





## Using Metabolic Testing to Personalize Behavioral Obesity Treatment

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#### **ABSTRACT**

**Background:** There are large individual differences in weight loss and maintenance. Metabolic testing can provide phenotypical information that can be used to personalize treatment so that people remain in negative energy balance during weight loss and remain in energy balance during maintenance. Behavioral testing can assess the reinforcing value and change in the temporal window related to the personalized diet and exercise program to motivate people to maintain engagement in healthier eating and activity programs.

**Objective:** Provide an expository overview of how metabolic testing can be used to personalize weight control. Ideas about incorporating behavioral economic concepts are also included.

**Methods:** A broad overview of how resting metabolic rate, thermic effect of food and respiratory quotient can be used to improve weight control. Also discussed are behavioral economic principles that can maximize adherence to diet and activity protocols.

**Results:** Research suggests that measuring metabolic rate can be used to set calorie goals for weight loss and maintenance, thermic effect of food to increase energy expenditure, and respiratory quotient to guide macronutrient composition of the diet and maximize fat loss. Developing programs that foster a strong motivation to eat healthier and be active can maximize treatment success.

**Conclusion:** Incorporating metabolic measures can personalize behavioral weight loss programs, and the use of behavioral economic principles can increase the probability of adherence and long-term success in weight control.

#### 1 | Introduction

Obesity is due to positive energy balance, as people who gain excess weight and adiposity consume more calories than they expend [1, 2]. The core principle of obesity treatment is to

change a person from positive to negative energy balance to burn more calories than they are consuming. While this general principle can lead to weight loss, individual differences in response to diet and exercise prescriptions vary widely. These variations may influence the effectiveness of behavioral weight

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loss programs, which combine diet and exercise recommendations with behavioral strategies to foster lasting change [3-6]. In addition, as people lose weight, their resting metabolic rate, which can comprise up to 75% of the total energy expenditure [7], decreases to a greater extent than their weight or fat-free mass [8, 9]. When and if people reach a desired weight, and their metabolic rate has stabilized, they will need a different dietary and activity prescription, which is seldom quantified in terms of what their body needs to maintain weight. Research suggests that women who are experiencing food insecurity may adapt to reduced and unpredictable access to food by metabolic adaptations to store fat during times of food deprivation [10-12], and based on irregular meal patterns, they may become more fuel efficient when metabolizing food leading to lower thermic effect of food [13–16], which may make weight loss challenging. A logical approach may be to use metabolic testing to personalize dietary and activity recommendations through the weight loss and maintenance phases.

Individual differences in energy balance may be even greater for children and adolescents who are growing, and subject to changes in hormones that modify body composition. While a program for a 20- or 40-year-old adult with obesity may be similar, a program for an 8- or 15-year-old may need to differ significantly. An 8-year-old is likely prepubescent and has not yet experienced their growth spurt, whereas a 15-year-old is typically post-pubertal and has completed most of their growth. These developmental differences can affect body composition differently in boys and girls.

The goal of this conceptual paper is to provide an overview of the potential ways in which metabolic testing can be used to personalize weight control programs for adults and youth. In reviewing the literature, no behavioral programs could be identified using metabolic testing to personalize weight control, though research has discussed the potential of this approach for weight control [17, 18].

# 2 | How Much Energy Does a Person Need to Consume to Lose Weight

An important part of energy balance is to know how much energy (calories) an individual is expending to know what their initial calorie intake goal should be. This determination is based primarily on two factors: their resting metabolic rate (RMR) and how many calories they burn during movement/activity. Both can be directly measured. Metabolic rate can be measured using direct or indirect calorimetry, and free-living activity energy expenditure can be estimated using accelerometer activity monitors, portable indirect calorimetry, and doubly labeled water. Activity monitors need to be worn all day to assess both awake and sleep activity expenditures as sleep, resting and activity energy expenditures can differ between people [19-21]. Newer wrist worn accelerometers have been validated [22, 23] and can achieve full day energy expenditure to include day and nighttime wear that waist worn accelerometers cannot easily achieve [24]. Wrist worn accelerometers also can provide information on heart rate, heart rate variability and oxygen

saturation, which can be useful to assess exercise intensity, stress, and health. Activity monitors use algorithms based on regression models to convert activity counts to estimated energy expenditure, which is related to measured energy expenditure [25, 26]. These equations could be further individualized by studying the energy expenditure for that person during physical activity and exercise testing [26–28]. Doubly labeled water represents a more expensive, but accurate, approach to measuring average energy needs over a two-week time span [29–31].

There has been a very limited discussion of metabolic factors in behavioral weight loss literature. We discuss several of these factors below. The digestion of food requires energy, which is generally 10% of the energy a person consumes [32, 33]. This is called the thermic effect of food (TEF), which we will be discussing as a way to personalize diets and integrate this information into the energy balance equation. When discussing the application of these ideas to children, we also discuss the potential for measuring energy requirements for brain development, which has been related to the development of obesity in youth [34, 35].

Of course, energy requirements will change as people lose weight, as a function of the changes in resting metabolic rate, as well as changes in physical activity. The reductions in RMR with weight loss can be quite large, and they will change over time, and may need to be repeatedly measured to ensure the appropriate number of calories are being consumed [8, 9, 36–38]. Given that people will differ on these metabolic changes and weight loss, it may be advisable to schedule testing based on how much weight is lost rather than based on time.

As RMR is decreasing, there may be changes in the rate of weight loss until a weight loss plateau occurs, which may require a new dietary goal, as well as continued weight control therapy, as weight loss and weight maintenance may involve different processes [39, 40]. One change during the maintenance phase may be for someone to increase their activity expenditure to counteract the reductions in metabolic rate that occur with weight loss [39, 40], so that people are not only relying on reduced energy intake to maintain their weight loss. Furthermore, the more energy expenditure, the more calories a person can consume to maintain the same weight loss. There are differences in the types and times of activities in terms of energy expenditure and substrate oxidation, which will be discussed later in the paper. These various components need to be considered together, ideally, when setting energy intake goals for individuals. A research framework moving toward such integration is needed.

## 2.1 | Eating Also Involves Energy Expenditure: The Thermic Effect of Food

Food consumption requires energy to digest and absorb the food consumed. On average, people burn about 10% of the energy they consume in metabolizing the food, so that someone who normally consumes 1800 calories can burn 180 calories to digest the food. This can be quite meaningful in comparison to the

amount of calories someone burns during voluntary exercise [33, 41]. The thermic effect of food (TEF) differs based on the macronutrient content of the food. For example, the thermic effect of energy from fat is between 2% and 5% of the energy consumed, the thermic effect of carbohydrates is between 5% and 15%, while protein takes more energy to break down and digest, with changes in thermic effect of food by 20%–30%. Thus, two people can eat the same number of calories, but based on the macronutrient composition of the diet, will have differences in the TEF and potential differences in the degree of weight loss.

The TEF may also be related to the food pattern and the predictability of food. Research has shown that unpredictable versus predictable meals are associated with differences in the TEF, with higher TEF for those who have regular meal patterns, with lower TEF when food is consumed in irregular patterns [13–16]. A lower TEF is related to fuel efficiency so that people can extract more calories and nutrients from their food [14, 16, 42]. However, this change in TEF based on eating patterns has only been studied in healthy females, and research in this area needs to be extended to men and people with obesity to determine the generalizability of the relationship between eating pattern and changes in the TEF.

The TEF can be measured by assessing changes in metabolic rate over a 2–5-h period after consumption of a standardized food stimulus. There is limited data on changes in the TEF over time [14, 43–45], particularly in relation to changes in metabolic rate as people are losing weight; however, this is an area that needs to be examined to better understand how diet contributes to weight loss. As exercise requires energy, research on exercise and the TEF shows changes in TEF when exercise is engaged in after eating, or when eating is engaged in after exercise [46–48].

The pattern of eating may influence how many calories are expended based on TEF. People can choose to eat regular meals, regular meals plus snacks, or smaller meals throughout the day. Research suggests that consuming regular meals (vs. irregular meals) is associated with greater TEF [49, 50], but increasing the frequency of smaller meals may increase intake, even if the meals are planned to be small, as people with obesity have problems with satiation after eating has begun [51–53]. Preliminary research suggests that the cumulative TEF may be greater for eating several large meals rather then distributing calories over smaller meals [54–56]. To our knowledge, there is no research on the impact of meals plus snacks on the TEF. Obviously, the increase in calories burned from large meals must be balanced with the total energy intake from large meals, considering the macronutrient composition of the meals.

## 2.2 | Exercise and Metabolic Rate

All exercises are not equal in terms of their influence on energy expenditure and weight loss. Extensive lists of energy expenditure for different types of activities have been published to aid in choosing the types of activities that burn the most calories [57, 58]. In general, aerobic exercise will burn more calories than resistance exercise, which can burn more calories per minute than stretching/flexibility exercise [57]. The duration of

these types of exercises can differ greatly, as well as changes in body composition as a function of the different types of exercise. The intensity of the exercise is important, and some people will benefit from high-intensity interval training, in which people alternate very high intensity intervals with rest of low intensity intervals in comparison to longer periods of moderate intensity exercise [59]. Both volume of exercise and intensity are relevant for aerobic exercise, as in general people burn the same number of calories per mile walking or running, but a person can get fit faster if they engage in higher intensity exercise [60, 61].

Resistance exercise can build muscle, which is relevant as the biggest determinant of metabolic rate is lean body mass [62]. The metabolic rate of two people who weigh the same can differ as a function of the percentage of lean body mass [63]. Thus, it may be advantageous to attempt to maintain as much muscle mass as possible during weight loss, which ideally may involve aerobic exercise to burn calories and resistance exercise to maintain muscle mass. It is unrealistic for most people to prevent loss of some muscle mass when losing weight, as people gain muscle mass to carry around their extra weight [64]. As discussed later in this article, the best exercise program is one a person will continue to do, and find reinforcing, but the choice of the preferred exercise program should be informed by basic metabolic research and how their body responds to different types of exercise programs and which programs the person is motivated to do that are metabolically advantageous.

The timing of eating in relation to exercising may be relevant for many people who are attempting to lose weight. The ideal situation would be for someone to exercise at a time when they benefit the most from the energy expenditure due to their activity. There are two considerations. First, research on circadian rhythms of exercise suggests that exercising in the evening after eating may be associated with larger energy expenditure than exercising earlier in the day [65] along with improved insulin sensitivity that can impact energy utilization [66]. Second, the metabolic effects of exercise do not stop when the exercise is ended, but rather the effects on expenditure persist beyond the termination of exercise until the metabolic rate returns to baseline [67]. This will differ based on the intensity and duration of the exercise, but in general, intense exercise is associated with higher energy expenditure, and greater post-exercise energy expenditure [68, 69]. For people with obesity who are sedentary, there may be advantages to breaking exercise into smaller "exercise snacks" to increase their energy expenditure [70], and perhaps take advantage of the repeated post-exercise expenditure effects.

#### 2.3 | Substrate Oxidation

The goal of any diet program is to reduce body weight by burning fat. The energy source that a person uses can be measured by assessing a person's respiratory quotient (RQ). This, in combination with measuring urinary nitrogen and stable isotopes, can be used to establish whether a person is burning fat, protein, or stored carbohydrates [71, 72]. There can be large individual differences in RQ at rest, and changes in RQ and substrate oxidation during food consumption and exercise

[73, 74]. As discussed in the next section on metabolic flexibility, RQ can vary based on dietary intake and activity, and it can increase after eating or exercising. It is optimal for RQ to decline as rapidly as possible to foster fat oxidation. A program that maximizes fat oxidation and minimizes protein oxidation is best for most people.

There may be large differences in RQ for people before they start a weight control program. This is based on part on their usual diet, as people who consume high carbohydrate diets may have a higher RQ and are relatively burning more carbohydrates than someone with a low carbohydrate diet [75–77]. In fact, people who are following a ketogenic diet to help regulate seizure activity can register resting RQs that maximize fat oxidation [78]. In addition, diet can influence the source of energy used during exercise, so that people may burn more carbohydrates or fat based on what they ate before exercising [79, 80].

The pattern of eating can also influence RQ. Research suggests that food insecurity, which is associated with irregular patterns of eating, missing meals and sometimes going hungry, is associated with a higher RQ and greater utilization of carbohydrates than people who are not experiencing food insecurity [11, 12].

Extensive research has shown that a higher RQ is associated with greater weight gain over time [81–84], as people are not using fat as a source of fuel as much as possible. RQ is also predictive of energy intake in ad-libitum choice experiments [85, 86]. This may be due in part to the observation that people with a high RQ can have declining or lower blood glucose levels [71, 87], which is relevant for eating as a reduction in blood glucose is a major signal to the brain for hunger and the need to eat [88–90].

### 2.4 | Metabolic Flexibility

Metabolic flexibility refers to shifts in fuel oxidation when metabolic needs change, such as during a fast, diet, or exercise program [91]. Individual differences in metabolic flexibility to fasting, diet, or exercise programs, determine which type of fuel a person is using and whether they are prioritizing fat when trying to lose weight [92]. While differences in metabolic flexibility exist in response to the same dietary challenge [93, 94], people with obesity may tend to be metabolically inflexible, as they are less able to shift nutrient oxidation [74, 95]. For example, after consumption of carbohydrates, it would be appropriate for a person to shift to carbohydrate oxidation, and have the flexibility to return to fat oxidation, which may be relevant to eating behavior and weight loss [96].

### 3 | Designing the Optimal Diet/Exercise Program

When someone changes aspects of their diet or activity program, their metabolic needs may change, and their diet and exercise should adapt to reflect these changes. This will be discussed in relation to energy needs, substrate oxidation, and the thermic effect of food and activity.

#### 3.1 | Energy Needs

The crux of weight loss is to consume fewer calories than you expend, which will change as you lose weight. Rather than putting everyone on a specific caloric target, such as 1200 or 1500 kcals [97, 98], it is possible to measure their resting metabolic rate (RMR) and physical activity generated energy expenditure, and set their caloric goals based on a set number of calories below that value.

Extensive research has shown that RMR decreases when people lose weight [99-102]. Your body can become more energy efficient (i.e., adaptive thermogenesis) as you consume fewer calories, and this should be taken into account as you lose weight. There will be large individual differences in the rate of weight loss and the changes in RMR, which would dictate different trajectories for energy intake/energy expenditure as weight loss continues. At some point, weight loss may plateau. If this occurs at the point at which the person has attained a desirable weight, the goal needs to be establishing the energy balance needed to maintain this weight, which will be different from the number of calories needed to lose weight. In addition, research suggests that exercise energy expenditure may be more important for weight control during maintenance than during weight loss [103, 104], due in part to lower constraints on dietary intake if the person expends extra energy due to increased physical activity. While the amount of energy expended per minute will be less after a person loses weight, it will be much easier to be active when a person weighs less [105-107]. The timing of when to measure RMR and activity generated expenditure is not known, it could be based either on the number of pounds lost, or on intervals of time, with more testing as the person is losing to understand how reductions in metabolic rate influence weight loss.

The mantra of energy deficit has been to lose a pound a week, you should create a negative energy balance of 500 kcal/day, which is equivalent to 3500 kcal/week. This is based on research showing that burning a pound of fat generates 3500 kcal of energy in a bomb calorimeter [108, 109]. This assumes that all weight loss is fat loss, which is not true. During the initial phases of weight loss, people may lose water weight [110, 111], which will accelerate the weight loss more than if only body fat was decreased. In addition, as weight loss proceeds, some of the weight loss may be due to muscle, not fat loss [112, 113], which would require a different energy deficit.

During the process of weight loss, the energy deficit will change to lose or maintain weight loss, so that the required energy deficit to lose a pound will change. The amount of energy deficit may be greater for people with more body fat, and may be reduced as people shift from loss of body fat to some loss of lean body mass [108]. Since weight loss and maintenance may be associated with differences in energy balance [114], as well

as differences based on the composition of the diet [115], it may be particularly important to assess individual differences in a person's metabolic profile to adapt the diet to their unique needs.

#### 3.2 | Thermic Effect of Food

This will differ for two people based on many factors, the most important of which is the macronutrient distribution in the diet. In general, TEF is highest for protein, next highest for carbohydrates, and the lowest TEF is for dietary fat [116]. Thus, given the same calories, a higher protein diet will lead to the greater TEF than a high fat, low carb diet, and the type of protein may differentially influence the thermic effect of food [117].

It may also be worth considering the pattern of eating and when the different macronutrients are consumed. As noted earlier, several large meals may be preferable to many smaller meals and snacks [54–56]. The time of the day when the foods are consumed may matter. Research suggests that many people are more insulin sensitive earlier in the day, so that carbohydrate intake may have lower effects on blood glucose excursions early in the day [118]. This differential sensitivity may influence the effect of carbohydrates on TEF.

### 3.3 | Substrate Oxidation

The goal for any treatment for obesity is to optimize fat oxidation and maintain or add to muscle. This requires a diet that can shift substrate oxidation from high to lower RQ values. This could be accomplished by consumption of foods that are associated with a lower RQ or maintain a reduced RQ and greater metabolic flexibility during the intervention. This would favor low-carbohydrate, low glycemic index foods. To our knowledge, there is only one study that has done this by providing feedback on daily carbon dioxide production using a hand-held device for people with prediabetes [119]. Results showed significant reductions in body weight and improvements in glycemic control, with 85% of body composition changes being fat loss and only 10% being muscle mass [119]. This study used metabolic information as feedback to initiate and maintain change, as well as to individualize treatment. Metabolic feedback can be used to choose what types of foods should be consumed to maximize fat oxidation, as well as to provide continuing information relative to the energy balance target to continue weight loss or foster weight loss maintenance.

As noted above, metabolic flexibility describes shifts in substrate oxidation in relation to the characteristics of the diet or activity program [92]. Research is needed to understand how diet or exercise can improve metabolic flexibility. This would help individuals, particularly those with higher RQs, adapt to changes in diet and exercise, promoting fat loss while preserving muscle and stored glycogen. Diet can also impact substrate oxidation during exercise. A high-carbohydrate diet will lead to greater RQ and more carbohydrate utilization during exercise [75–77], but also the potential for greater fat storage if the energy intake exceeds energy expenditure.

### 4 | Genetics and Weight Loss

As has been stated, there is a large range of weight changes following a weight loss intervention. It is believed that genetics may play a role in individual differences in weight loss and maintenance, which is supported by an early twin study testing changes in body weight and metabolic efficiency in response to a very low calorie diet [120]. Both the Diet Intervention Examining The Factors Interacting with Treatment Success (DIETFITS) and the Personalized Nutrition Study (POINTS) trials included genetics to assess their influence in weight control [121, 122]. Unfortunately, despite many retrospective genotyping studies demonstrating that single nucleotide polymorphisms (SNPs) provide potential therapeutic targets with weight loss [123], no gene x weight loss interactions were found. Examining how carbohydrate and fat genotypes interact with substrate metabolism during weight loss and maintenance is understudied. Based on baseline RO measurements, a secondary analysis suggested that participants who had increased fat intake decreased their RQ and were more successful in weight loss [124]. Studies should examine how genetics and changes in RQ may potentially maximize weight loss. To our knowledge, no studies have examined the effects of diet and genotype in a pediatric population.

## 4.1 | Genetics, Insulin Resistance and Weight Loss

Research suggests that weight loss is attenuated in patients with type 2 diabetes (T2D [125]), and these individual differences to intensive lifestyle interventions could in part be due to genetic differences. Compared to those without T2D, data suggest that T2D may modestly increase resting metabolic rate [126-130], but decrease insulin-induced thermogenesis [131–133], whereas RQ is increased in those with T2D [73, 134]. Few prospective trials have examined the effects of insulin resistance and genetics on weight loss and weight loss outcomes. The Action for Health in Diabetes (Look AHEAD) trial examined whether an intensive lifestyle intervention would result in decreased cardiovascular morbidity and mortality in participants with T2D [135]. Unfortunately, the trial did not find decreased morbidity and mortality after the intervention [135], but found in secondary analyses that those who successfully lost  $\geq 10\%$  at year 1 (i.e., those with large weight loss) showed a ~20% risk in cardiovascular events [136].

Preventing Overweight Using Novel Dietary Strategies (POUNDS Lost) collected genetic information in the examination of one of four diets that contained either 15% or 25% protein and 20% or 40% fat studied using a factorial design in persons with overweight or obesity [137]. Metabolic testing was used to collect RMR, multiplied by an activity factor to establish total daily energy expenditure, which was reduced by 700 kcal/day. Multiple genomic variants were associated with weight loss [123, 138], and IRS-1, PCSK7, and HNF1A were related to insulin sensitivity. Participants with the IRS-1 variant rs2943641 with the CC (vs. CT+TT) genotype demonstrated the greatest reductions in insulin and HOMA-IR to the higher carbohydrate diet [139]. Also, by selecting a higher dietary carbohydrate intake, persons with a Proprotein convertase subtilisin/kexin type 7 gene (PCSK7) rs236918 G

allele might show greater reductions in fasting insulin levels and HOMA-IR. Hepatocyte nuclear factor  $1\alpha$  (HNF1A) rs7957197 also tended to be associated with improved fasting insulin and insulin resistance in POUNDS Lost. When data from POUNDS Lost trial were combined with the DIRECT trial, another 2-year weight loss trial comparing low-fat and high-fat diet arms, results demonstrated a statistically significant improvement in weight loss and insulin resistance for individuals with the HNF1A rs7957197 T allele when provided a hypocaloric and high-fat diet [140]. This suggests that an interaction between genetics and diet composition may be relevant for weight control for these participants. Research is needed to further assess how genetics may impact the effect of increased fat intake on reduced RQ [124], particularly in patients with insulin resistance and high RQ [73, 134], thus potentially increasing fat oxidation and weight loss for these patients.

### 5 | Sex Differences

Differences in energy and metabolism may exist between the sexes. Both sexes have high rates of obesity; however, females enroll in weight loss trials more often [141, 142]. Men tend to lose more weight than women (in terms of kg) [143, 144]. Men also have higher resting metabolic rates than women [145, 146]. While one study demonstrated women having a higher TEF than men [147], other studies have not shown sex influences TEF [33, 148]. Women are thought to have lower RQ values suggesting higher fat (vs. carbohydrate) oxidation rates especially during exercise [149, 150].

## 6 | Importance of Collecting Metabolic Information for Children and Adolescents

The previous information on the importance of using metabolic information to treat obesity is relevant for everyone, but it may be even more relevant for children and adolescents who are still growing with rapid changes in body composition. Children grow at different rates, and have different trajectories of body composition as they grow [151]. The adiposity rebound is a classic example of individual differences in body composition [152]. When children are very young, they show rapid changes in body mass index (BMI) and body fat, which reaches a nadir at about age 6, when growth is faster than girth. At around age 6, adiposity rebound occurs, which shows a greater increase in adiposity than growth, leading to increases in BMI [153, 154]. There are wide individual differences when the adiposity rebound occurs, and the timing of the adiposity rebound predicts body fatness during adolescence. Thus, the differential trajectories of increases in fatness versus height predict later obesity [155]. This suggests that individual differences in the trajectories of body composition across children are important to take into account when designing obesity treatment. Advances in electronic health records that allow for the long-term tracking of weight, height, and BMI in growing children can enable such treatment possibilities.

There are reliable differences between children when they reach maximal height velocity, and when it is easier to lose weight relative to height gain. From birth, children continue to show incremental growth, which reaches a peak during maximal height velocity and then slows down until the final adult height is reached [156]. Given that BMI is based on the relationship of weight to height, it will be easier to modify zBMI when children are growing then when they are fully grown. We have shown that less absolute weight loss is needed relative to height gain when children are still growing than when they are older and growth is slower [157]. We have also shown that the commonly observed reduction in RMR during weight loss is not observed in children who are still growing, as their BMI change is due both to reductions in weight and increases in height [158]. In other words, children can show a reduction in percent overweight without a reduction in RMR [158, 159], which is not typically seen in adults [160].

There are also reliable changes in body fatness after puberty in girls versus boys, as girls show larger increases in body fat to prepare for gestation, while boys are more likely to show increase in lean body mass [161, 162]. These differences would alter the metabolic processing of food and the dietary requirements needed to lose weight [163]. The differences in development between boys and girls may also influence metabolic processes relevant to body weight. It is well known that girls enter puberty earlier than boys [164, 165], and hormonal changes during puberty may influence metabolic processes that regulate body weight differently for the same aged boy and girl, and even the same aged boy and girl who weigh the same [166, 167]. The differential trajectories in body fatness and puberty may be very important for weight loss and maintenance and it may be more challenging for girls during specific developmental stages to lose and maintain weight based on their metabolic profiles.

In addition, there can be considerable energy needs for youth brain development that are not generally considered in energy balance, as it is very complicated to measure, but is worthwhile considering for future research [34, 35, 168]. Research suggests that the developing brain can use up to 2/3 of RMR in the period before the adiposity rebound, and brain requirements for energy are related to weight gain from infancy to puberty [35]. This is an area that should be addressed in future studies of the development and treatment of obesity in young children through adolescence.

It is important to acknowledge that older people with obesity may also have unique metabolic profiles due to changes in body composition and metabolic changes, including sarcopenia, and may benefit from metabolic testing to personalize their weight control programs. A complete discussion of the benefits of weight control for older adults, and how to personalize weight control for older adults is important but outside the scope of this review.

## 7 | The Potential of Portable Metabolic Measures for Clinical Weight Control

There are different methods to measure metabolic processes based on the purpose of the measurement. Doubly labeled water is ideal for measuring free living energy expenditure over two weeks, metabolic chambers are ideal for short-term metabolic

testing in which people live for hours to days, while metabolic carts are useful to collect oxygen and carbon dioxide at rest, to measure thermic effects of food or during controlled exercise. These different methods have many advantages in measurement, but they require specialized equipment that may not be available to clinical weight control programs, and they have limitations in their use for collecting metabolic information. For example, doubly labeled water provides an elegant way to assess free living energy requirements, but is expensive, not easily available, and requires a two week period to collect accurate data [169]. Metabolic chambers may not allow people to assume their usual activity, and metabolic carts limit opportunities for activity to activities that can be measured while attached to the metabolic cart. In addition, each of these devices require considerable expertise to implement and analyze. Thus, there is a need for portable metabolic equipment that is easy to use and can be adapted for clinical behavioral weight loss.

There has been the development of several easier to use devices that can be used to assess a person's unique metabolic signature to potentially personalize obesity treatment. For example, several portable devices that measure metabolic rate have been validated and could be used in clinical weight control programs [170-172]. These new devices can be used outside the traditional clinical setting for self-monitoring of metabolic measures that can enhance treatment efforts. Continuous glucose monitoring, which is now available for people without diabetes and without a prescription, can provide information on the glycemic effects of a diet, which can provide information that can help modify a person's respiratory quotient and substrate oxidation. A good example of a portable device that can be used to selfmonitor carbon dioxide production is the Lumen, which has been validated against metabolic cart measures and tested in a study to improve weight loss and glycemic control in people with prediabetes [119, 173, 174]. These easy to use devices, which can provide information in a controlled office/laboratory setting as well as in the natural environment, may advance the use of metabolic measures in behavioral weight control programs.

There has been no reported use of metabolic measurement to optimize behavioral weight control. There are several potential reasons for this. First, the idea of personalized behavioral weight control is relatively new, and there have been few reports of personalized behavioral treatment programs [175, 176], and none we could identify that utilized metabolic measures. Second, historically, measurement of these metabolic processes has required access to and expertise in metabolic measures, which may not be in the training or usual tool kit of behaviorally oriented weight control specialists. However, as we note below, there are many opportunities to use metabolic measures to individualize and improve short- and long-term effects of behavioral weight control programs.

## 8 | Integrating Behavioral Economic Behavior Change Theory and Metabolic Research

The use of metabolic information to modify energy balance, lose and maintain weight loss assumes a lot of behavior changes and maintenance of behavior change. A long history of research suggests that long-term behavior change is challenging [177, 178]. This is due to many reasons, but we will highlight several reasons that can be assessed and treatments altered to minimize their effects on behavior change.

A logical first step is that the behaviors that are recommended for change should be reinforcing so that people are motivated to engage in those behaviors. Dietary change can be challenging as food is a powerful primary reinforcer, and many high energydense (HED) foods that are related to obesity are highly reinforcing [179, 180]. Food reinforcement is both cross-sectionally [181, 182] and prospectively positively related to obesity [183, 184]. Food reinforcement is also positively related to energy intake using a variety of approaches to measure dietary intake [185-187]. The typical dietary approach attempts to reduce intake of high energy-dense foods and replace them with healthier food, but these foods may not be as reinforcing or motivating to eat [188, 189]. This can lead to deprivation in reinforcers, which can make intake of those high energy-dense foods even more reinforcing [190], which can lead to an increase in craving to consume those foods. The alternative foods in the new diet are chosen for their nutritional characteristics, not for their reinforcing value. Imagine how much easier it would be for people to stick to a diet if highly reinforcing high energydense foods were replaced with highly reinforcing low energydense (LED) foods. These food items could be selected based upon their thermic effect food profile and substrate metabolism for the individual. People would not necessarily feel deprived and crave the former foods they consumed that caused them to become obese while matching their energy and metabolism profile.

In behavioral choice theory, the alternatives to HED foods need not be highly reinforcing foods, but particularly in the case of snacks, highly reinforcing non-food alternatives. We have demonstrated that non-food alternatives can serve as substitutes for highly reinforcing HED foods [191]. A combination of highly reinforcing, LED foods and highly reinforcing behavioral substitutes may make it easier to reduce access of previous HED foods that led to the obesity. It is important to recognize that the reinforcing value of all commodities can change with their repeated consumption. An important aspect of reinforcing value is choice. It is important that people choose behaviors to engage in, as forcing people to engage in a behavior will not make it reinforcing. Animal research has shown that the reinforcing value of alcohol and opiates is based on choice, as these commodities do not develop as reinforcers if the animals are forced to consume these [192]. Likewise, children who are provided choices of physical activities are more active than children who have no choice, even when the single available activity was the child's favorite [193]. Similar data are available for adults who are provided prescriptive exercise plans versus those who are provided free access to the exercise equipment [194]. This is an issue since many dietary and activity programs are highly prescriptive, and do not provide choice.

It may also be important to shape a new behavior. Rather than expecting someone who eats an unhealthy diet to quickly adopt a healthier diet, it may be relevant to gradually adopt healthier dietary habits. This is certainly the case with exercise, as a

sedentary person is not expected to run a marathon but gradually build up their endurance. This is not the usual approach for modifying diet, but perhaps using shaping to gradually approximate the final goal may be an approach that can foster long-range health behaviors.

It may also be worthwhile to consider the principle of reinforcer sensitization when attempting to shift dietary behaviors. When introducing a new food, research has shown that repeated consumption of HED foods can lead to reinforcer sensitization, or an increase in reinforcing value [195]. Research has shown a relationship between obesity and sensitization of HED foods, and sensitizers are more likely to gain weight than nonsensitizers [196]. To date, research has not shown LED foods sensitize [196, 197], though research has not sampled a wide variety of LED foods to see which might become more motivating to eat with repeated consumption. On the other hand, research has shown that repeated consumption of a food can lead to satiation, or a reduction in the desire to consume that food [198]. This suggests that the ability of an LED food to substitute for an HED food may change over time, and new LED foods may need to be introduced based on patterns of satiation.

Research is needed on sensitization of exercise behavior. Exercise can be highly reinforcing for some people but not for the average person with obesity who leads a sedentary lifestyle. Investigators have begun to assess the impact of different exercise formats to improve the reinforcing value of being active with the goal of sensitizing the reinforcing value of being physically active [199, 200].

Another important aspect of program adherence is a prospective mindset. For a person to be successful in weight loss, they need to defer immediate gratification associated with HED and highly palatable foods to obtain the later gratification of weight loss in the future. This challenge can be captured by the behavioral economic construct of delay discounting, in which people are faced with the choice of small but immediate reinforcers versus larger but delayed reinforcers. This can be a challenge as research has shown obesity is strongly related to high discounting of the future, and a strong preference for HED, palatable foods that activate brain reward networks and provide immediate reinforcement [201]. The combination of high reinforcing value of food and high discounting of the future defines reinforcer pathology, which has been related to obesity [201-203], to greater energy intake [204, 205], and to worse outcomes in behavioral treatment programs [206, 207]. This suggests that programs that teach people prospective thinking, such as episodic future thinking [208], can teach people to make decisions that foster reaching long-term goals rather than immediate gratification, and may be very useful in facilitating long-term behavior change.

Both reinforcing value [209] and delay discounting [210] can be assessed throughout treatment using brief assessment tools, and interventions to take into account how reinforcing certain foods are, as well as how much people discount the future can be modified over time, just as dietary and exercise programs can be adjusted based on metabolic testing. Based on the fact that obesity is a transgenerational process, it may be important to test reinforcing value and delay discounting in parents with

obesity and their children with obesity as a way to use family-based treatment approaches to impact obesity across generations within a family [211].

We believe it is time to combine evidence-based principles of behavior change with metabolic measures to personalize weight loss and weight maintenance. Metabolic testing in combination with behavioral treatment can lead to novel approaches to personalized weight regulation.

### 9 | Summary and Conclusions

We have reviewed how accounting for individual differences in RMR, TEF, and RQ can help tailor personalized strategies for weight loss and long-term weight maintenance, rather than assuming everyone will benefit from the same diet or exercise program, which has been shown to not be true [3-6]. We hypothesize that using RMR plus energy expenditure due to physical activity, in combination with a diet that fosters higher TEF and lower RQ that is associated with burning rather than storing fat, may be essential to optimal weight control for that person. We recognize that these parameters should be regularly assessed and that energy balance behaviors should be adapted to changes in metabolic parameters. We discussed why this is important for weight loss in growing children and adolescents, and how behavioral principles related to choice and reinforcer pathology can facilitate short- and long-term adherence to achieve successful weight regulation and can lead to novel applications if measured alongside with metabolic parameters. Combining these principles into a comprehensive approach to weight control may lead to new approaches to helping people achieve and maintain a healthier weight and reduce diseases associated with excess weight and obesity.

#### **Author Contributions**

L.H.E. was responsible for the idea for the paper, L.H.E. and J.W.A. developed ideas about metabolic testing and obesity treatment, and all authors contributed feedback and revisions of the manuscript.

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### **Conflicts of Interest**

The authors declare no conflicts of interest.

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