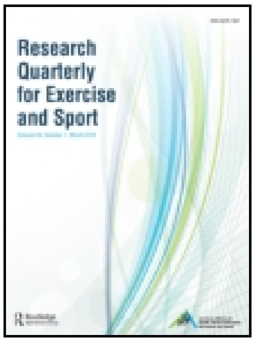

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Top 10 Research Questions Related to Energy Balance

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Obesity is the result of a mismatch between the amount of calories consumed and the amount of calories expended during an extended period of time. This relationship is described by the energy balance equation, which states the rate of change in energy storage depots in the body are equal to the rate of energy intake minus the rate of energy expenditure. Although this relationship may appear easy to understand based on simple mathematics, in reality, a variety of known and unknown systems influence the components of energy balance (energy storage, energy intake, energy expenditure). Clearly, if a complete understanding of energy balance was apparent, worldwide levels of obesity would not have reached pandemic proportions due to effective prevention and treatment strategies. The aim of the present article is to provide a brief overview of the components of energy balance and to identify 10 key topics and unanswered questions that would move the research field forward if addressed. These topics are intentionally diverse and range from general themes (e.g., methodological issues) to specific areas (e.g., intensity of exercise required to alter energy intake). Although this list is not meant to be exhaustive, it does provide a research agenda for scientists involved in the study of energy balance and recommendations for public health professionals developing obesity interventions.

Keywords: body weight, energy expenditure, energy intake, obesity

Obesity, in the absence of disease, can only occur as a result of a chronic positive mismatch between energy intake and energy expenditure resulting in fat accumulation. This storage of excess calories as adipose tissue is a normal biological response to a positive caloric balance. Conversely, weight loss, in the absence of disease or surgical intervention, can only occur as the result of a chronic negative mismatch of energy intake and expenditure. These basic facts are why the study of energy balance is a significant scientific area with important public health implications.

The challenge for researchers is to identify the determinants of these mismatches of energy intake and expenditure. Unfortunately, it is rarely as simple as "Eat less, move more," and instead involves complex relationships between biological, physiological, psychosocial, and environmental factors. The purpose of this article is to provide a brief overview of the energy balance concept and the components involved. The second half of the article lists important topics within the study of energy balance and highlights unanswered questions, which, if answered, would serve to move the field forward (Table 1). These questions are intentionally diverse and include general themes (e.g., methodological issues) to very specific topics (e.g., intensity of exercise). They are not meant to be exhaustive and are in no particular order.

ENERGY BALANCE OVERVIEW

The first law of thermodynamics is the law of conservation of mass and energy (von Helmholtz, 1847), which states that energy can be transferred from one form to another, but it cannot be created or destroyed. In the context of human physiology, this is expressed as:

$$\mathrm{ES} = \mathrm{EI} - \mathrm{EE}, \qquad (1)$$

where ES = rate of change of energy storage, EI = rate of energy intake, and EE = rate of energy expended (Ganong,

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TABLE 1
Top 10 Questions in the Study of Energy Balance

1. What are common misunderstandings associated with the application of the energy balance equation?
2. What are the short-term and long-term implications of energy balance and imbalance? Are imbalances during the course of days related to or different than imbalances over months?
3. What is the relationship between energy intake, energy expenditure, and energy storage, particularly during periods of diet- or activity-induced weight loss?
4. What is the role of physical activity, specifically intensity and volume, on the components of energy balance?
5. What is the role of energy balance in interventions for weight loss or weight maintenance?
6. What is the role of genetics in energy balance?
7. What are the environmental influences on the components of energy balance?
8. What is the extent of racial and sex differences in energy balance?
9. What are the primary methodological challenges in the study of energy balance?
10. What future research approaches and strategies are needed to move the study of energy balance forward?

2001). An often-overlooked but key principle is the time-dependent nature of each of the variables, and energy balance as a concept depends on the time domain during which it is considered (Alpert, 1990; Hall et al., 2012). At any given moment, we are in energy imbalance (e.g., following a meal), but this acute status does not necessarily predict changes in ES over longer periods of time. A second key point is that the energy balance equation describes what occurs to ES when EI and EE are in balance or imbalance. What it does not tell us is where or how these changes occurred (e.g., decreases in resting metabolic rate [RMR] results in decreases in EE, or increases in dietary fat consumption lead to increases in EI; Bray, 2008).

Components of Energy Balance

Energy Intake

EI represents the metabolizable energy content of food (expressed as kilocalories or kcals) provided by the four macronutrient categories: carbohydrates (4 kcals/g), protein (4 kcals/g), fat (9 kcals/g), and alcohol (7 kcals/g; Goran, 2000). These values represent the net caloric content of food as approximately 2% to 5% of the gross ingested amount is lost during digestion due to fecal losses (Leibel, Rosenbaum, & Hirsch, 1995).

Energy Expenditure

EE occurs through three sources: RMR, thermic effect of food (TEF), and physical activity. Basal metabolic rate is the "minimal level of energy expended to sustain life" in a neutrally temperate environment while in a postabsorptive state, and it includes the energy cost of physiological functions such as muscle contractions, respiration, and brain function (Goran, 2000; Henry, 2005). Measurement of basal metabolic rate can be a difficult task, so measurement of RMR is typically utilized instead, with the only methodological difference being that basal metabolic rate is measured shortly after waking (< 45 min) but before arousal (Ravussin, Lillioja, Anderson, Christin, & Bogardus, 1986), while RMR is measured after arousal (Goran, 2000). Because the values are similar (RMR is approximately 3% higher), the two terms are frequently used interchangeably and for simplicity, RMR will be used for the remainder of this text. RMR constitutes 60% to 80% of daily EE (Goran, 2000).

Meal-induced thermogenesis, also referred to as the TEF, is the energy that is expended to digest, metabolize, and store ingested macronutrients (Goran, 2000). TEF constitutes approximately 6% to 10% of EE (Goran, 2000; Ravussin et al., 1986).

Thermic effect of exercise—or as it is more widely called, physical activity energy expenditure (PAEE)—describes the increase in metabolic rate that is caused primarily by contraction of skeletal muscles to perform work (Goran, 2000). It is important to note that PAEE includes EE from all skeletal muscular contractions throughout the day, and not just structured leisure time exercise. PAEE constitutes 10% to 30% of total EE.

Additionally, two minor components of EE also exist. The energy cost of growth contributes to EE but is inconsequential beyond the 1st months of life (Goran, 2000). Adaptive thermogenesis resulting from exposure to environmental temperatures or fluctuations in diet may also result in EE, but also rarely occurs outside of the initial months of life, extreme temperature changes (humans have a broad thermoneutral zone with relatively small changes in metabolic rate occurring over relatively wide temperature changes, primarily due to behavioral responses such as changes in clothing), or extreme changes in diet such as starvation or extreme overeating (Doucet et al., 2001; Goran, 2000; Lowell & Spiegelman, 2000).

Energy Storage

Humans store energy in different forms within the body based on acute needs for biological function and how efficiently storage can occur. There is a wide variation in adult body sizes and compositions, but a 70-kg reference man with 20% body fat (14 kg) stores approximately 167,000 total kcal of energy, including 2,000 kcal of carbohydrates, 40,000 kcal of protein, and 125,000 kcal of fat (Galgani & Ravussin, 2008). Alcohol cannot be stored in the body and is quickly metabolized, though it may influence oxidation of the other macronutrients (Shelmet et al., 1988).

Carbohydrates are stored in relatively small amounts in the body as glycogen in the skeletal muscle and liver (1% of total body kilocalories stored). Turnover of glycogen is rapid; up to 50% is metabolized in a given day (Galgani & Ravussin, 2008). It is used as a short-term energy source, which is easily depleted after a 12-hr dietary fast or bout of exercise. From an efficiency viewpoint, the storage of carbohydrates is metabolically expensive; 3 g of water are required to store 1 g of carbohydrate, whereas no water is needed for fat storage. Additionally, the energy density of stored glycogen is 1 kcal/g (vs. 4 kcal/g when ingested as carbohydrate and 9 kcal/g of stored fat; Goran, 2000), and both factors make the storage of carbohydrates less desirable compared with alternative energy sources (i.e., fat). Carbohydrate levels in the body are closely regulated and maintained, which means storage of excess carbohydrates is limited. Indeed, when excess carbohydrates are consumed in the diet, higher levels of stored carbohydrates are used as fuel, thus maintaining a relatively constant level (Galgani & Ravussin, 2008).

Protein stores represent about one third of the total stored energy in a 70-kg reference man (Galgani & Ravussin, 2008). Protein is primarily stored in skeletal muscle and serves a range of biological purposes, including muscular contractions, immune function, activation of biochemical reactions, and hormone functions. Metabolically speaking, protein requires more energy to be stored in the body compared with fat, and these storage depots only increase in the presence of a growth stimulus such as growth hormones or physical training (Abbott et al., 1988; Galgani & Ravussin, 2008).

Fat is the largest component of ES in humans and represents approximately 125,000 kcals (75% of total stored kilocalories) in the reference man described earlier, while an obese adult may have 4 times that amount (Hirsch & Knittle, 1970). As mentioned previously, the storage of fat in the body is aided by the metabolic efficiency of how it is stored. Unlike carbohydrates, when excess fat is consumed, it has no alternative (i.e., oxidation of fat stores is not increased) other than storage (Galgani & Ravussin, 2008), and no energy is required in the process of storing fat (Goran, 2000). Each of these factors favors fat as the preferred macronutrient for storage, which has conferred an advantage throughout human evolution when food availability is low and has enabled survival during periods of famine.

Rate

As mentioned earlier, a key concept relating to energy balance is the rate-dependent nature of all the components. For example, EE is relatively constant throughout the day for most individuals as fuel is metabolized for normal physiologic functions associated with daily living (e.g., RMR is relatively stable within individuals and varies only ±5% between days; Murgatroyd, Davies, & Prentice, 1987), but it increases occurring during physical activity and decreases during sleep. In contrast, EI fluctuates throughout the day based on the occurrence of meals. Measured at any given moment, individuals are likely in a positive or negative energy balance depending on the time since the last meal or bout of physical activity. However, when examined for longer periods of time, individuals maintain remarkable levels of energy balance. For example, an average adult man consumes 1,237,221 million kcals each year (Speakman & Westerterp, 2010) and gains 0.5 kg of body weight (Van Wye, Dubin, Blair, & Dipietro, 2007), resulting in an energy surplus of only 3,296 kcals during the course of the year, or 9 kcals/day (Speakman et al., 2011).

TOP 10 RESEARCH QUESTIONS

We identified research questions in four major categories. First, we propose research questions that address the general understanding of energy balance and related components. Second, we identified research questions related to energy balance under conditions in which an imbalance occurs, such as dietary restriction or physical activity. Third, we proposed research questions addressing internal and external influences on energy balance. And fourth, we identified research questions that address barriers and challenges for future energy balance research.

Understanding Energy Balance

We believe there is a general misunderstanding surrounding the energy balance and its application in both the research and real-world settings. Accordingly, we posed two research questions, which, if answered in future investigations, will clarify the role energy balance plays in weight maintenance, gain, and loss.

1. What Are Common Misunderstandings Associated With the Application of the Energy Balance Equation?

Several excellent articles have recently addressed myths and preconceptions surrounding obesity and their detrimental impact on public opinion, mass media, and scientific decision making, and many of the topics covered are directly related to the study of energy balance (Bray, 2008; Casazza et al., 2013; Finkelstein & Bilger, 2012; Hafekost, Lawrence, Mitrou, O'Sullivan, & Zubrick, 2013; Hebert, Allison, Archer, Lavie, & Blair, 2013). Each of these articles are extremely informative and are suggested reading for more information on the topic. For the purposes of this manuscript, perhaps the most important misunderstanding is in regards to the application of the energy balance equation itself. For example, one recent review of public health interventions to reduce obesity found nearly all were based primarily on a simplistic model of energy balance (i.e., "eat less, move more") with little consideration of the dynamic relationship of the energy balance components (Hafekost et al., 2013). Further, individuals and the popular media often confuse the limitations of the energy balance model in describing the small factors that influence the energy balance components as a failure of the model itself (Bray, 2008). For example, two bouts of exercise (one at moderate intensity the other at high intensity) matched for EE may have different effects on hormones that regulate appetite, therefore resulting in differences in 24-hr EI. A simplistic understanding of the energy balance equation would imply "a calorie is a calorie" and would fail to explain this occurrence, but a homeostatic view of energy balance as a multifaceted regulatory system would suggest otherwise. Future research should recognize the strengths and limitations of the energy balance equation when designing research studies and weight-loss interventions to maximize results and proper interpretation of findings.

2. What Are the Short-Term and Long-Term Implications of Energy Balance and Imbalance? Are Imbalances During the Course of Days Related to or Different Than Imbalances Over Months?

One of the classic studies in the field is that of Edholm, Fletcher, Widdowson, and McCance (1955) in which detailed measures of EI and EE were made among military cadets for 2 weeks. The authors found that EI and EE were poorly associated with each other on a day-to-day basis but were closely matched during the entire 2-week period, and these findings have been extended more recently to include changes in ES (Levitsky & DeRosimo, 2010; Levitsky, Obarzanek, Mrdjenovic, & Strupp, 2005). As mentioned previously in this article, at any given moment, individuals are likely in energy imbalance, and this "snapshot" does not necessarily reflect energy balance during an extended period of time. Given the limitations of human research, it is important to identify feasible data collection periods that minimize participant burden and monetary cost while providing an accurate assessment of energy balance and its components. For example, does EI need to be continually assessed during a 7-day period, or are random assessments on 3 days acceptable (Hebert et al., 2002)? What is the minimum duration of activity monitoring on body time to provide a representative assessment of EE?

Energy Imbalance

Most members of the research community and general public are justifiably interested in the study of energy balance as it relates to weight gain or loss. As a result, we proposed three research questions to better understand the dynamic changes in energy balance components during periods of positive and negative imbalance.

3. What Is the Relationship Between Energy Intake, Energy Expenditure, and Energy Storage, Particularly During Periods of Diet- or Activity-Induced Weight Loss?

Based on simple mathematics, it is obvious that the components of the energy balance equation, ES, EI, and EE, are related; however, the precise interactions between these variables and the mechanisms that regulate these interactions are not well understood. Classic studies from the 1950s were among the first to identify a nonlinear relationship between EI, EE, and ES. In 1950, Keys, Brozek, Henschel, Mickelson, and Taylor placed individuals on a very low-calorie diet, which induced a 25% reduction in body weight, ultimately resulting in a plateau of weight loss. Upon release from caloric restriction, body weight increased rapidly rather than at a rate similar to the weight loss, suggesting a strong hyperphagic response to depletions of fat mass and, to a lesser extent, lean mass (Dulloo, Jacquet, & Girardier, 1997). Instead of EI, Mayer et al. (1954) manipulated EE and found points at which: (a) Decreases in EE did not result in corresponding decreases in EI; (b) during longer bouts of exercise, EI increased linearly with EE, and ES was maintained; and (c) at high levels of EE, both EI and ES decreased. More than four decades later, Leibel et al. (1995) examined responses in EE to increases and decreases in ES and found a 10% increase in body weight was associated with a 16% increase in EE, while a 10% decrease in body weight was associated with a 15% decrease in EE. When body weight was further decreased to 20% below the initial weight, no further decreases in EE occurred. Each of these studies demonstrates the variable and nonlinear relationship between ES, EI, and EE; what is not clear is the exact relationship between these variables. Are they each regulated individually? Is there a unifying regulatory system that senses changes in one variable (e.g., fat mass) that influences other variables (e.g., appetite)?

Multiple theories have been generated to explain the relationship between the components of the energy balance equation, including the set-point theory (Kennedy, 1953), the settling-point theory (Wirtshafter & Davis, 1977), carbohydrate balance theory (Galgani & Ravussin, 2008), the general intake model (de Castro & Plunkett, 2002), and the dual intervention point model (Levitsky, 2002). These hypotheses cannot be fully expounded upon in the limited space here, but an excellent review can be found by reading Speakman et al. (2011). Each of these theories has strengths and weaknesses in their attempts to explain the control system(s) involved in energy balance, and questions still remain as to the processes responsible, more than 50 years since an interaction was first observed. Regardless, it is important to understand this relationship so effective obesity interventions can be developed, as those interventions that fail to recognize compensatory responses will result in less-than-expected results. For example, an intervention involving dietary restriction will likely correspond with a compensatory reduction in EE, with the combined effect being a negative energy imbalance (and in turn weight loss) smaller than originally prescribed.

4. What Is the Role of Physical Activity, Specifically Intensity and Volume, on the Components of Energy Balance?

As previously mentioned, the classic work by Mayer et al. (1954) described decreases in EI at both very low and very high levels of EE, achieved through the manipulation of physical activity. More recent work has explored the role of physical activity intensity rather than volume. Work by Thivel et al. (2012) revealed 24-hr dietary intake among obese adolescents was 6% lower following a single bout of high-intensity exercise (cycling at 75% of maximal oxygen consumption [VO_2max]) compared with a single bout of light-intensity exercise (cycling at 40% of VO_2max), with the duration of each individually calculated so the two bouts were matched for caloric expenditure (approximately 330 kcal). These findings were independent of feelings of hunger and satiety (which were unchanged) and 11% below the control condition during which no exercise was performed. There was a similar finding in overweight men, with high- and very high-intensity exercise (cycling at 60-s intervals at 100% of peak oxygen consumption [VO_2peak] and 15-s intervals at 170% VO_2peak, respectively, matched for caloric expenditure) resulting in decreases of 23% and 22%, respectively, in ad-libitum 24-hr EI (Sim, Wallman, Fairchild, & Guelfi, 2013). Unlike Thivel et al.'s study, in this study, hunger and satiety were decreased following the high- and very high-intensity exercise, along with decreases in ghrelin, a hormone known to regulate appetite, but there was no change in leptin, another appetite-regulating hormone.

These studies have focused on acute bouts of exercise on EI, but other studies have shown that regular physical activity or high cardiorespiratory fitness (CRF) levels also are involved in energy balance. For example, moderate and high levels of CRF and physical activity are associated with elevations in RMR by 5% to 20% compared with low-fit or sedentary individuals (Broeder, Burrhus, Svanevik, & Wilmore, 1992; Shook, Hand, Paluch, et al., in press; Tremblay et al., 1986; Van Pelt, Dinneno, Seals, & Jones, 2001). These findings are in addition to the widely known effects of high EE on ES by reducing fat mass and increasing fat-free mass (Willis et al., 2012). Future research should continue expanding beyond the study of only moderate physical activity and should identify the relationship with light bouts of physical activity ($\leq$3.0 metabolic equivalents of task [METs]) and short bouts of moderate-to-vigorous physical activity on the components of energy balance. These are important unanswered questions given that levels of moderate-to-vigorous physical activity ($>$3.0 METs) obtained in $\geq$10-min bouts (as recommended by the *2008 Physical Activity Guidelines for Americans* (U.S. Department of Health & Human Services, 2008) were relatively unchanged from 1997 to 2006 (Centers for Disease Control & Prevention, 2008); if there are benefits in terms of body weight control with light-intensity activity or shorter bouts of moderate physical activity, perhaps these forms of physical activity are more feasible intervention targets for weight reduction.

5. What Is the Role of Energy Balance in Interventions for Weight Loss or Weight Maintenance?

One of the most common beliefs in the general public and even academic thinking is 1 lb of body weight is equivalent to 3,500 kcals of stored energy, and this figure is frequently used to calculate weight change over time (Hall, 2008). However, the "3,500-kcal rule" typically underestimates weight loss, and the reasons can help us understand what actually occurs during weight loss. First, the "3,500-kcal rule" is based on the number of calories needed to expend 1 lb of fat mass (Wishnofsky, 1958). However, changes in ES vary depending on the source of the energy imbalance, with interventions involving exercise resulting in decreases in fat mass with little change in fat-free mass (i.e., skeletal muscle), while a low-calorie diet approach will reduce both (Thomas et al., 2012). Because the metabolizable energy of fat, protein, and glycogen body stores are not equal (Livesey & Elia, 1988), the "3,500-kcal rule" is not accurate if anything other than fat mass is lost. Second, during weight loss, several compensatory mechanisms are initiated—for example, by reducing EE from RMR when reductions in EI occur (e.g., low-calorie dieting), which reduces the prescribed net negative energy imbalance resulting in lower-than-expected weight loss (Thomas et al., 2012).

A more realistic expectation of weight loss is rapidly evolving thanks to advanced mathematical models that account for EI, EE, baseline ES, and the dynamic relationship between the three during weight loss (http://www.pbrc.edu/research-and-faculty/calculators/weight-loss-predictor; http://bwsimulator.niddk.nih.gov). These tools have been created by modeling existing data from a variety of research settings using multiple measurement techniques, all of which limit internal validity, critical for the study of a topic with such a small degree of error. Although these models were clearly created to quantify gaps in the existing literature, future research should validate these models using truly experimental study designs with characteristics such as random selection of participants, multiple weight-loss intervention strategies, and uniform valid and reliable assessments of ES, EI, and EE.

Factors Influencing Energy Balance

A multitude of factors influence the components of energy balance and are likely responsible for large portions of the interpersonal variations observed in response to weight gain and loss. We proposed three research questions that address these factors, which, when answered, will allow for a better understanding of individual responses to energy balance and imbalance.

6. What Is the Role of Genetics in Energy Balance?

There are known genetic influences to multiple components of the energy balance equation and systems involved in their regulation. Genomewide association studies have identified several loci related to obesity, suggesting that as much as 50% to 70% of the variance in body mass index (BMI) is due to genetic differences (Allison et al., 1996; Segal & Allison, 2002; Segal, Feng, McGuire, Allison, & Miller, 2009). Genes have also been shown to explain variability in weight gain (Bouchard et al., 1990), food intake regulation (Speakman et al., 2011), and physical activity (Mustelin et al., 2012). What is less clear is how genes interact with the environment to affect EI, EE, and ES. For example, recent analyses indicate that physical activity level interacts with gene risk score (a sum of BMI-related alleles) to influence predisposition for obesity (Ahmad et al., 2013; Li et al., 2010). The potential benefit from further study of gene–environment interactions is great given the recent advances in the genetics field in terms of improved measurement and understanding of large multistudy investigations involving hundreds of thousands of participants.

7. What Are the Environmental Influences on the Components of Energy Balance?

While the components of the energy balance equation represent physiological variables and processes, human behavior undoubtedly interacts with many or all of the components. The term "obesogenic environment" describes factors in which we live that influence behavior by promoting or supporting obesity, such as increased availability of food or decreased requirements for physical activity (Egger & Swinburn, 1997; Hill & Peters, 1998; Hill, Wyatt, Reed, & Peters, 2003). Environmental factors that may influence physical activity include neighborhood factors such as traffic lights and crossing aids (Lee, Mama, Medina, Ho, & Adamus, 2012), sidewalk quality (Hoehner, Brennan Ramirez, Elliott, Handy, & Brownson, 2005), bike lanes and bike facilities (Sallis et al., 2009), and occupational (Church et al., 2011) and household demands (Archer et al., 2013). Factors that may alter body weight include television viewing (Epstein et al., 2008; Jordan, 2010), attending college (Cluskey & Grobe, 2009), and getting married (Sobal, Hanson, & Frongillo, 2009). Environment may influence EI through the availability of energy-dense foods (Rolls, 2010), portion sizes (Duffey & Popkin, 2011; Piernas & Popkin, 2011; Rolls, Roe, & Meengs, 2007), eating location (Thornton, Crawford, & Ball, 2011), and eating during television watching (Epstein, Paluch, Smith, & Sayette, 1997; Epstein, Rodefer, Wisniewski, & Caggiula, 1992). Future directions should identify those environmental factors where interventions may be effective, either through changing the actual environment or altering the perception of that environment (Kirtland et al., 2003).

8. What Is the Extent of Racial and Sex Differences in Energy Balance?

Racial differences have been described for numerous components of energy balance, including EE (Hunter, Weinsier, Darnell, Zuckerman, & Goran, 2000), RMR (Gannon, DiPietro, & Poehlman, 2000; Shook, Hand, Wang, et al., in press), ES (Flegal, Carroll, Kit, & Ogden, 2012), distribution of ES within the body (Jones et al., 2004), and EI (Lovejoy, Champagne, Smith, de Jonge, & Xie, 2001). Similar differences can be found between men and women (Arciero, Goran, & Poehlman, 1993; Flegal et al., 2012; Goran, 2000). Differences in obesity between sexes may be explained partly by the influence of hormonal influences on body composition and appetite, and psychosocial and chromosomal factors may also play a role (Lovejoy & Sainsbury, 2009). However, unanswered questions still remain regarding differences among other ethnic groups, and longitudinal studies are needed to determine causality between variables associated cross-sectionally with obesity such as low RMR.

Barriers, Challenges, and Future Directions

The study of energy balance can be a challenging undertaking given the dynamic relationship between the components and methodological issues relating to their assessment. We proposed two research questions, which, if answered, will address these challenges and enable scientists and public health professionals to develop research and intervention strategies.

9. What Are the Primary Methodological Challenges in the Study of Energy Balance?

As illustrated by the example earlier in which an estimated 9 kcals/day are sufficient to explain the amount of weight gained by most adults, the small degree of error to which the principles of the energy balance equation functions limits our understanding of the field. The development of the doubly labeled water technique allows us to objectively measure EE among free-living adults using biomarkers with an unmatched level of accuracy (though the precision of the measure is ∼5%; International Atomic Energy Agency, 2009). Additionally, wearable activity monitors are now readily available to assess not only total EE, but also descriptive characteristics such as duration and intensity of physical activity in an objective manner that has high validity and reliability (Johannsen et al., 2010). ES can also be measured with similar accuracy using dual energy X-ray absorptiometry, which provides estimations of fat mass, fat-free mass, and bone mass ($r = .96$ for agreement of skeletal mass via magnetic resonance imaging [MRI]; Jones et al., 2004). Meanwhile, the accuracy and precision for measuring EI is much lower (Hebert et al., 2002; Schoeller et al., 2013), with correlations between EE via doubly labeled water and self-report EI typically below $r = .50$, though the use of multipass interview techniques (Thompson & Subar, 2013) and statistical adjustment for known confounders such as social desirability show promise for reducing this error (Mossavar-Rahmani et al., 2013). Taken as a whole, the strengths of certain measures and weakness of other measures can be utilized for the triangulation of results (Hand et al., 2013; Kabagambe et al., 2001; Natarajan et al., 2010). For example, triangulation has been used to estimate the correlation between long-term EI and intake using objective measures (biomarkers), references measures (dietary recalls), and subjective measures (food frequency questionnaires; Kabagambe et al., 2001).

10. What Future Research Approaches and Strategies Are Needed to Move the Study of Energy Balance Forward?

Assessment techniques aside, it is costly and methodologically difficult to measure on a timescale of sufficient length to accurately describe the components of energy balance given at any given moment individuals are in energy imbalance, which may not present an accurate representation of overall energy balance. Despite these barriers, more research studies are needed involving repeated measurements of EE, EI, and ES during a period of time greater than 6 months with designs that consider energy balance not as a simplistic model but instead an interrelated and dynamic regulatory system (Hafekost et al., 2013; Hall et al., 2012; Hand et al., 2013). Researchers should utilize highly valid and reliable measures (e.g., objective activity monitoring using accelerometers and other devices instead of self-report; Hand et al., 2013) and should utilize statistical techniques to correct for known errors in other measures (e.g., adjusting for level of social desirability in dietary measures; Hebert et al., 2002). Additionally, probative research (as opposed to association studies designed to raise publicity; Casazza & Allison, 2012) and multilevel research and policy approaches are needed to understand the causes of the obesity epidemic, including longitudinal observational studies, randomized control trials when appropriate, and interventions that treat weight gain and weight loss not as a simplistic result of "calories in and calories out," but as a complex system with multiple internal (e.g., hormonal) and external (e.g., environmental) influences (Hafekost et al., 2013; Hand et al., 2013; Hebert et al., 2013).

CONCLUSIONS

A fundamental principle in the study of obesity is that changes in body weight are the direct result of a chronic, positive imbalance between EI and EE. The energy balance equation describes this relationship mathematically, but it does not identify where the imbalance between EI and EE occurs. Progress has been made during the past 60 years to identify determinants of this caloric mismatch, but many questions remain unanswered, which is evident by the high rates of obesity worldwide. To address these problems, we have identified 10 important research questions that, if answered, would move the field forward. The questions are intentionally diverse, as are the research techniques required to answer them. Although this list is not meant to be exhaustive, it does provide a research strategy for scientists engaged in the study of energy balance and recommendations for public health professionals developing obesity interventions.

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