but a decrease in NEAT should be avoided.

## 6.2 Differences in study outcomes

It may be clear that the outcomes from studies discussed in this paper varied. Regarding the effects of exercise on several energy balance parameters, some studies found no effect on energy intake, TDEE and a decrease in NEAT, supporting the hypotheses of compensatory mechanisms in physical activity, whereas others made no such observations. There are some remarks as to the interpretation of those results.

### 6.2.1 Study design

First of all, the change in NEAT may depend on the type and volume of training, the length of the intervention, as well as the method employed to measure NEAT. A difference in outcomes was mentioned between aerobic and resistance training.

Furthermore, the implementation of aerobic exercise reduces the participant's energy, which might cause a feeling of overall tiredness, resulting in less non-exercise activity. On the other hand, resistance training increases overall fitness and lean body mass, enabling participants to perform exercises more easily as the intervention continued. It might have made them feel less tired on exercise days, after which there is no need to move less (Drenowatz *et al.,* 2015).

Also, differences in duration of intervention might explain variation among study results. In short-term studies (16 days or less), such as those of Alahmadi *et al.* and Stubbs *et al.,* it was suggested that there was no compensation in physical activity in response to exercise, whereas studies with a duration of 8 weeks or longer (Goran *et al.,* 1992; Morio *et al.,* 1998; Meijer *et al.,* 1999) did find a decrease in NEAT. It has been suggested that the compensatory mechanisms only take place when energy imbalances have occurred for a longer period of time. In addition, a limit of physical activity might be reached when increasing exercise frequency and intensity (Pontzer, *et al.,* 2011). Taking these studies in mind, it seems that only when a certain threshold of physical activity is reached, exercise is

compensated by a reduction in NEAT: activitystat. This indicates that activitystat is one of the reasons why the effect of weight loss programs is less-than-expected at the long-term.

Next, the way of measurements varies between studies. Whether assessment of movement pattern and/or energy expenditure took place determines the interpretation of the outcomes. For example, in some studies, NEAT energy expenditure was based on calculations and estimates, which make the results a lot less reliable (Goran *et al.,* 1992). In other studies, no TDEE was measured, only NEAT (Meijer *et al.,* 1999), and others only used accelerometry (Drenowatz *et al.,* 2015) or only energy expenditure measurements (Goran *et al.,* 1992), instead of a combination of both. These differences in measurements make it difficult to compare studies and to draw conclusions about activitystat, and so more research is needed.

Also, differences in supervision and compliance, and controlled and free-living conditions can cause differences in results. When not supervised, participants are more likely to non-comply and since they do not complete their prescribed exercise physical activity, they do not need to reduce their NEAT.

### 6.2.2 Subjects

Studies were performed with a variety of subjects, among which healthy (Goran *et al.,* 1992) or obese (Morio *et al.,* 1998) elderly, healthy young men and women (Stubbs *et al.,* 2002) and overweight or obese young people (Colley *et al.,* 2010). It may be clear that these differences in age, gender and BMI cause interindividual variation within effects of exercise in weight loss interventions. For example, it has been suggested that subjects have an energy storage, which might need to be depleted first in order for energy expenditure to reduce via reduction in NEAT (Stubbs *et al.,* 2002). In normal-weight subjects, the achieved energy imbalance from exercise is generally lower than expected compared to overweight participants, suggesting that their compensatory mechanisms are more needed and therefore their NEAT might decrease faster. Since this paper focuses on the effects of exercise-based weight loss programs, most information was based on studies with overweight and obese participants, because they represent the people that are in need of losing weight the most.

Next to this, differences between men and women were found: women appear to have more trouble losing weight compared to men, and thus might have better compensating mechanisms (Donnelly *et al.,* 2003).

A last important remark to make is that level of fitness at baseline could interfere with results. In previously active people, the effect of exercise might not be as impactful as in sedentary participants.

In summary, effects of exercise on total physical activity level and NEAT are very variable between individuals, due to differences in age, BMI, gender and activity level. The variations between

study designs and individuals make it difficult to compare studies, however, it may be clear that activitystat interferes with the rate of success of exercise-induced weight loss programs.

## 6.3 Summary

The variations between study designs and individuals make it difficult to compare studies, however, it may be clear that activitystat interferes with the rate of success of exercise-induced weight loss programs. Despite the small effect on weight loss, it is important to implement exercise in daily life, because of its many beneficial health effects. It is also important that, next to exercise, people need to be encouraged to increase, or prevent a reduction in NEAT, in order to overcome compensatory mechanisms in physical activity.

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