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Factors that may impede the weight loss response to exercise-based interventions

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Summary

The results of exercise programmes designed to reduce body fat are disappointing. However, the reporting of weight loss as mean values disguises those individuals who do lose significant amounts of fat. Why some participants produce significant exercise-induced fat loss whereas others lose little or increase fat stores is likely to be an outcome of a range of behavioural (e.g. sleep deprivation, caloric intake), inherited (e.g. muscle fibre type, gender) and physiological (e.g. hyperinsulinaemia, hypothyroidism) factors. The following review highlights possible factors involved in weight loss and discusses how individual differences may determine the extent of weight loss after an exercise intervention. Finally, implications for the treatment and prevention of obesity are discussed.

Keywords: Exercise, non-responders, obesity, weight loss.

obesity reviews (2009)

Introduction

The prevalent view of public health organizations is that both diet and exercise are important for weight loss (1,2). Of the two interventions, energy restriction through dieting is seen as the most important factor for a change in weight with exercise making a contribution to the retention of fat-free mass and long-term maintenance of weight loss (2). The actual weight loss brought about by exercise programmes is usually less than expected and results are typically disappointing (2,3). However, exercise weight loss studies typically report their outcomes as a group average; thus, the larger weight losses of some individuals are depressed by those who show little or no weight loss. Also, prior research has assumed a static model of energy balance and typically behavioural, inherited and physiological factors that may impede exercise-induced weight loss have not always been considered. Thus, this review describes factors that may inhibit exercise-induced weight loss and provides an interactionary model to account for individual differences in the weight loss response to exercise.

Energy balance

It has been pointed out that static models of energy balance based on the first law of thermodynamics are simplistic and fail to consider interactive components such as a reduction in resting metabolic rate (RMR) and an increase in spontaneous physical activity (4). Thus, the view that an individual's fat content is determined solely by an imbalance of caloric intake and energy expenditure caused by an exercise programme ignores both the dynamic nature of energy balance and the multitude of factors that can prevent weight loss. For example, during an exercise weight loss programme individuals may successfully increase their energy output but negate these effects by eating more (5) (e.g. eating a treat as a reward after an exercise session) and decreasing other forms of physical activity (e.g. taking the elevator after exercise rather than using the stairs). These behaviours and a host of other behavioural, inherited and physiological factors may interact to prevent significant exercise-induced weight loss.

The effects of exercise on weight loss

As some studies in this area did not assess body fat but instead measured weight change, the term weight loss will be used when describing research outcomes. Results of exercise programmes designed to reduce weight are typically small with outcomes being less than expected.

Reviews have typically reported weight loss of less than 1.5 kg for exercise interventions lasting between 15 weeks

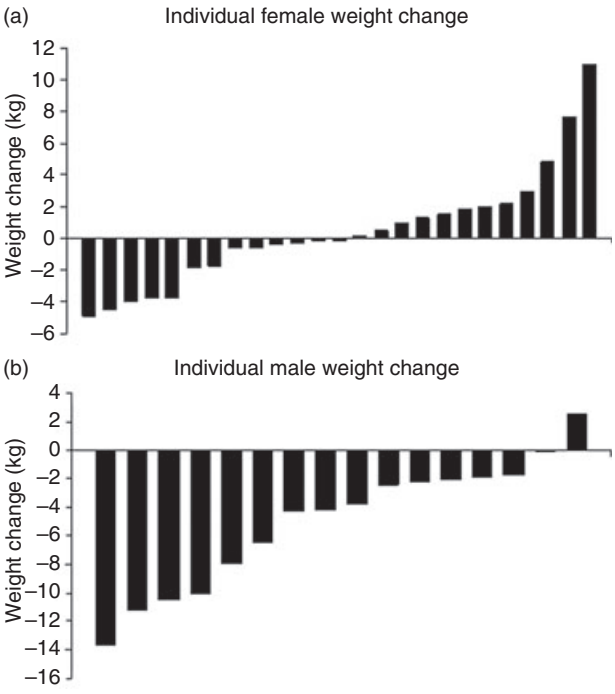

Figure 1 Individual 16-month weight change in exercise groups by gender: a, women; b, men [adapted from Donnelly *et al.* (14)].

and 1 year (6–11). Diet-only interventions show greater weight loss, whereas the combining of both diet and exercise appears to be the most effective (7,8,11). The effects of dieting alone on long-term weight maintenance, however, are negligible as the majority of individuals who undergo hypocaloric or starvation diets end up gaining back weight within 5 years (12). With regard to exercise-induced weight loss, both the reporting of weight loss as mean values and the failure to differentiate between males and females distort the exercise-induced weight loss effect.

For example, there are likely to be responders and non-responders in every exercise weight loss trial and reporting the overall effect as a mean change disguises the significant weight loss achieved by some subjects. Figure 1 illustrates this situation where it can clearly be seen that the top four male responders lost about 11 kg of weight, whereas the bottom four male responders lost less than 2 kg (13). In this study, the weight loss response for women was more variable and was less than that reported for males (Fig. 1). Although studies in this area have not typically reported individual responses and have not reported males and females separately, those studies that have show a similar pattern of results (1,5,14). The gender difference discussed above has been present and absent (2) in other interventions. Thus, it is reasonable to suggest that exercise weight loss programmes are effective for producing a clinical decrease in weight (greater than 6% of body mass) for some but not all male and female participants (4). There are a range of programme-designed factors that may explain why some studies have reported more weight loss than others. Mode, intensity, duration and frequency of the exercise programme vary considerably across studies and may contribute to the inconsistency of results and the presence of responders and non-responders. For example, non-responders may typically complete fewer exercise sessions and may have exercised at too-low exercise intensity (5,6). However, a number of studies have controlled these factors but still find variability in weight loss after exercise (2). Thus, it is likely that other individual factors that are behavioural, inherited and physiological in origin also affect weight loss response to exercise.

Factors that could impede exercise-induced weight loss

Factors that reduce the ability of exercise to bring about weight loss have been poorly examined in exercise weight loss research. However, there is growing evidence in other research literatures that a variety of factors may play a determining role in the exercise–body composition relationship. These factors can be grouped into behavioural, inherited and physiological categories.

Behavioural

As mentioned previously, two major compensatory factors for depressing exercise/weight loss effects are decreased spontaneous physical activity and increased caloric intake (5). Another related behaviour is digesting high-glycemic carbohydrate foods before, during or after exercise. It has been shown that a 30-g snack of fructose or glucose before exercise significantly suppresses fat oxidation in exercising humans (15). Ingestion of certain proteins can also result in significantly increased levels of blood insulin (16). Thus, it is feasible that regular intake of sugary drink or eating a protein snack before exercise may prevent or reduce fat oxidation and long-term weight loss. A related phenomenon is exercising in the fasting or fed condition. For example, it has been found that exercise following fasting results in significantly lower respiratory quotient (RQ) during exercise compared with the same exercise performed in the fed state (17,18). Collectively, these acute dietary factors may result in less fat oxidation with each exercise bout resulting in decreased weight loss over the duration of an exercise intervention.

Another behavioural influence is weight cycling which involves repeated dieting resulting in significant losses and gains in weight. Mice that lost a significant amount of weight through a hypocaloric diet took twice as long to lose the same amount of weight during a second dieting bout. Also, compared with the first dieting bout, they took half the time to put the weight back on when their normal

eating patterns were resumed (19). Although these results are difficult to replicate in human beings, it has been shown that human beings who weight cycle repeatedly end up fatter (20) and have a higher incidence of cardiovascular disease (21,22) than overweight individuals who consistently remain at the same weight. The implication of these data is that adults who have a history of weight loss and weight gain may have difficulty losing weight through an exercise intervention. Also, it has been demonstrated that severe dieting typically results in a loss of both fat and muscle (23). When subjects put weight back on, upon resumption of their normal diet, the lean muscle lost was replaced with fat. Thus, repetitive dieting or weight cycling tends to increase fat mass and decrease muscle mass.

Related to weight cycling are nutritional habits of subjects undergoing exercise-induced weight loss programmes. For example, some subjects may decide to supplement their exercise programme with micronutrients (e.g. calcium, green tea, vitamins B_6 and B_{12}) that have been shown to induce fat oxidation (24,25) and control food intake (26). Others may reward themselves with carbohydrate-dense high-fat foods which appear to have the opposite effect (27). Collectively, changing the diet with either unhealthy or healthy foods while trying to lose weight through exercise may impede or encourage weight loss (5).

Differences in the amount of sleep have also been implicated in body composition changes. Studies have recently shown that individuals who sleep less tend to possess higher body mass index (BMI) (28,29). The mechanism underlying this effect may be the balance between hormones that boost and those that suppress hunger. For example, Spiegel *et al.* (30) found that subjects who slept 5 h per night possessed 15% more ghrelin and 15% less leptin compared with those who slept 8 h. Sleep deprivation has been hypothesized to contribute to obesity by decreasing leptin, increasing ghrelin and reducing insulin sensitivity (29–31). Sleep deprivation has also been associated with elevated resting cortisol levels. Cortisol activates lipoprotein lipase (LPL) (32) which has been shown to encourage fat storage. Thus, sleep duration may be an important regulator of body weight and metabolism and may indirectly influence exercise-induced weight loss. For example, some subjects undergoing an exercise-based intervention may be sleep-deprived during the trial resulting in a suppressed weight loss response.

Cortisol is also increased by exposure to psychological stress (33). Individuals experiencing a high level of stress during an exercise programme may be less likely to lose fat as their stress levels may result in increased cortisol levels which then enhance fat deposition. Often, cortisol is also accompanied by increases in insulin or insulin resistance (IR) (33). Thus, when an individual has increased cortisol and insulin levels, lipid mobilization may be suppressed which has been shown to impede weight loss (33,34). Cortisol has also been associated with increased energy intake and leptin resistant states (32).

Related to psychological stress is depression. Depressed individuals typically possess an exacerbated hypothalamic-pituitary-adrenal axis (HPA) which has been shown to lead to 'burn out' and chronic increased levels of cortisol (32). With individuals experiencing a high level of stress, the feedback loop designed to control the cortisol secretion has been shown to become insensitive resulting in elevated cortisol levels (32). Augmented levels of cortisol have been shown to contribute to diabetes, decreased lean body mass and visceral adiposity (35). Also, neuroendocrine perturbation caused by exposure to stress can lead to accumulation of fat in visceral depots (32).

Increased inflammation is another outcome of being exposed to psychological stressors (32) and has been linked to obesity development (36,37). Central glucocorticoid receptors control cortisol levels, and as adrenocorticotrophin secretion is more highly concentrated in visceral fat, accumulation of fat is more likely to occur in this area (32).

Stress may also play a role in fat deposition by depressing growth hormone and testosterone levels (32). Growth hormone counteracts the actions of cortisol related to fat by inhibiting LPL activity that triggers lipid mobilization (32). Low levels of testosterone in men and high levels in women can also increase central adiposity because of increased HPA activity and increased cortisol (32). Collectively, a range of stress-induced metabolic or neuroendocrine abnormalities may impede exercise-induced weight loss and thus should be screened before the undertaking of an exercise-based weight loss intervention.

Inherited characteristics

There is evidence suggesting that women have greater difficulty in losing weight after exercise than men. Preliminary evidence suggests that women compared with men have a different rate of lipolysis, less sympathetic nervous system (SNS) activity and a smaller catecholamine response at a given intensity to exercise (34). Research has shown that women tend to lose significantly less weight than men (Fig. 1) after an exercise programme (9,14,38,39). Thus, exercise-induced weight loss results should be reported by gender (9).

A related individual factor is body composition. Women who possess upper body obesity have been shown to lose more fat than those with lower body obesity (40,41). This may be due to the effect of exercise-induced catecholamines that have a site-specific effect on body fat (34,41). For example, lipolysis is increased in intra-abdominal adipose tissue because of more catecholamine-sensitive β-receptors compared with subcutaneous adipose tissue which has a higher density of α_2-receptors (34). Thus, both males and females possessing more intra-abdominal adipose tissue

may lose more fat when undertaking exercise interventions, especially when exercise is performed at an intensity that brings about increases in catecholamines. Consequently, it is possible that, in prior research, women compared with men may have possessed more subcutaneous rather than intra-abdominal fat and had increased gluteofemoral adipose tissue which could account for their lack of exercise-induced weight loss compared with males.

Initial adiposity may also impact changes in body mass after an intervention (42,43). Participants with a higher BMI lost more weight after an intervention compared with those possessing a lower BMI (44).

Low birth weight has been shown to predict IR, obesity, hypertension, diabetes and HPA abnormalities (31,32,45,46). The causative factor underlying this relationship has been suggested to be a thrifty genotype/phenotype (46). Thus, it is likely that adults who were low-birth weight babies possess genes that are biased to storing as opposed to oxidizing fat. The inability to oxidize fat may contribute to the lack of weight loss of some individuals after undertaking exercise programmes.

Formula fed, poor foetal nutrition, low maternal BMI and the older the mother is at birth may also influence the weight loss response (45). Also, recent research has shown that in childhood adipocyte number is set and remains more or less unchanged during adulthood (47). Thus, individuals who become obese during adolescence are likely to possess greater number of adipocytes which may predispose them for weight gain compared with those individuals who become obese as adults (47).

Cold climate genes have been suggested to influence thermogenesis in offspring of cold climate ancestors. Thus, people who have evolved from the cold regions of the world have been shown to possess higher basal metabolic rates (48) which could lead to greater fat oxidation and therefore better control of body composition. The influence of cold climate genes and exercise-induced weight loss, however, is undetermined.

The adenovirus-36 has also been shown to be implicated in obesity (49). For example, 36% of obese subjects were found to possess the adenovirus-36 (49). A causal relationship between the adenovirus-36 and obesity is yet to be determined but adenovirus-36 may impact body weight by bringing about greater pre-adipocyte differentiation (49).

With regard to ethnicity, certain genes have been shown to increase susceptibility to obesity but none appear to cause obesity. Thus, genes may influence body composition by interacting with a range of environmental and lifestyle factors (e.g. physical activity levels, taste preferences for healthy and unhealthy foods, muscle fibre and metabolic characteristics). Differences in gene–environment interactions could influence the weight loss response to exercise (50,51); therefore, ethnic and racial background should be considered.

Physiological

A chronic increase in insulin or a disruption to the insulin-signalling pathways could lead to IR resulting in elevated leptin, SNS activation (52) and deposition of hepatic fat (53). IR is common in individuals with metabolic syndrome, diabetes and obesity (53–56). However, IR is one of the earliest manifestations of metabolic syndrome and has been found in young adults free of other metabolic abnormalities such as dyslipidemia, high blood pressure, high fasting blood glucose levels and abdominal obesity (57). As insulin increases LPL activity, which leads to fat storage and decreased lipolysis (34), chronically elevated insulin levels are likely to negatively impact fat oxidation and thus impair exercise-induced weight loss (58). LPL activity with or without the influence of insulin promotes fat accumulation. The actions of LPL are regulated by feeding; thus, changes in feeding patterns could promote storage of fatty acids by LPL. Consequently, variations in IR or LPL activity could explain the inability to lose weight of some individuals undertaking an exercise intervention.

Mitochondrial inefficiency or dysfunction refers to the inability of the mitochondria to oxidize fat. A decreased mitochondrial oxidative capacity and reduced mitochondrial ATP synthesis in people that were IR compared with healthy non-IR people has been shown (59). Oxidative stress and an imbalance of reactive oxygen species (ROS) could also negatively impact mitochondria. It has been shown that ROS influences ATP synthesis, regulation of the intracellular lipid homeostasis and permeability of mitochondrial pores (60) through cytotoxic lipid peroxides and free radicals. Although the body's natural defence mechanisms (antioxidants) monitor and keep ROS at low levels, any disturbance to mitochondrial function, as seen with obesity and IR, may lead to increased levels of ROS (60). It has also been found that obese subjects (compared with lean) have smaller mitochondrial size and less bioenergetic activity (61). Obese and type 2 diabetics typically possess impaired fat oxidation and mitochondrial dysfunction (62). Thus, it appears that obese and/or IR individuals have reduced fat oxidation at the mitochondrial level.

Uncoupling proteins (UCP) are related to mitochondrial activity as they allow protons to leak through the inner mitochondrial membrane resulting in substrate oxidation (63). It has been shown that when mitochondria are damaged or dysfunctional, UCP function improperly (63). Thus, without proper function of the mitochondria, fat oxidation may not occur efficiently and fat accumulation may preside (63). Consequently, differences in mitochondrial and UCP efficiency induced by obesity, IR or other factors may contribute to the lack of exercise-induced weight loss experienced by some individuals.

Also, there is evidence that muscle morphological characteristics affect fat oxidation rates and adiposity levels. Individuals with a high percentage of slow twitch (type 1) fibres tend to have higher fat oxidation rates and lower levels of overall fat and central abdominal fat (64,65). The ratio of slow and fast twitch fibres in skeletal muscle of type 2 diabetics and obese people has been shown to be related to IR (66). Diminished oxidative capacity in the obese and diabetic populations is also associated with fewer slow twitch fibres and, consequently, fewer mitochondria (59). Glucose-intolerant individuals have been found to have faster twitch than oxidative muscle fibres (67). The transport of glucose by insulin, however, has been shown to be greater in oxidative skeletal muscle (66). Therefore, individual differences in muscle fibre composition and efficiency may induce a varying weight loss response to an exercise-based intervention.

Another related factor is skeletal muscle lipid droplet size. Intramuscular lipid size has been shown to be decreased with an increase in fitness, a decrease in weight and an increase in insulin sensitivity (68). The positive changes seen in insulin sensitivity were correlated to lipid droplet size. Thus, the lipid amount in muscle appears not to change but the size of the lipid droplets decreases leading to greater insulin sensitivity and heightened oxidation of lipid within the muscle (68).

Fat cell number, size and lipolytic activity (69) may also influence the rate of weight loss. It has been shown that after 20 weeks of exercise men with a large fat cell size lost six times more fat mass (4.4 kg) than men with small fat cell size (70).

Reduced SNS activity may affect weight loss through its influence on food intake, energy expenditure and fat oxidation. For example, low SNS activity predicted weight gain and increased abdominal adipose tissue in Pima Indians (71). Also, variability in energy expenditure was related to variability in sympathetic activity (measured by microneurography) (72). Therefore, low levels of SNS activity may contribute to a decreased metabolic rate causing increases in weight (72). Also, lower compared with higher SNS activity was related to eating more in both animals (73) and human beings (74). Furthermore, low levels of SNS activity were associated with decreased fat oxidation rates (75). Thus, individual differences in SNS activity could explain why some subjects lose or do not lose weight when undertaking an exercise intervention.

Resting metabolic rate is the energy expended when resting in bed after an overnight fast under thermoneutral and stable environmental conditions. Although RMR is correlated with fat-free mass, it varies considerably even when factors such as fat-free body mass, age and gender are taken into account (76). It has been shown that there is a genetic determinant of RMR (77). It also seems that gender, physical training, disease or disorder status, age, muscle metabolism and SNS activity may contribute to RMR intersubject variability. A study examining Pima Indians found that low RMR was a risk factor for weight gain (78). Over a 4-year period, the risk of gaining about 10 kg was about seven times greater in subjects with the lowest RMR.

Also, a high RQ has been shown to predict the inability to lose weight (78–80). High RQ indicates elevated carbohydrate and reduced fat oxidation (78–80). Although the influence of RMR and RQ on fat response to exercise interventions in different populations is yet to be determined, it is reasonable to assume that variations in the ability to oxidize fat may play some role in the weight loss response to exercise.

Low-grade inflammation is associated with risk of metabolic syndrome (81) and cardiovascular disease (82). In obese states, increased C-reactive protein (CRP), interleukin-6 and tumour necrosis factor alpha elicit proinflammatory states that potentially could alter insulin-signalling pathways. Zambon *et al.* (81) have suggested that an increase in CRP, and thus low-grade inflammation, is due to increased central adiposity and IR. Support for this notion has come from Maachi *et al.* (37) who showed that an increase in fat mass correlated with increases in CRP, interleukin-6 and tumour necrosis factor alpha. Systemic inflammation (increased CRP) was also lower in obese but metabolically healthy individuals compared with obese females at risk for disease (83). The interesting finding with this study was that the 'metabolically healthy' possessed significantly less low-grade inflammation and visceral fat than the metabolically unhealthy. Consequently, the recruiting of metabolically healthy and unhealthy obese subjects may contribute to the variations in weight loss associated with exercise programmes.

Individuals with obesity and/or IR have been shown to possess increased resting leptin levels (34) and leptin resistance (84). Adiponectin is an adipokine that promotes insulin sensitivity, fat oxidation and glucose use by skeletal muscle (36). Adiponectin levels are decreased in obese, IR populations (85) and type 2 diabetics (86,87). Leptin and adiponectin may interact together or one may cause a change in the other. Thus, individual differences in leptin/adiponectin levels may induce weight loss variability.

Reduced thyroid levels could also decrease the ability to lose weight. Triiodothyronine, a thyroid hormone, is a metabolic rate stimulator and interacts with catecholamines to increase adipose tissue lipolysis. Triiodothyronine is involved in triglyceride mobilization out of adipose tissue (34). Interestingly, it has been shown that abnormally low thyroid secretion was associated with increased CRP and insulin levels in men and women (88). Thus, low thyroid levels and insensitivity appear to contribute to both low-grade inflammation and IR.

Other mediators of insulin secretion could also play a role in weight loss. For example, inherited and acquired

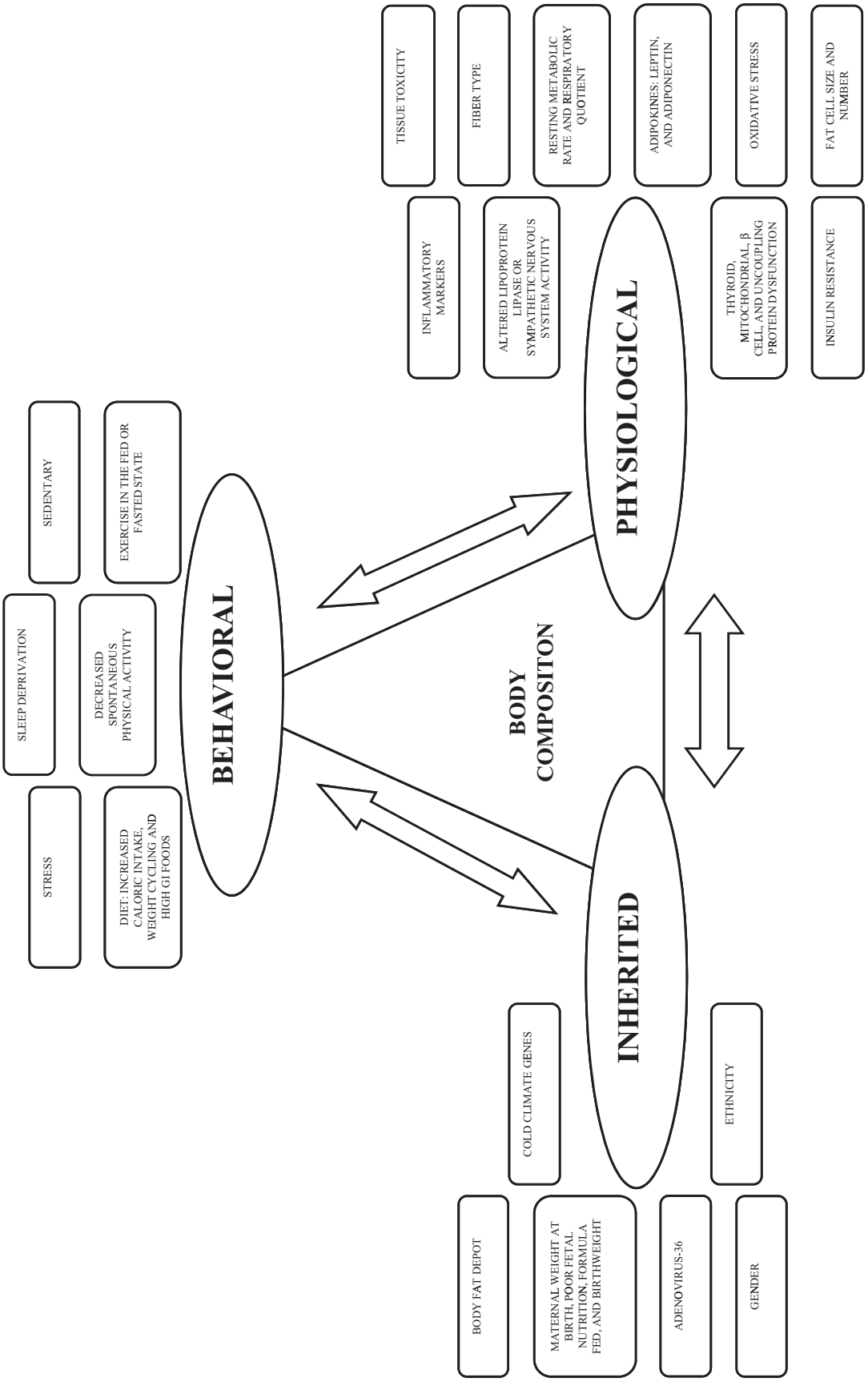

Figure 2 Behavioural, inherited and physiological factors that have the potential to impede exercise-induced weight loss.

β-cell dysfunction could lead to abnormal insulin secretion and disturb the metabolic processes underlying weight loss (59). When blood glucose levels increase, the β-cells typically increase in size and replicate; however, malfunctioning of the β-cells occurs when this process cannot keep up with demand (59). It has been shown that β-cells can fail and die causing a loss of glucose control and the eventual development of obesity, IR and type 2 diabetes (59). Consequently, β-cell dysfunction may be another physiological factor that could directly or indirectly affect the weight loss process.

An accumulation of toxins within tissue could also influence the ability of individuals to lose weight. Pesticides used on fruit and plants or contained in animal feed can be consumed by human beings and lead to increased toxin tissue accumulation. It has been shown that adipose cells provide a storage site for toxins which when stimulated release both fatty acids and stored toxins (89). The release of toxins from adipose tissue has been shown to slow fat loss, which may be another factor that impacts on exercise-induced weight loss. Dioxins and polychlorinated biphenyls may also affect weight loss through their ability to alter thyroid hormone status (90).

Collectively, these factors are summarized in Fig. 2 where it can be seen that a host of behavioural, inherited and physiological variables has the potential to reduce the ability of exercise to decrease weight. These variables may cluster in any individual making it extremely difficult for a person to lose weight. Some variables such as gender and birth weight are unchangeable, whereas others such as carbohydrate ingestion and IR are amendable to intervention.

An important characteristic of weight loss exercise interventions is that variables interact and change over time. For example, it has been shown that individuals engaging in weight loss programmes lose weight at differing rates (91). Thus, some may start to lose weight at the start of a programme and then stabilize, some may reduce weight towards the end, whereas others may lose weight in a linear pattern throughout the programme. Mechanisms underlying these individual patterns are important to establish.

Clinical implications

The majority of variables previously described do not have direct empirical support for their role in impeding weight loss after an exercise programme. However, it appears that there is enough evidence to suggest that their effects should be examined in future exercise weight loss research. Both researchers and weight loss practitioners should be aware that there are individual factors that likely make it impossible for certain groups of individuals to lose weight even though they carry out the exercise programme correctly. For some of these individuals, their goal should be to increase fitness as it has been shown that fit, overweight, aerobically trained females had significantly better metabolic profiles than their overweight, untrained counterparts (83). However, some individual variables (e.g. IR) are amendable to change and their aberrant characteristic may have to be normalized before weight loss through exercise can occur. Individual weight loss response patterns and their underlying mechanisms are important to establish to better understand why some individuals can and others can not lose weight through exercise interventions.

Conflict of Interest Statement

No conflict of interest was declared.

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