REVIEW

From the past to future: from energy expenditure to energy intake to energy expenditure

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Although most recent research on energy balance focusses on energy intake (EI) there is still need to think about both sides of the energy balance. Current research on energy expenditure (EE) relates to metabolic adaptation to negative energy balance, mitochondrial metabolism associated with aging, obesity and type 2 diabetes mellitus, the role of EE in hunger and appetite control, non-shivering thermogenesis and brown adipose tissue activity, cellular bioenergetics as a target of obesity treatment and the evolutionary and ecological determinants of EE in humans and other primates. As far as regulation of energy balance is concerned there is recent evidence that EE rather than body weight is under tight control. Biologically, EE is maintained within a narrow physiological range. An EE-set point has been proposed as the width between the upper and lower boundaries of the individual EE range. Regulation of EE may fail in very obese patients with an EI above their upper boundary and after drastic weight loss when patients may go far below their lower EE boundary and thus are loosing control. In population studies, fat-free mass (FFM) and its composition (that is, the proportion of high to low metabolic rate organs) are major determinants of EE. It is tempting to speculate that tight biologic control of EE is related to brain energy need, which is preserved at the cost of peripheral metabolism. There is a moderate heritability of EE, which is independent of the heritability of FFM. In future, metabolic phenotyping should focus on the EE–FFM relationship rather than on EE-values alone.

INTRODUCTION

Thirty years ago, research on regulation of energy balance nearly exclusively focussed on energy expenditure (EE). At that time individual components of daily energy expenditure (=total energy expenditure, TEE) had been characterized in detail. A 70 kg man has a TEE of 2500 kcal/day with 1500 kcal (or 60%) for resting energy expenditure (REE), about 750 kcal (or 30%) for activity-related energy expenditure (AEE, the most variable component of TEE), 250 kcal (or 10%) for diet-induced thermogenesis and another variable component of +/− 250 kcal for metabolic adaptation to negative or positive energy balance.[1–4] This period of intensive research is reflected by some highly ranked and so-called landmark papers addressing the association between EE, weight gain and overweight. Longitudinally, a low REE relative to size was found to be a predictor of weight gain.[5–8] These findings fed a long-lasting discussion about whether obesity is due to either high energy intake (EI) or low EE (for example, refs 9–11). As (i) most obese subjects have a high rather than a low EE,[12] (ii) intra-individual variance of EE is small,[1,3] (iii) no differences in EE were found either between adults living in developing compared with industrialized countries[13] or between hunter gatherers and western groups[14] although they were different in mean BMI, and (iv) longitudinally, AEE slightly increased rather than decreased in an European population with an increasing prevalence of overweight,[15] and was not protective against weight gain,[16,17] the focus of research had shifted from EE to EI as the major determinant of a positive energy balance and obesity.[18–20]

Population-wide increases in EI were considered to explain the increases in obesity prevalence observed during the last 40 years. However, this idea remains to be proven in individual patients. In humans, assessment of EI is inaccurate and severely biased in overweight subjects.[21–23] It was only recently that accurate assessment of changes in body composition together with TEE as measured by doubly labeled water and advanced mathematical modeling allowed objective measures of EI.[24–26] When compared with EI, research on EE downsized during the last decades leaving a relatively small number of experts in this area only. However, research on EE is still challenging and currently relates to (i) metabolic adaptation to negative energy balance,[27,28] (ii) mitochondrial metabolism associated with aging, obesity and type 2 diabetes mellitus,[29–36] (iii) the role of REE in hunger and appetite control,[37] (iv) non-shivering thermogenesis and brown adipose tissue,[38–40] (v) cellular bioenergetics as a target of obesity treatment[41] and (vi) on the evolutionary and ecological determinants of TEE in humans and other primates.[42] It is obvious that there is still need to think about both sides of the energy balance.

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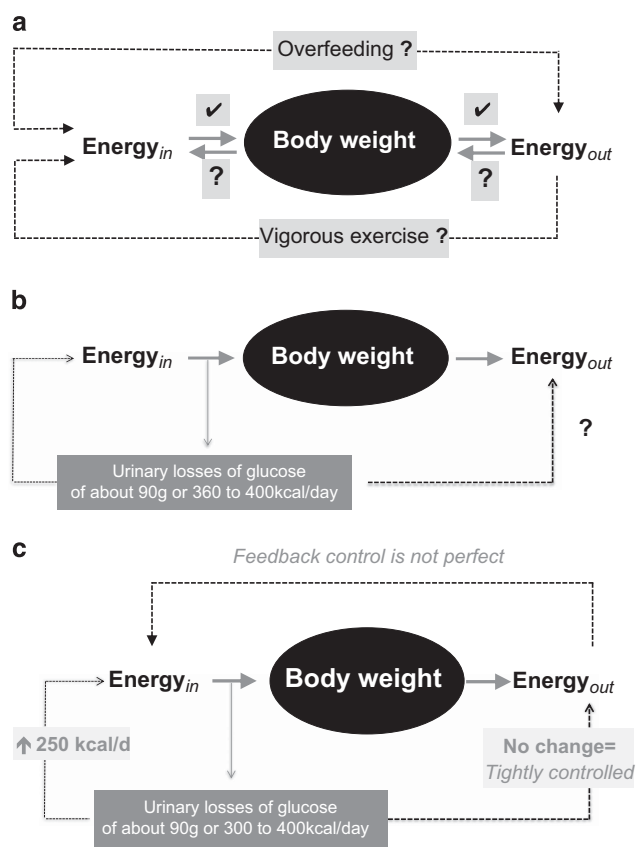E-mail: mmueller@nutrfoodsc.uni-kiel.de

Figure 1. Schematic presentation of the energy balance paradigm. (a) Body weight follows the difference between EI (energy$_{in}$) and EE (energy$_{out}$). With increasing body weight energy$_{out}$ increases. By contrast, reducing body weight decreases energy$_{out}$. Vice versa there are no effects of increases in energy$_{out}$ by strenuous exercise on body weight. An increase in body weight does not automatically result in a compensatory decrease in energy$_{in}$. Body weight-independent feedback controls between energy$_{out}$ and energy$_{in}$ had been proposed but have only been shown for underfeeding. (b) Pharmacological inhibition of the sodium-glucose co-transporter 2 (SGLT2) results in glucosuria of about 90 g/day. To test the energy balance paradigm the effects of SGLT2-inhibition on energy$_{in}$ and energy$_{out}$ has to be tested. (c) SGLT2-inhibition resulted in an increase in energy$_{in}$ with no changes in energy$_{out}$. However, an unchanged EE the increase in energy$_{in}$ does not match urinary energy losses resulting in a negative energy balance. See Ferrannani et al. 43 and text for further details.

EI OR EE? THE CASE OF SODIUM-GLUCOSE CO-TRANSPORTER 2 INHIBITION

Pharmacological inhibition of the sodium-glucose co-transporter 2 (SGLT2) is now used for metabolic control of patients with type 2 diabetes mellitus. It results in glucosuria of about 90 g/day. This intervention also provides some insights into the regulation of energy balance (Figure 1a). Mathematical modeling of energy balance revealed that SGLT2-inhibition resulted in an increase in EI at unchanged EE.[43] Again, this finding gives rise to the idea that regulation of energy balance is about EI, which is also in line with genetic studies in which all known causes of human obesity are related to defects in the regulation of EI.[19,20] However, taking a second look at the SGLT2-inhibition data,[43] it is obvious that EI increased only by 200–250 kcal/day (Figure 1b). As urinary energy losses were between 300 and 400 kcal/day, an energy gap remained, which resulted in an involuntary weight loss of about 2 kg within the observation period.[43]

Thus, during SGLT2-inhibition EI increased but was not perfectly controlled to match urinary energy losses and EE. By contrast, EE was kept constant suggesting that it is tightly controlled (Figure 1c). It is worthwhile to remember that oxygen consumption (similar to body temperature and heart rate) is vitally important and has to be strictly controlled as a matter of survival. The SGLTs-inhibition experience also showed that there is no tight feedback control of EI by EE. This is against the idea of other authors.[37] Altogether the data give evidence for the idea that EE rather than EI is under tight control and thus is the major determinant of energy balance.

It remains unclear why EE did not slow down with weight loss observed during GLT2-inhibition.[43] Pharmacologically-induced glucosuria was associated with a fall in circulating insulin levels together with a shift of fuel utilization to fats and a considerable increase in the plasma concentration of ketone bodies resembling metabolic adaptation to starvation.[44] It has been shown previously that adaptive thermogenesis (AT) is an immediate response to negative energy balance and the fall in insulin secretion, AT occurs even in the absence of significant weight loss.[45,46] However, (i) detailed body composition analysis to adjust EE has not been performed in the group of diabetic patients[43] and (ii) AT is in the order of 70 kcal,[45] which is within the precision of 3 or more than 5% of either indirect calorimetry and doubly labeled water measurements, respectively.[27,47] Thus, minor changes in EE may have been overlooked in the clinical data on GLT2-inhibition.[43] Anyhow, the observed weight loss of diabetic patients points out to the energy gap reflecting that EI and EE did not exactly adapt to each other.

PUTTING EE INTO PERSPECTIVE

Energy balance and body weight are under biological control allowing compensatory adjustments in both, EI and EE. This idea is mainly based on animal data. In humans, intra-individual and long-term observations suggest that body weight is relatively constant, which is taken as indirect evidence for a precisely controlled set point of body weight.[48] The idea is also in line with clincial observations that after weight loss most obese patients more or less return to their original fatness suggesting a pre-given target weight (or set point;[48]). As far as energy balance is concerned, some basic assumptions of regulation of body weight come true. For example, an increase/decrease in EI results in an increase/decrease of body weight with a subsequent increase/decrease in EE. By contrast, increasing AEE by strenuous exercise has no or only minor effects on EI and body weight, which has been explained by compensatory decreases in REE,[49,50] reflecting an exercise-induced reduction in stress, endocrine and inflammatory activities. Furthermore, increasing body weight by an increase in EI does not inhibit EI or stimulate AEE as possible compensatory mechanisms. Finally, overfeeding does not result in a weight-independent adaptation of EE, that is, energy dissipation, whereas a mass-independent reduction of EE occurs with underfeeding.[51] Obviously, regulation of energy balance does not always result in a stable body weight. In fact EI is not only determined by homeostatic metabolic mechanisms (regulating EI and EE to keep body weight at a set point), but is also influenced by non-homeostatic hedonic mechanisms (related to an obesogenic environment and irrespective of body's energetics). Following that idea two different types of obesity, metabolic vs hedonic obesity have been defined.[52]

An alternative view on the biology of energy balance is that EE rather than body weight is under tight control. Physiologically, EE is maintained within a target range suggesting that there is an EE-set point, which has been proposed by Pontzer et al.[42,49] Intra-individual variations of EE are below 10% with between subject variation between 10 and 20%.[3,42,53] Among human populations, EE is similar and independent of lifestyles and

cultural or socioeconomic conditions.[50] EE increases with low and moderate physical activity but plateaus at long-term high activities to maintain EE within the target range (that is, EE is constraint with respect to physical activity[49]). EE does not increase with high EI.[51] As a first concept, intra-individual changes in body weight follow the missmatch between (imperfectly controlled) EI and (tightly regulated) EE. When EI is outside the target range of EE, a missmatch between EI and EE occurs.

To understand changes in body weight, the EE-set point model has to be extended because there is an additional (and may be to some degree independent of the EE-set point) regulation of allocation or partitioning of energy to (during overfeeding) or from (during underfeeding) fat mass and FFM, respectively. Partitioning of either fat mass and FFM or organ and tissue masses within FM and FFM or FM and FFM between different regions of the body or at the molecular level within cells explains the variance in individual weight changes at a given energy balance.[54] Besides energy balance and macronutrient intake partitioning is determined of fat mass, age, gender, physical

activity, inactivity, growth and reproduction, it is controlled by endocrine determinants (for example, insulin, IGF-1, testosterone, cortisol and T3) and during chronic inflammation.

Energy transfer is central in physiology, EE is a physiological trait. FFM is it's major determinant accounting for 50–75% of the variance in EE between subjects living in Western societies.[3,42,53] Correlation coefficients between body mass (or FFM) and REE or TEE are high (Figure 2; refs 53,55). Concomitantly, REE per unit weight (or REE on FFM) decreases with increasing weight or FFM documenting that in addition to FFM composition (and thus the specific metabolic activity of FFM, which is explained by the proportion of high to low metabolic rate organs within FFM) adds to the variance of REE (Figure 2; ref. 55). Comparing these associations in different age groups the confounding effect of age becomes evident too (Figure 2).

Figure 3 illustrates the view of a putative EE-set point. This extends Pontzer's hypothesized concept on ontogenetic responses in body size and EE to environmental signals, food availability and physical activity in different populations.[42,49]
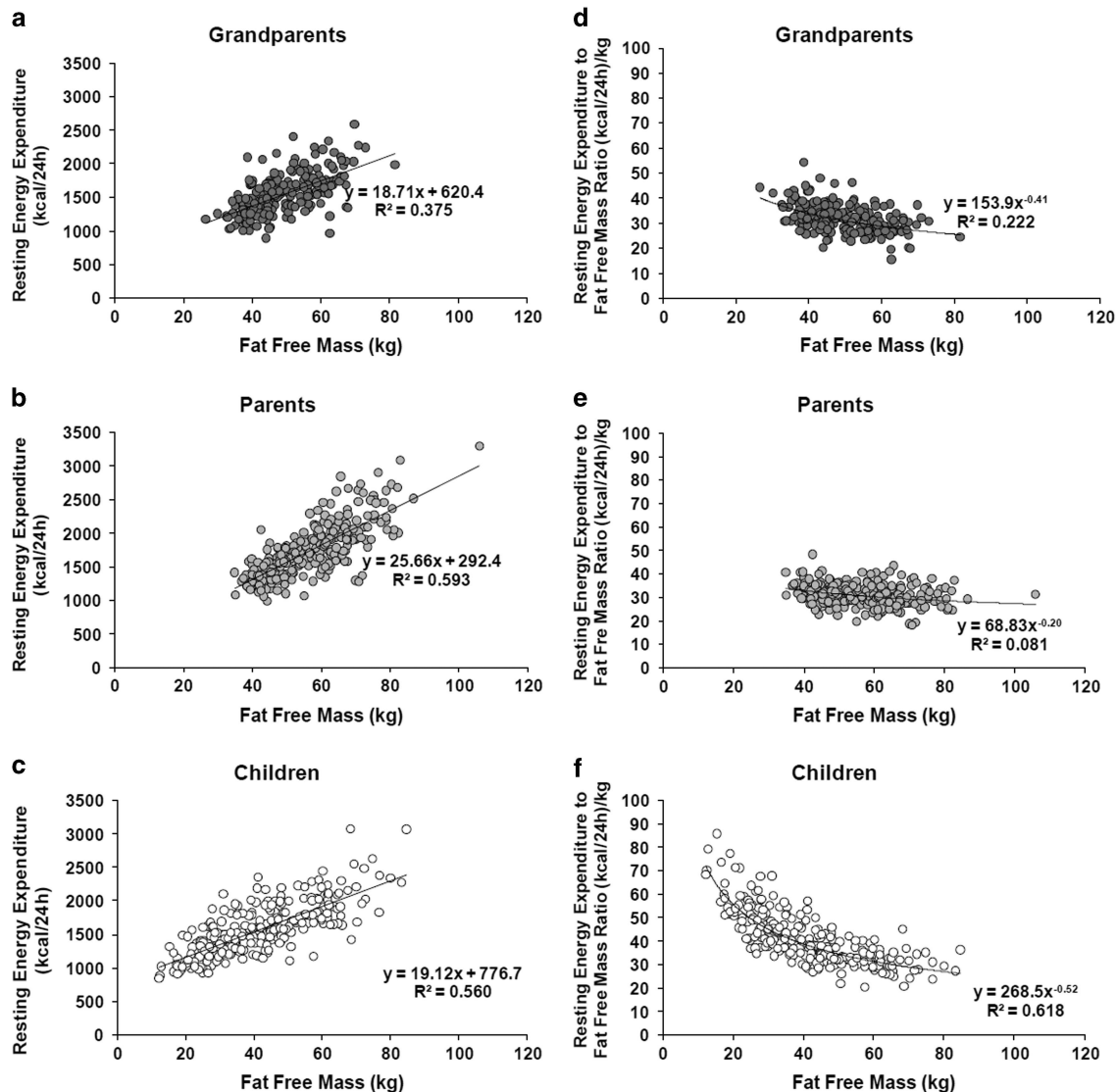

Figure 2. Associations between FFM and REE in grandparents (**a**), parents (**b**) and children (**c**) of 149 nuclear families of the Kiel Obesity Prevention Study. In addition, the corresponding associations between REE per FFM and FFM (reflecting specific metabolic activities of FFM) are shown (**d–f**). Data are from Bosy-Westphal *et al.*[69] Detailed characterization of the study population is shown in Table 1. See text for further details.
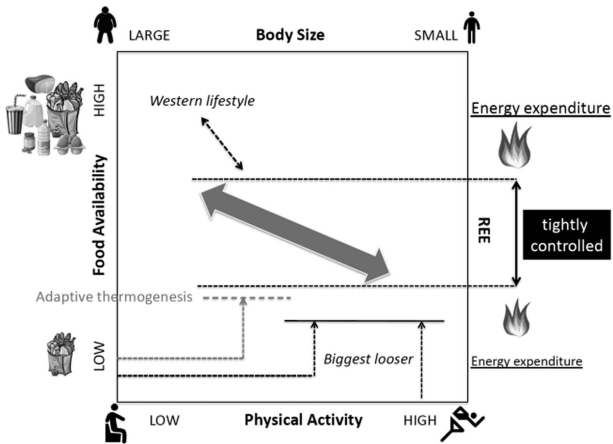
Figure 3. Hypothesized responses of body size and EE to physical activity and food availability. This graph has been modified according to the original idea published by Pontzer *et al.*[49,50] Pontzer proposed that physical activity and food availability are inversely correlated among human populations. Then populations vary along the axis given by the arrow in the center. Body weight and EE are high at high food availability and EI. Vice versa body weight and EE are low at low EI and high physical activity. At strenuous exercise EE is constrained. Contrary to Pontzer, we propose that EE is controlled within a relatively narrow range (characterized by an upper and a lower boundary) reducing the slope of the arrow in the original graph.[49] Then, obese subjects may be considered to be outside the EE control range, that is, at chronically high EI EE cannot increase above the upper boundary and match for EI. By contrast, during caloric restriction EI is below the lower boundary of EE. In this situation, EE can be slightly reduced below the lower boundary (that is, AT). However after considerable weight loss with drastic dieting together with heavy exercising (as shown in the 'biggest looser competition', see Speakmen *et al.*[56]) AT becomes more pronounced and may persist for years carrying the risk of weight regain.[28,51] This situation may reflect a damage of the biologic control of EE at the lower boundary. Our model assumes that tight biological control of EE results in a missmatch between EI and EE and thus changes in body weight.

During normal daily life conditions, shifts in EE with food intake and/or physical activity are mostly body mass-dependent. Changes in the EE–FFM relationship occur within a narrow target range. During short-term, the boundaries of that range are under biological control, whereas environmental and ecological factors may shift that boundaries over longer periods of time. Following a 'dual intervention point model',[56] the lower and upper limits are EE-set points where biologic control occurs. Between these boundaries EE is passively regulated following cellular ATP demand, which is given by ADP availability plus mitochondrial carbon load. For a given upper EE-set point a mass-independent increase in EE (that is, going beyond the upper boundary) with overfeeding does not occur in humans, whereas minor energy sparing (that is, going below the lower boundary) is seen with caloric restriction. This may be taken as evidence for regulation at the lower EE-set point, whereas there is no defense against weight gain.[51] This idea points to a possible asymmetry in the control of EE.[51] If this is true, regulation differs at both boundaries and is efficient in response to weight loss only.

The width between the two boundaries of EE may vary between individual subjects, which again may relate to inter-individual differences in the propensity of weight gain or weight loss. Regulation of EE may fail in very obese patients (Figure 3). They live in a 'low activity high food-availability setting'[49] and their EE is at or above the upper boundary of the body mass–EE relationship. If this is true the proposed upper EE-set point fails to match EI in
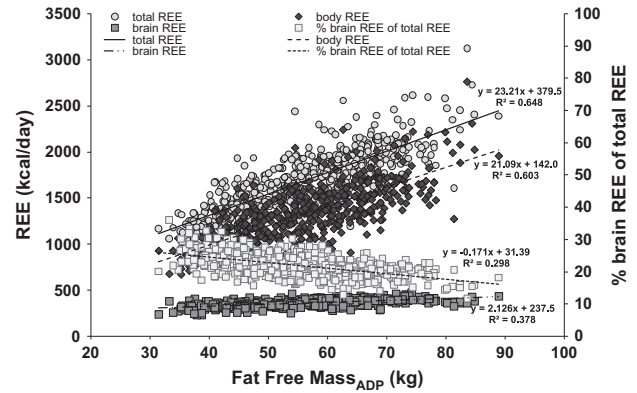

Figure 4. Association between FFM and total, brain and body REE in 267 subjects (55.8% females, 44.2% males) at a mean age of 28.9 years (range: 18–39.4 years). Brain REE was calculated from MRI-derived masses times-specific metabolic rate (for details see Müller *et al.*[63]). Body REE was then calculated as the difference between total REE (as measured by indirect calorimetry) and brain REE. For further details of the study population see Müller *et al.*,[74] Bosy-Westphal *et al.*,[75] Geisler *et al.*[76]

obese patients. As far as the lower boundary is concerned, drastic weight loss (due to severe dietary restriction plus excessive exercise) in very obese patients (as seen in the participants of the 'biggest looser' competition) may 'destroy' the lower set point resulting in persistent 'very low REE' as observed in the 'biggest looser' competition during re-gaining weight over a 6-year follow-up period (ref. 57; Figure 3).

ENERGY ALLOCATION TO THE BRAIN CONTROLS BODY EE
Within the body, allocation of available energy follows basal needs of individual organs and tissues with additional needs during growth, pregnancy, lactation or diseases. The brain has a hierarchical position in whole-body energy metabolism. Although brain mass accounts for 2% of body weight only, it's EE contributes to about one-fifth of REE, that is, in normal weight subjects 20% of the energy is allocated to the brain (ref. 58; Figure 4). Energy allocation differs by weight status and during changes of body weight. When compared with normal weight subjects the proportion brain EE to whole-body EE is 23% in underweight subjects, whereas obese subjects are down to 17% (Figure 4). Energy allocation to peripheral organs (like skeletal muscle) is relatively higher during growth and adolescence.[59] As brain is the only organ, which does not lose weight with weight loss,[60] its position within whole-body energy allocation is unique. Comparing humans and apes the larger brain size of humans explains their greater EE.[58,61,62] As correlations between human brain mass and FFM were low and FFM explained 5–6% of the variance in brain mass only,[58] EE of the brain and the rest of body mass have to be discussed separately.

Brain REE can be calculated from MRI-derived brain masses times brain's specific metabolic rate (see Müller *et al.*[63] for details). Both, brain EE and body EE increase with increasing FFM (Figure 4). However there is a 10-fold difference in the slopes of the EE–FFM relationships reflecting a relatively narrow range in brain mass and metabolism at different body masses (Figure 4). At a mean mass of 1.5 kg, brain REE accounted for 21.2% of whole-body REE, this number decreased with increasing FFM. For comparison, 27.5 kg of skeletal muscle mass contributed to 20.7% of REE with higher values at higher FFM (that is, specific metabolic rates of muscle and brain differ by a factor of 18). However, in a multiple linear regression analysis the proportion of

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brain to FFM explained 46% of the variance in REE, whereas the proportion of muscle mass to FFM explained 8% only.

These data may add to the idea that the brain demands a constant energy budget and thus keeps whole-body EE within a tight range to preserve its own energy supply. The brain tries to keep neuronal ATP concentrations constant and a constant energy supply from the body occurs by a so-called 'brain pull mechanism'.[64] This is obvious during food shortage where allocation of energy from body periphery towards the brain is brought about by a decrease in insulin secretion at concomitant increases in the pituitary and adrenal stress response reflected by an increased cortisol release and increased activity of the sympathetic nervous system.[64] Brain size and brain EE are preserved at the cost of peripheral metabolism.

IS EE A HERITABLE TRAIT?

Inter-individual differences in EE are partly influenced by the genotype. The genetic effect may reach 40% of the variance in EE.[65] However there are only few studies, which had addressed this issue limiting the present evidence on the genetics of EE. In monozygotic and dizygotic twins heritability estimates of REE were 42% but most of the effect was explained by the heritability of FFM.[65,66] Heritability estimates were lower based on the calculation of parent–offspring associations.[65,67–69] When compared with twin studies heritability of REE (adjusted for FFM, age and sex) was about 30% in family studies.

In a three generation study on 149 nuclear families, which was part of the Kiel Obesity Prevention Study (KOPS[70]), heritability (as calculated over three generations) was 33% for FFM and 30% for REE adjusted for FFM.[69] Re-calculation of the data of this study population (Table 1) revealed a generation effect (Table 2). Heritability of FFM was 73% in the older generation (that is, the grandparent–parent relationship) compared with 43% in the younger generation (that is, the parent–child relationship). By contrast, there was no difference in heritabilities between generations either in REE, REE adjusted for FFM and residuals of REE on FFM. After suitable adjustments for FFM, heritabilities of REE reached 38–45%, which is slightly higher than was previously assumed.[65,67] These data suggests that REE is moderately heritable and there is a genetic effect on REE, which is independent of the genetic effect on FFM. As heritability estimates (i) vary during childhood and adulthood,[71] (ii) do not differentiate between genetic effects, the effects of shared environments and a possible gene-by-environment interaction and (iii) are affected by body composition methodology,[72] the 'true' genetic effect on REE remains to be calculated.

The present heritability estimates do not really address the conceptual model shown in Figure 3. Following the 'dual intervention point model' of the EE-set point,[56] the genetic effect is not about one EE value but about a range of EEs and its boundaries, which are assumed to be under biological control. To address this issue intra-individual variations of EE in response to various controlled conditions (for example, during over- and underfeeding as measured for example, in the setting of a respiration chamber) are to be characterized in greater groups of twins or nuclear families.[73]

CONCLUSIONS

EE is a classical issue of nutrition research. Most of our knowledge about EE dates back to research done 20 and more years ago. As assessment of EE did not add much to explain weight gain and overweight most scientists had moved to the issue of EI. After a nearly 20 year period of intensive research on EI, EE is now coming back into the focus of research on body weight regulation. The

Table 1. Characteristics of the members of the three generation-nuclear families investigated as part of the Kiel Obesity Prevention Study[69]

	All (n = 813) Mean ± s.d.	Females (n = 427) Mean ± s.d.	Males (n = 386) Mean ± s.d.
Age (years)			
Grandparents[a]	67.5 ± 7	66.5 ± 7.2[b]	68.9 ± 6.4
Parents[c]	43.5 ± 6.4	47.0 ± 6.2[b]	45.1 ± 6.7
Children[d]	12.8 ± 4.7	12.3 ± 4.2	13.3 ± 5
BMI (kg/m^2)			
Grandparents	28.4 ± 5	28.9 ± 5.5[b]	27.6 ± 3.6
Parents	27.2 ± 5.2	26.7 ± 5.7	27.7 ± 4.5
Children	20.7 ± 5.2	20.4 ± 5.1	20.9 ± 5.3
FFMI (kg/m^2)			
Grandparents	17.5 ± 2.5	16.4 ± 2.1[b]	19.5 ± 1.8
Parents	18.4 ± 2.6	16.9 ± 1.9[b]	20.0 ± 2.1
Children	16.1 ± 2.7	15.3 ± 2.2[b]	16.7 ± 3
FMI (kg/m^2)			
Grandparents	10.8 ± 4.1	12.5 ± 4.0[b]	8.1 ± 2.5
Parents	8.7 ± 4.1	9.8 ± 4.4[b]	7.7 ± 3.4
Children	4.7 ± 3.7	5.2 ± 3.7[b]	4.2 ± 3.7
REE (kcal/24 h)			
Grandparents	1536.6 ± 307.4	1444.4 ± 271.2[b]	1687.4 ± 304.9
Parents	1730.8 ± 398.3	1511.3 ± 263.6[b]	1959.8 ± 386.5
Children	1567.9 ± 381.4	1409.7 ± 198.4[b]	1710.1 ± 411.2
REE$_{FFM}$ (kcal/24 h)			
Grandparents	1538.6 ± 242.9	1562.8 ± 221.1	1498.9 ± 271.8
Parents	1737.2 ± 253.8	1751.8 ± 192.1	1722.1 ± 305.2
Children	1567.9 ± 381.4	1494.0 ± 198.4[b]	1633.0 ± 277.8
Residuals REE (kcal/24 h) on FFM (kg)			
Grandparents	0.0 ± 242.9	24.2 ± 221.1	− 39.6 ± 271.8
Parents	0.0 ± 253.8	14.5 ± 192.1	− 15.2 ± 305.2
Children	0.0 ± 381.4	− 73.2 ± 198.4[b]	65.8 ± 277.8

Abbreviations: BMI, body mass index; FFM, fat-free mass; FFMI, fat-free mass index; FMI, fat mass index; REE, resting energy expenditure. [a] n = 223. [b]Significant difference between females and males; independent t-test (P < 0.05). [c] n = 296. [d] n = 294.

Table 2. Heritability estimates obtained in 149 nuclear families as part of the Kiel Obesity Prevention Study[69]

	Three generations	Two generations (old)	Two generations (young)
FFM (kg)	0.304	0.729	0.430
FM (kg)	0.504	0.562	0.542
REE (kcal/24h)	0.442	0.535	0.447
REE$_{FFM}$ (kcal/24h)	0.419	0.453	0.455
Residuals of REE on FFM	0.347	0.387	0.384

Abbreviations: FM, fat mass; FFM, fat-free mass; REE, resting energy expenditure; REE$_{FFM}$, fat-free mass adjusted resting energy expenditure. The study population is characterized in Table 1. We have used variance component methods as implemented in SOLAR with extended pedigrees to obtain heritability estimates (see Blangero et al.[77]). Calculations were based on either three generations (grandparents, parents and children) or two generations (old: pairs of grandparents and parents; young, pairs of parents and children).

present evidence suggests that EE is a vital sign, thus, it is under tight biological control. There is evidence for an EE-set point. By contrast, EI is not perfectly controlled. This is also reflected by the population-wide prevalence of weight gains and overweight. To get further insights suitable protocols for assessment of EE (that is, assessing EE in subjects during varying and controlled conditions) are warranted taking into account suitable concepts and methods for assessment of body composition.[73] In future, changes in the EE–FFM relationship rather than EE-values alone will give rise to appropriate phenotyping.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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