

Metabolic Determinants of Weight Gain in Humans

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Study Importance Questions

- What major reviews have already been published on this subject?

Many reviews have been published on the metabolic predictors of weight change in humans. However, this review responds to recent studies profiling specific phenotypes of individual human metabolism and not yet addressed in previous reviews.

- What does your study add?

This review focuses on recent findings demonstrating the existence of human metabolic phenotypes that characterize individual susceptibility to weight gain. Additionally, it treats the concepts of adaptive thermogenesis and “energy sensing” as potential metabolic determinants of weight change in humans.

Abstract

One of the fundamental challenges in obesity research is to identify subjects prone to gain weight so that obesity and its comorbidities can be promptly prevented or treated. The principles of thermodynamics as applied to human body energetics demonstrate that susceptibility to weight gain varies among individuals as a result of inter-individual differences in energy expenditure and energy intake, two factors that counterbalance one another and that together determine daily energy balance and, ultimately, bodyweight change. This review focuses on the variability among individuals in human metabolism that determines weight change. Conflicting results have been reported about the role of inter-individual differences in energy metabolism during energy balance in relation to future weight change. However, recent studies show that metabolic responses to acute, short-term dietary interventions that create energy imbalance, such as low-protein overfeeding or fasting for 24 hours, may reveal the underlying metabolic phenotype that determines the degree of resistance to diet-induced weight loss or the propensity to spontaneous weight gain over time. Metabolically “thrifty” individuals, characterized by a predilection for saving energy in settings of undernutrition and dietary protein restriction, display a minimal increase in plasma Fibroblast Growth Factor 21 (FGF21) concentrations in response to a low-protein overfeeding diet and tend to gain more weight over time as compared to metabolically “spendthrift” individuals. Similarly, inter-individual variability in the causal relationship between energy expenditure and energy intake (“energy sensing”) and in the metabolic response to cold exposure (e.g., brown adipose tissue activation) seems to some extent to be indicative of individual propensity to weight gain. Thus, an increased understanding and the clinical characterization of phenotypic differences in energy metabolism among individuals (metabolic profile) may lead to new strategies to prevent weight gain or improve weight loss interventions

by targeted therapies on the basis of metabolic phenotype and susceptibility to obesity in individual persons.

Introduction

Concordant with the laws of thermodynamics and the preservation of energy, the human body is in a state of energy balance when energy input (nutrient intake) continually equals energy output (energy expenditure and energy waste), thus allowing for the maintenance of bodyweight mass. Accordingly, even small but persistent deviations from energy balance, which may arise from altered energy expenditure or energy intake and which lead to sustained positive or negative energy balance states, must result in changes in body energy stores (mainly, adipose tissue) and consequent changes in body weight over time. Variability in weight change across the human population however, is extremely diverse. Some individuals are more prone to gain or lose considerable weight, even in shorter periods of time, than others who can more easily maintain their body weight even over the course of an entire lifetime. Accordingly, natural history studies have reported broad ranges of change in body weight over time in free-living conditions ([1](#), [2](#), [3](#), [4](#)). Notably, in a recent longitudinal study that included healthy subjects who were weight stable at admission ([5](#)), the standard deviation (a quantitative measure of inter-individual variability) of free-living weight change after six months was 4.7 kg with an average weight change of only 0.8 kg ([1](#)). Such broad inter-individual variability in weight change among humans implies that differences in underlying metabolism and/or energy intake among individuals are responsible for subject-specific propensity to weight gain/loss. This review takes into account the role of inter-individual variability in energy metabolism in relation to human weight change. First, it focuses on measures of energy metabolism obtained during conditions of energy balance. Second, it discusses short-term adaptation in energy metabolism (i.e., adaptive thermogenesis) as a response to acute changes in energy intake (fasting or overfeeding). Third, it briefly discusses other metabolic predictors of weight change such as the metabolic response to cold exposure and

the activation of brown adipose tissue. Finally, it discusses the putative “energy-sensing” link between energy metabolism and energy intake, which may determine weight change.

1) Measures of energy metabolism obtained during energy balance

The study of energy metabolism in humans relies on the precise measurement of energy expenditure (EE) as well as of substrate oxidation as quantified by the non-protein respiratory quotient (RQ), an index of the ratio of carbohydrate to fat oxidation. Daily EE and RQ can both be continuously and precisely measured via indirect calorimetry methods (6, 7). The main determinants of 24-h EE include body size and composition, but also to a lesser degree, age, gender, ethnicity, glucose tolerance (8, 9, 10, 11, 12, 13, 14), and familial membership (heritability of 24-h EE=0.52 (15)) as reflections of genetic variability (15, 16, 17, 18, 19). Taken together, physiologic determinants explain more than 80% of inter-individual variance in 24-h EE in a given population (9). Given the high accuracy and reproducibility of indirect calorimetry methods (variance of methodologies <5%) (8), this leaves the remaining 10-15% variance in EE as a potential predictor of future weight change.

Several prospective studies have been carried out with the goal of assessing the causal association between future weight change and variability in energy metabolism as measured in conditions of near energy balance. The results of these longitudinal studies are extremely variable. Some showed an inverse relationship, that is, a relatively low EE (i.e., relative to body size and composition) associated with weight gain. For example, in American Indian adult populations with high prevalence of obesity, a relatively low EE (i.e., low 24-h EE and low resting metabolic rate, RMR) is a predictor of long-term weight gain (4, 17, 19, 20). Similar results were obtained in studies of infants (21) and children (22, 23), as well as in another study in adult whites (24) in which reduced RMR longitudinally predicts increased adiposity over time.

By contrast, other studies reported a positive association. For example, in lean Nigerian populations, a relatively high RMR predicts an increase in weight over time (25); similar results were found in prepubescent girls (26) (although RMR was not adjusted for body size in this study). Several other studies instead have shown no association between RMR and weight change in humans (27, 28, 29, 30). Results for RQ measured during energy balance are similarly mixed. A relatively higher RQ has been shown to be predictive of weight gain in some studies (19, 27, 31), while others failed to demonstrate an association between inter-individual variability in RQ during energy balance and future weight change (28, 32).

The reasons for these mixed results are unclear. They may be due to population-specific characteristics comprising both genetic and environmental factors, different pre-test conditions, varying durations of measurement (e.g., ranging from 20-30 minutes to several days), or disparate methods for assessing energy metabolism (e.g. ventilated hood system vs. whole-room indirect calorimeters vs. doubly labeled water). Such mixed results may also be due to different methods for adjusting energy metabolism for body size (e.g., normalization to lean mass vs. statistical regression methods) and the inclusion of different covariates, unequal sample sizes across studies (e.g., ranging from few subjects to hundreds or thousands of subjects), or differences in the follow-up time to assess free-living weight change. Such differing results prompt contrasting interpretations in light of the principles of energy balance. On the one hand, a small but persistent positive energy balance as a result of reduced EE can lead to weight gain over a longer period of time (e.g., months or years) even as energy intake remains consistent and weight does not change substantially over short periods of time (e.g., days). On the other hand, even as the laws of thermodynamics state that negative energy balance may be a result of increased EE, studies have nevertheless somewhat counterintuitively shown that increased EE

results in weight gain. Given that weight gain can only happen under conditions of positive rather than negative energy balance, it must be that positive energy balance results from increased energy intake to the degree that it overcomes EE. Thus, in a context of increased EE, weight gain could be the result of an effort to restore energy equilibrium (i.e., energy sensing) through over-compensatory increases in energy intake, as will be discussed in further detail in Section 4 below.

In summary, the question of the role of energy metabolism on weight change remains controversial and the inter-individual variability in EE measures during energy balance does not seem to explain broad differences in weight change as observed among individuals in the current obesogenic environment. Moreover, the degree to which these metabolic measures predict future weight change (regardless of directionality) is very limited as it explains little (<5%) of the inter-individual variance in weight change.

2) Measures of energy metabolism in response to changes in energy intake

Based on the principles of energy homeostasis, weight gain can only be achieved with a persistent state of positive energy balance, e.g. overeating sustained to a degree that constantly exceeds daily EE (33). Accordingly, it is reasonable that assessments of EE in a context of positive energy balance would be more informative of the etiology of weight gain than are measurements done in settings of energy balance and weight maintenance (34). Indeed, the disruption of energy balance through acute, short-term changes in energy intake and the assessment of the resulting metabolic response to such dietary interventions may reveal the subject-specific capacity to promptly increase/decrease the metabolic rate in response to excess/limitation of ingested nutrients. In other words, it is possible that EE responses to acute change in energy intake (such as during 24-h overfeeding or fasting) can quantify the different

susceptibilities to long-term weight change observed across individuals (35, 36), because they may be informative of an individual's propensity to weight loss/gain achieved by sustained, long-term dietary regimens. For instance, short-term metabolic assessment to 24-h fasting (as an extreme dietary intervention that leads to maximum daily energy deficit) may quantify a given individual's ability to adapt his/her metabolism (metabolic "thriftiness") to a less extreme but sustained low-calorie diet that achieves an energy deficit and, thus, weight loss over time.

Such inter-individual differences in the short-term EE response to overfeeding or fasting must arise from diet-induced changes in each component of daily EE (37, 38): sleeping EE; "awake and fed" thermogenesis (39), or the thermic effect of food and the cost of being awake; and the energy cost of physical activity. In particular, the thermic effect of food represents a direct link between energy intake and EE insofar as it quantifies the increase in resting EE after food consumption (40, 41, 42). It may thus constitute the daily EE component that promptly changes and best characterizes the subject-specific metabolic adaptation to acute, short-term changes in energy intake (e.g., overfeeding or fasting for 24 hours), which may be indicative of a propensity to weight gain. On average, the thermic effect of food accounts for approximately 10% of total ingested calories and, in conditions of near energy balance where energy intake is almost equal to EE, it also represents an average 10% of 24-h EE (43) with a broad inter-individual variability ranging from 1% to 20% (36). However, the extent of the increase in 24-h EE during overfeeding depends on the total caloric content (44, 45) and on the macronutrient composition (36) of the diet, ranging from an approximately 3%-increase in the case of a low-protein high-fat diet to 14% with a high-carbohydrate normal-protein overfeeding diet (46), with both overfeeding diets representing twice the daily energy needs. Despite limited increases in 24-h EE (average increase ~10%) in response to extreme changes in energy intake during this overfeeding diet (=200% of

eucaloric needs), the EE response to 24 hours overfeeding show a large inter-individual variability with standard deviation values for the increases in 24-h EE of about 5% (46).

Overfeeding studies suggest that there is substantial inter-individual variation in the energy cost of weight gain, particularly in response to macronutrient-unbalanced diets (47, 48). In fact, overfeeding diets with low-protein (<10%) content have been shown to most effectively uncover the individual propensity to weight gain (2, 47, 49), presumably due to the energy required to maintain lean body mass (50, 51). In a pilot study aimed at investigating how the metabolic responses to short-term (i.e., 48 hours) overfeeding and fasting relate to one another in individuals, it was confirmed that humans have the ability to respond to overfeeding and fasting with an increase and decrease in EE, respectively, and that these adaptive changes to the perturbation of energy balance vary considerably among individuals (52). More importantly, this study also revealed that individuals with the greatest increase in 24-h EE during overfeeding tend also to have the smallest decrease in 24-h EE while fasting (proposed metabolic “spendthrift” phenotype), and vice versa (proposed metabolic “thrifty” phenotype) (34, 52) (Figure 1). These two human metabolic phenotypes as revealed through acute, short-term dietary manipulation consist of a more metabolically efficient, or “thrifty” phenotype that can save energy both in conditions of energy surplus (overfeeding) or deficit (fasting), and a more “spendthrift” phenotype that maintains higher EE in settings of energy deficiency (such as fasting) while also capable of expending more energy settings of energy surplus. It must be noted that the human metabolic phenotype is defined over a continuum. Namely, it is quantified by the extent of change in 24-h EE during fasting or overfeeding from energy balance conditions. That is, the more 24-h EE decreases with fasting, or the less 24-h EE increases with overfeeding, the more metabolically thrifty is the individual. Nevertheless, and for the sake of clarity, in this review

individuals are exclusively classified as either metabolically thrifty or spendthrift (the two extremes of the spectrum) based on an arbitrary cutoff such as the median value of the decrease in 24-h EE during fasting, as recently done in studies that identified these phenotypes ([53](#), [54](#)). For instance, metabolic thrifty individuals are those subjects who decrease their 24-h EE during fasting by a degree more than the median value calculated in the entire cohort of a study.

Based on the characteristics of these two metabolic phenotypes, it is possible that individuals with different energy profiles (thrifty vs. spendthrift) would show differences in their rates of weight change. Indeed, two recent studies have provided such evidence, namely that these metabolic phenotypes can characterize an individual's propensity to weight gain or weight loss. The first study (ClinicalTrials.gov #NCT00523627) ([2](#)), which included healthy subjects with a wide range of body size, confirmed previous findings that EE responses to fasting and overfeeding (particularly, low-protein overfeeding) are correlated. More importantly, this study further confirmed for the first time that metabolically thrifty individuals are more prone to gain weight in free-living conditions as compared to metabolically spendthrift individuals ([2](#)). Specifically, a larger decrease in 24-h EE during fasting (Person correlation coefficient: $R=-0.35$, Table 1) and a smaller increase in 24-h EE during 200% low-protein overfeeding ($R=-0.55$, Table 1), both of which are features of the metabolic thrifty phenotype, predicted 6-month weight gain in free-living conditions ([2](#)). The second study (ClinicalTrials.gov #NCT00687115) ([53](#)), which included overweight subjects who underwent six weeks of 50% caloric restriction showed once again that metabolically thrifty individuals who had a greater reduction in EE during 24-h fasting before beginning the caloric restriction period, lost lesser amounts of weight as compared to metabolically spendthrift subjects who instead lost greater amounts of weight during 6-week caloric restriction ($R=-0.84$, Table 1) ([53](#)). Further, in a

second arm of this clinical trial that included only lean healthy men, metabolically spendthrift individuals who have smaller decreases in 24-h EE during fasting demonstrated lower rates of weight and fat mass gains during six weeks of 150% overfeeding a low-protein diet ($R=-0.84$, Table 1) ([55](#)).

Taken together, these two independent studies provide compelling evidence that different human metabolic phenotypes exist in both lean and overweight individuals and that they may explain part of the inter-individual variability in weight change. The physiologic determinants underlying these metabolic phenotypes are not known but may include hormonal mediators that might explain metabolic differences in response to fasting and overfeeding conditions, particularly low-protein overfeeding. In rodents, low-protein overfeeding leads to an increase in EE that is mediated by Fibroblast Growth Factor 21 (FGF21) ([56](#), [57](#), [58](#), [59](#)), thus indicating that this hormone may have a role in the metabolic response to low-protein overfeeding in humans as well. Indeed, in the previously mentioned study showing that metabolically thrifty individuals had a tendency to gain more weight in free-living conditions ([2](#)), circulating FGF21 concentrations acutely and consistently increased approximately threefold only after two different overfeeding diets with low-protein content (one high in carbohydrate, and one high in fat), while decreasing after 24-h fasting and other overfeeding diets with either normal or high protein content ([1](#)). Importantly, the increases in plasma FGF21 concentration following both low-protein overfeeding diets were associated with concomitant changes in 24-h EE, where a greater increase in FGF21 concentration was associated with a greater increase in EE during those diets ([1](#)). Further, the extent of the increase in FGF21 concentration following low-protein overfeeding was associated with free-living weight change after 6 months ([1](#)), indicating that an impaired ability to increase plasma FGF21 concentration in response to low-protein overfeeding

is one of the hormonal features of the thrifty metabolic phenotype inclined to gain weight over time. The mechanisms by which FGF21 may increase EE in humans are not known, but one may include increased glucose uptake in peripheral tissues. This would occur as FGF21 stimulates glucose uptake in murine 3T3-L1 adipocytes in an insulin-independent manner (60) and possibly due to transcriptional activation of the *GLUT1* gene (61). Additional evidence for the role of FGF21 was found in a caloric restriction study, where a change in FGF21 concentration, following six weeks of dietary restriction, was associated with both a change in the *UCP2* gene expression level in skeletal muscle and diet-induced weight loss (62). This suggests that FGF21 may regulate energy production in skeletal muscle by exerting an effect on mitochondrial ATP production, thus potentially influencing the metabolic response to caloric restriction and ultimately determining the degree of weight loss.

So-called *metabolic flexibility* (63, 64, 65, 66, 67) – or the individualized ability to switch substrate for oxidation in response to changes in energy intake to match macronutrient availability in the diet – was also tested as a metabolic predictor of weight change. In particular, an impaired ability to increase fat oxidation in response to dietary fats in settings of positive energy balance such as during overfeeding leads to greater weight gain as fat balance (rather than carbohydrate or protein balance) is the main determinant of total daily energy balance (68). Excess ingested fats that are not oxidized are stored in the body as adipose tissue (67), ultimately leading to weight gain. In a recent study, reduced fat oxidation during sleep following 140% overfeeding a balanced diet for three days predicted greater free-living weight gain after five years (3). Similarly, a failure to increase fat oxidation during one day of 200% overfeeding a diet with 60% calories from fats also predicted weight gain over the period of a year (manuscript in preparation)(69), indicating that impaired metabolic flexibility (or inflexibility) in the context of

a high-fat overfeeding diet is a metabolic predictor of weight gain. Although the use of such extreme and unusual diets given over 24/56-hour periods may not be reflective of real-life settings over longer periods of time, such metabolic “stress tests” may well allow for the evaluation of metabolic flexibility in different individuals and their varying capacities to adjust to daily changes in the extent and composition of diet in free-living conditions.

In summary, all these results for both EE responses and metabolic flexibility strongly suggest that short-term perturbation of energy balance by acute overfeeding or fasting may uncover the underlying metabolic phenotype of single individuals and proactively identify subjects who are more at risk of weight gain.

3) Other measures of adaptive thermogenesis

In the context of daily EE compartmentalization, thermogenesis is defined as the production and release of heat by the human body that reflects the changes in EE in response to a broad range of stimuli that include not only food consumption (i.e., diet-induced thermogenesis or thermic effect of food), but also heat or cold exposure (i.e., cold-induced thermogenesis), voluntary (e.g., exercise-associated thermogenesis) or non-voluntary (non-exercise related thermogenesis) physical work, psychological and emotional states such as stress, anxiety or fear, and all pharmacological treatments that produce the same physiological response to such stimuli.

Among all the forms of human thermogenesis, cold-induced thermogenesis has recently gained the most ground due to its putative role in human energy metabolism ([70](#), [71](#)) via brown adipose tissue activation as assessed by hybrid positron emission tomography and computed tomography ([71](#), [72](#), [73](#), [74](#), [75](#)). Interestingly, one study including 13 healthy men demonstrated that the metabolic response of one individual to 160% overfeeding positively correlates with the metabolic response to mild cold (16°C) ([76](#)), such that individuals who had a greater increase in

EE after overfeeding also showed a greater increase in EE during cold exposure. This relationship between metabolic responses to feeding and to cold exposure was otherwise confirmed in another study including 21 healthy men (77). Specifically, subjects with a higher cold-induced activation of brown adipose tissue (thus, presumably, higher cold-induced thermogenesis) had a higher diet-induced thermogenesis during energy balance in conditions of thermoneutrality as compared to those individuals with less activation of brown adipose tissue who instead had a lower diet-induced thermogenesis during eucaloric feeding (77). Taken together, these two studies suggest a potential link between cold-induced thermogenesis mediated by brown adipose tissue activation and diet-induced thermogenesis which, as discussed above, could reveal an individual's propensity to gain weight. Supportive of this hypothesis is a small study including 16 healthy individuals that showed the degree of brown adipose tissue activation after cold exposure was inversely associated with the change in body fat mass after six months in free-living conditions (54), such that subjects with a lesser degree of cold-induced activation of brown adipose tissue had an increase in fat mass (54). Yet, another study of 9 healthy men instead reported no association between diet-induced thermogenesis during 150% overfeeding and cold-induced thermogenesis (78). Although the impact of brown adipose tissue on daily EE is limited (79), cold exposure assessments occurring on one occasion (much like the aforementioned metabolic assessments to acute, short-term dietary interventions) may identify the metabolic phenotype of an individual. Indeed, the extent of adaptive thermogenesis to cold temperatures may be reflective of the overall metabolic phenotype of an individual, which in turn is indicative of his/her propensity to gain weight. Yet, given the small sample size of studies assessing brown adipose tissue activation and EE, further research is warranted to clarify the role

and the underlying physiologic mechanisms of cold-induced thermogenesis on energy balance and bodyweight regulation.

4) Energy Sensing as a Predictor of Human Weight Change

In addition to individual-specific responses in energy metabolism to various metabolic stimuli (fasting, over-eating, and cold exposure), another possible determinant in human weight change might be located in the relationship between EE and energy intake, which act together in determining daily energy balance ([33](#), [80](#), [81](#), [82](#), [83](#), [84](#)). Supportive of this hypothesis are several recent independent studies that consistently report a positive relationship between energy intake and EE ([80](#), [83](#), [85](#), [86](#), [87](#), [88](#), [89](#)), suggesting that EE may drive energy intake. However, the link between energy intake and EE was also previously explored in pioneering studies conducted more than 50 years ago ([90](#), [91](#), [92](#), [93](#)). In the seminal study by Elholm *et al.* where both energy intake and EE were measured daily for 2 weeks in army cadets ([90](#)), a positive relationship between energy intake and EE was observed when data were averaged over the entire length of the study, although no association was found within the same day ([90](#)). Similarly, in the classic study of Mayer *et al.* on Bengal jute mill workers ([91](#)), a positive relationship was also found between the physical demands of work (a proxy for daily EE) and daily energy intake. However, a positive relationship was only detected for relatively higher levels of EE ([91](#)) as opposed to an inverse relationship that was instead observed for relatively lower levels of EE. Taken together, these classic studies demonstrate that a coupling between EE and energy intake does exist in humans and that this link may only manifest over longer periods of time and at specific levels of physical activity and daily EE.

As mentioned in Section 1 above however, some studies have observed that relatively high EE measured during energy balance coincides with a greater susceptibility to weight gain over time

([25](#), [26](#)), perhaps because an over-compensatory increase in energy intake as a result of greater energy requirements. However, the precise (putative) mechanism that elicits this response (higher energy intake) to increased EE remains unclear. Recent studies have begun to examine this potential causal link between EE and energy intake, tentatively calling it “energy sensing,” given that energy sensing mechanisms may regulate energy intake to match EE and ultimately achieve energy balance. As is known, EE is mainly determined by fat free mass ([8](#)), which is itself strongly associated with energy intake ([85](#), [86](#), [94](#)), raising the question as to whether the key regulator of energy intake in humans is body composition *per se* or EE, or both. Although interventional studies have not yet demonstrated the causality of the relationship between EE and energy intake, cross-sectional analyses from two independent research groups that employed a mediation-analysis framework have convincingly demonstrated that EE, indirectly and irrespective of its association with fat free mass, is the physiological mediator by which fat free mass exerts its effect on energy intake ([88](#), [95](#)). Accordingly, these two studies have provided compelling evidence of the existence of energy-sensing mechanisms that may regulate energy intake in humans on the basis of the body’s energy demands ([50](#), [82](#)). The biological architecture of energy sensing warrants further research as the physiologic and genetic mechanisms underlying energy sensing are not fully understood. Biological mediators may include circulating hormones such as myokines and adipokines as well as metabolites such as glucose and free fatty acids that, in concert, may act centrally to inform the hypothalamus and the brain areas involved in appetite and eating behaviors regarding the rate of energy expended by the organism.

If there indeed is a causal link between EE and energy intake (i.e., energy sensing), it is possible that there are differences in the way some individuals are (un)able to sense the extent to which they must compensate for their own particular EE by eating. That is, some individuals may

“sense” to offset their EE to a degree greater (or lesser) than is truly needed by consuming more (or less) food than required. Thus, this metabolic sensing mechanism may vary widely across individuals and the degree to which it varies may be informative of the propensity of an individual to gain weight over time (Figure 2). A recent study in Native Americans has explored broad, inter-individual variability in the energy-sensing relationship between 24-h EE and *ad libitum* food intake, as measured by a computerized vending system in an inpatient setting. Although nearly all subjects tended to overeat in this context of *ad libitum* food intake, some subjects ate comparatively more than what was predicted according to their body energy requirements (96), implying that these particular individuals could not adequately “sense” (or perhaps better, they “over-sensed”) their metabolic demands. Importantly, a longitudinal analysis observed that the greater degree to which subjects over-ate in the inpatient setting (i.e., a positive deviation from the energy-sensing relationship linking EE and energy intake), the higher the rate of weight gain in free-living conditions after a median follow-up time of 1.7 years (96), indicating that subjects who ate to a degree that positively deviated further from their body metabolic requirements were more at risk of weight gain than others who “under-sensed” their metabolic needs. These results suggest that reactions to EE vary across individuals in terms of the amount of food consumed, such that some individuals over-sense while others under-sense their metabolic requirements. Specifically, for those who over-sense and thus, positively misconstrue their energy needs by consuming food as though they had higher EE, the propensity to gain weight is greater. In sum, the degree to which some individuals over-sense (or, over-estimate) their metabolic demands may be another indicator of the susceptibility to weight gain in humans.

It goes without saying that over-eating leads to weight gain. What remains to be established however, is how to properly define "over-eating." That is, how can an individual's "ideal" caloric intake be correctly identified? If the goal is to consume food in order to maintain body weight, it is necessary to consider body energy requirements, namely, EE. Given that EE is a continuous process throughout an individual's lifetime, whereas energy intake is episodic and sporadic, it is conceivable that an individual consumes food at a rate and to an extent relative to persistent energy demand, and further, that the rate and extent to which individuals consume varies, perhaps in the way they sense their energy needs. Any measure of suitable caloric intake is relative to an individual's particular daily EE, but it may be that individuals prone to over-consuming inaccurately sense their EE. That is, they misconstrue their energy needs, consume more than is necessary, and thus, gain weight over time.

While it is clear that the propensity to overeat informs a person's tendency to gain weight over time, the mechanism dictating this propensity has hitherto remained unclear. It may, indeed, hinge on the putative, causal link between EE and energy intake as driven by the body's ability to sense EE and consequently regulate energy intake by altering hunger to meet body's energy requirements ([80](#), [83](#), [85](#)). From an evolutionary standpoint, a link between EE (i.e., energy needs) and energy intake would ensure that an organism experiences a physiologic drive to find enough food to maintain both life and reproduction. Thus, the higher EE associated in some individuals may well be associated with the demonstrable increased hunger and food-seeking behavior, which often lead to a greater-than-necessary intake and weight gain. However, interventional studies are necessary in order to clarify the mechanisms by which EE may act as a physiological mediator driving energy intake. An increased understanding of the ways in which EE may alter energy intake may provide further insight into the pathophysiology of obesity. For

example, energy sensing may explain why some obesity therapies that act to increase EE do not effectively result in weight loss, presumably because of compensatory increases in energy intake driven by increased metabolism. Further, there is a need to more fully understand inter-individual variability in the degree of over-sensing EE and the resulting proclivity to increase food consumption in order to identify those subjects more at risk of gaining weight as a consequence of impaired (or dysregulated) energy sensing.

Conclusion

There is substantial variability in weight change among individuals that can be explained in part by inter-individual differences in energy metabolism, particularly when metabolic measurements are obtained under conditions of energy imbalance like during fasting and low-protein overfeeding. By studying the EE response to acute, short-term changes in energy intake such as fasting or overfeeding, it is possible to uncover and quantify individual inclination or resistance to obesity. As shown in Table 1, the predictive power of these metabolic parameters in relation to future weight change ranges from 0.35 to 0.84 (absolute values of the Pearson Correlation coefficient), thus explaining more than 10% of the inter-individual variance in bodyweight change. These results for metabolic parameters obtained in conditions of energy imbalance are significantly more informative than those obtained by metabolic assessments in conditions of energy balance (~5% as reported above in Section 1). Metabolic phenotypes (thrifty vs. spendthrift), uncovered by low-protein overfeeding and characterized by plasma FGF21 concentrations, can identify subjects who are more/less susceptible to weight gain. Namely, individuals with a modest FGF21 response to a low-protein diet have a thrifty metabolism and they are more at risk of future weight gain. These results may suggest that FGF21 supplementation could assist metabolically thrifty individuals to increase their metabolism by

targeting a metabolic defect and ultimately become more “spendthrift” by increasing their EE, thus preventing future weight gain or favoring diet-induced weight loss.

Continued research into metabolic phenotypes is warranted in order to further the development of clinical tests (e.g., measuring plasma FGF21 concentration following a low-protein meal) that will proactively gauge individual susceptibilities to weight gain. Once the unique metabolic phenotype of individuals can be successfully identified through such tests, it will be possible to proactively intervene through counseling or therapies to achieve a clinical outcome. For instance, for lean individuals shown to have “thrifty” metabolisms, it will be possible to counsel against chronic overeating on account of their higher susceptibility to future weight gain. For individuals with obesity shown to have “spendthrift” metabolisms, we will be able to predict that caloric restriction will indeed have an effect on weight loss. Conversely, for individuals with obesity shown to have “thrifty” metabolisms, it will be immediately clear that caloric restriction alone will not be sufficient to fully achieve weight loss and that, thus, additional therapies, such as prescribing physical therapy and/or anti-obesity medications, will be needed to favor diet-induced weight loss.

In summary, a better understanding of the metabolic differences among individuals may lead to individualized therapies for preventing or treating weight gain by identifying subjects at risk on the basis of each person's metabolic phenotype and susceptibility to obesity.

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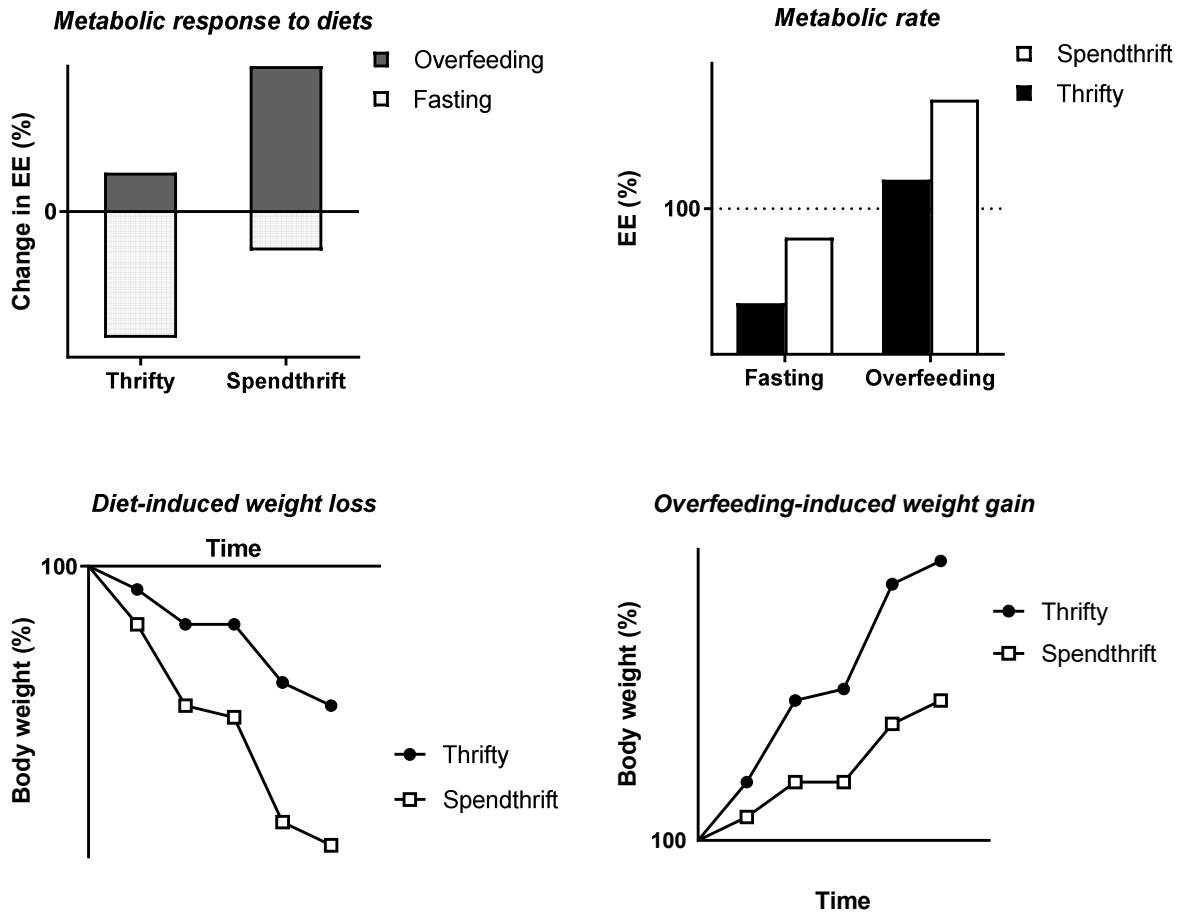
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Table 1. Strength of the relationships between metabolic phenotype variables and weight change assessments in human studies.

Study	Metabolic phenotype variable	Weight change variable	Strength of relationship*
Schlögl M, <i>et al.</i> (2)	Decrease in 24-h EE during fasting	Free-living weight change after 6 months	R = -0.35
Schlögl M, <i>et al.</i> (2)	Change in 24-h EE during 200% low-protein overfeeding	Free-living weight change after 6 months	R = -0.55
Reinhardt M, <i>et al.</i> (53)	Decrease in 24-h EE during fasting	Weight loss after 6 weeks of daily 50% caloric restriction	R = -0.84
Hollstein T, <i>et al.</i> (55)	Decrease in 24-h EE during fasting	Weight gain after 6 weeks of daily 150% low-protein overfeeding	R = -0.84
Vinales KL, <i>et al.</i> (5)	Change in plasma FGF21 after 24 hours of 200% low-protein overfeeding	Free-living weight change after 6 months	R = -0.36
Begaye B, <i>et al.</i> (69)	Change in 24-h RQ during 200% high-fat overfeeding	Free-living weight change after 1 year	R = +0.39

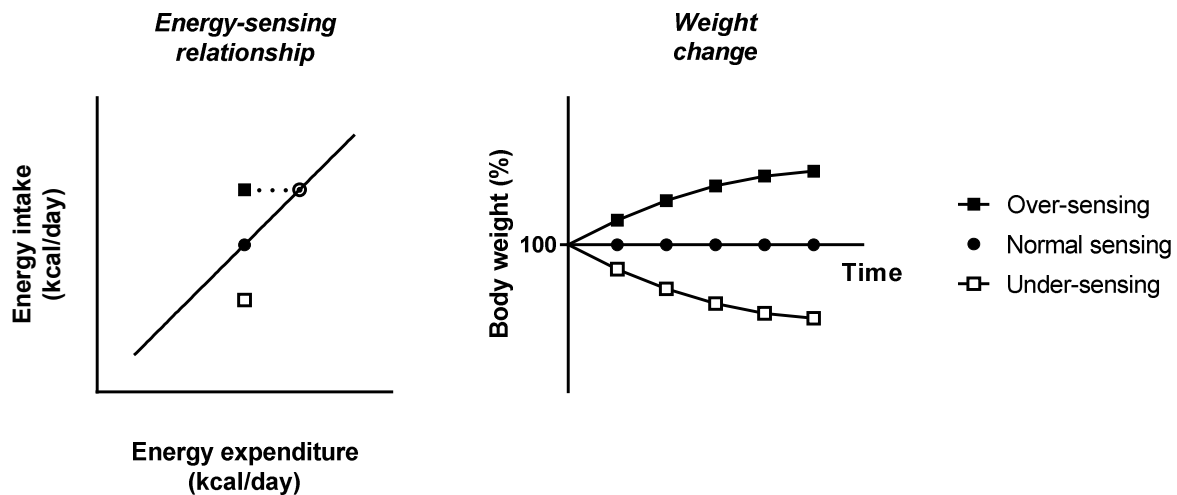
*: quantified by the Pearson correlation coefficient (R)

Figure 1. Definition of thrifty and spendthrift metabolic phenotypes.



Human metabolic phenotypes can be revealed by measuring the short-term (24 hours) response to fasting and overfeeding (especially, low-protein overfeeding) from conditions of energy balance. Compared to metabolically spendthrift individuals, subjects with a thrifty metabolism demonstrate a greater decrease in 24-h energy expenditure from energy balance during fasting and smaller increase in energy expenditure during overfeeding (upper-left panel), thus showing relatively lower metabolic rates in both dietary conditions (upper-right panel). Subjects with a thrifty metabolism lose less weight during sustained caloric restriction (lower-left panel) and gain more weight during prolonged overfeeding (lower-right panel).

Figure 2. Variability in energy sensing and its effects on weight change.



Positive linear relationship between energy intake and energy expenditure (EE) as determined by energy-sensing mechanisms (left graph). Inter-individual variability in the degree of energy sensing (i.e., over- vs. under-sensing) might explain the degree of susceptibility to weight gain or loss (right graph). Over the entire range of this energy-sensing relationship (e.g., low EE or high EE), there are subjects who normally sense their EE and eat accordingly (black circle), thus they can better maintain their weight over time. At any given point of the energy-sensing relationship, there are also subjects who over-sense their EE (solid square) and, as such, positively misconstrue their energy needs by consuming food as if they had higher EE (open circle), thus overeating relative to their energy needs and being more inclined to gain weight over time. Conversely, subjects that under-sense their EE (open square), eat less food than what they expend, thus are more prone to lose weight over time.