

Energy balance and weight regulation: genetics versus environment

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The prevalence of obesity is reaching epidemic proportions in many industrialized countries. There is growing evidence that, even if the trigger of this epidemic is found in changes in the environment, genes are interacting with the environment to cause weight gain. Studies of twins reared apart indicate that approximately two-thirds of the variability in BMI is attributed to genetic factors. From prospective studies in Pima Indians we can ascribe 12 % of the variability in BMI to metabolic rate, 5 % to fat oxidation, and another probable 10 % to the level of spontaneous physical activity. These data indicate that at least 40 % of the variability in BMI is related to genetic factors involved in the regulation of food intake and/or volitional activity. This indicates that the most likely successful therapy for obesity may target pathways of the regulation of food intake. Similarly, an environment favouring engagement in physical activity should be promoted.

Energy balance: Weight regulation: Obesity: Genetics: Environment: Energy metabolism

Throughout the world, in parallel with industrialization, the prevalence of obesity is increasing dramatically. It is estimated that one in two Americans is overweight or obese (Flegal *et al.* 1998). Between the late 1970s and the early 1990s, the prevalence of overweight subjects (BMI \geq 25.0 kg/m²) increased moderately from 46 to 54 % in the USA. However, during the same period the prevalence of obesity (BMI \geq 30.0 kg/m²) increased from 14.5 to 22.5 %. The economic burden of obesity was estimated at US\$99 billion in 1995, including US\$52 billion in direct medical costs (Wolf & Colditz, 1998).

Obesity results from a chronic disruption of energy balance. The energy balance equation states that energy stores are a reflection of the difference between energy intake and energy expenditure. Energy intake consists of food and drink consumption. Total energy expenditure can be divided into three major components: resting metabolic rate, thermic effect of food, and the energy cost of physical activity. While food intake has been difficult to measure in humans (Lichtman *et al.* 1992), all components of energy expenditure can be measured accurately in a respiratory chamber (Ravussin *et al.* 1986) and free-living physical activity can be assessed by using the doubly labelled water technique (Schoeller & Field, 1991).

Although the pathogenesis of obesity is not completely understood (Ravussin & Swinburn, 1992; Rosenbaum *et al.* 1997), in most cases excessive accumulation of fat is probably due to the interaction between genetic factors and environmental conditions. Studies of energy intake and expenditure in humans have shown that obesity is not

only the result of bad behaviour, or so-called 'sloth and gluttony'. In most cases inherited metabolic characteristics, combined with unfavourable environmental conditions such as constant access to energy-dense food and minimal physical demands of daily living, cause the development of obesity. We have previously described our present westernized environment as a 'pathoenvironment' (Ravussin, 1995), whereas Egger & Swinburn (1997) have introduced the concept of an 'obesigenic environment'. This provocative concept seems to call for a cure of the environment rather than the people living in it. However, even in this environment, so favourable to weight gain, there are many people who do not gain weight, perhaps due to a constant struggle against their nature or because of a genetic make-up that is protective against obesity.

Genetics of obesity

Studies of adoptees and twins clearly indicate that a large part of the variability in body size and body composition is attributable to genetic factors (Bouchard, 1994). In contrast, migration studies indicate an important role of the environment. Taken together these studies suggest that among different populations the prevalence of obesity is largely determined by environmental factors. However, among individuals from the same population, living in a given environment, the variability in body size and body composition is mostly related to genetically determined response to that environment. Studies of twins reared apart indicate that approximately two-thirds of the variability in

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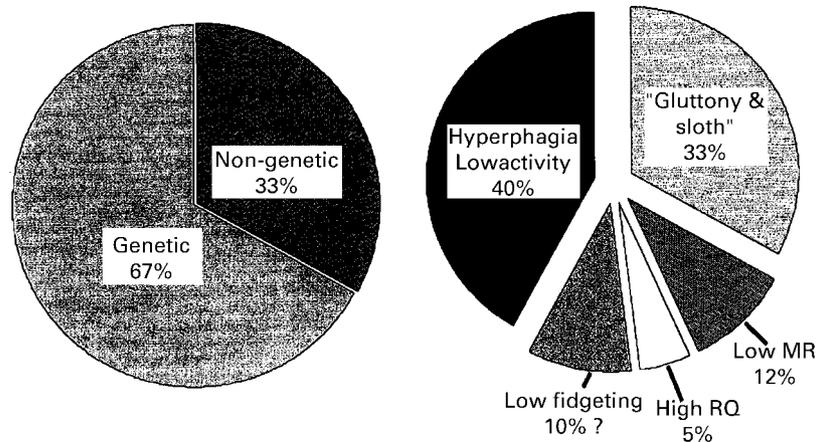


Fig. 1. (a) Studies of monozygotic twins reared apart (see Table 1) indicate that approximately one-third of the variability in BMI is attributable to non-genetic factors and two-thirds to genetic factors. (b) Breakdown of the genetic part of the variability in BMI into effects of metabolic rate (MR), respiratory quotient (RQ), spontaneous physical activity (fidgeting) and hyperphagia. Values for MR, RQ and fidgeting were obtained from prospective studies conducted among the Pima Indians of Arizona.

BMI can be attributed to genetic factors (Table 1, Fig. 1; Stunkard *et al.* 1990; Price & Gottesman, 1991; Allison *et al.* 1996). However, some have argued that the role of genes in determining BMI may be inflated in these studies, as the data were collected in developed countries where the environmental influences are likely to be consistent. Assuming that two-thirds of the variability in BMI is genetically determined, it is now important to determine how much of the genetic predisposition (or resistance) to obesity is related to energy metabolism (metabolic rate, spontaneous physical activity and fat oxidation) and how much is related to food intake.

Metabolic predictors of weight gain

The Pima Indians were studied in order to identify metabolic predictors of body weight gain and diabetes (Ravussin & Swinburn, 1993). In these prospective studies body composition was assessed by hydrodensitometry, and measurements of energy metabolism were performed after a minimum of 3 d on a weight-maintenance diet provided at a clinical research centre. Total energy expenditure, 24 h respiratory quotient (RQ) and spontaneous physical activity were all simultaneously measured in a respiratory chamber as described previously (Ravussin *et al.* 1986). In both men and women, total energy expenditure increases with body

weight, although at any given weight the variability in energy expenditure is 500–700 kcal/d. After adjustment for differences in fat-free mass, fat mass, age and sex, most of the variance was found to aggregate in families, indicating a genetic determinant of metabolic rate. Furthermore, the variability in metabolic rate is associated with such biological factors as body temperature (Rising *et al.* 1995) and the activity of the sympathetic nervous system (Spraul *et al.* 1993). Most importantly, after adjustment for the above covariates a low relative metabolic rate was associated with body-weight gain over a 3–4-year period of follow-up. The inverse relationship between weight change and adjusted 24 h energy expenditure had a coefficient of determination (R^2) = 0.16 indicating that 16 % of the variability in weight change was related to the variability in metabolic rate. However, as described below, part of this 16 % may be related to variability in spontaneous physical activity. One can safely conclude that at least 12 % of the variability in weight is caused by the variability in metabolic rate. We have previously emphasized that only prospective studies can identify metabolic predictors of weight gain, since there is a normalization of these factors in response to the development of obesity. Obesity is the price to pay for re-establishing an equilibrium (Ravussin & Gautier, 1999).

The RQ is used to determine the relative amount of energy derived from carbohydrate and fat (Zurlo *et al.* 1990; Seidell *et al.* 1992). In studies of weight gain in Pima Indians over a period of 3 years, individuals with a high RQ were more likely to gain weight than those with a low RQ. The coefficient of determination of this relationship indicated that 5 % of the variability in weight gain was related to the variability in RQ, adjusted for energy balance and percentage body fat. Respiratory quotient was also found to be a familial trait, and is probably, like metabolic rate, genetically determined (Zurlo *et al.* 1990). As with metabolic rate, the RQ is also related to such biological factors as the activity of the sympathetic nervous system. Similar results of high RQ predicting weight gain were

Table 1. Estimated heritability of obesity from studies of twins reared apart

Study	Number of pairs	Heritability (h^2)
Stunkard <i>et al.</i> (1990)	93	0.66f, 0.7m
Price & Gottesman (1991)	34	0.61
Allison <i>et al.</i> (1996)		
Finnish	17	0.65
Japanese	10	0.73
American	26	0.85

obtained in older subjects (Seidell *et al.* 1992). In a dietary model of obesity, Pagliassotti *et al.* (1997) showed that, when placed on a high-fat diet, obesity-prone rats had a higher RQ than obesity-resistant rats. The authors observed that a high RQ is the major link with increased energy intake when animals are placed on a high-fat diet. Taken together, these results indicate that metabolic rate and RQ are two genetically determined traits which affect weight regulation in Pima Indians and probably in other populations.

Another component of 24 h energy expenditure is the energy cost of spontaneous physical activity which accounts for 8–15 % of daily energy expenditure (Ravussin *et al.* 1986). Some of the 24 h energy expenditure variability is due to variability in the level of spontaneous physical activity (Ravussin *et al.* 1986; Zurlo *et al.* 1992). Most cross-sectional studies have shown a decrease in spontaneous physical activity in obese subjects. In longitudinal studies in Pima Indians, even in the confined environment of a respiratory chamber, spontaneous physical activity is a familial trait, and a low level of spontaneous physical activity was associated with subsequent weight gain in males (Zurlo *et al.* 1992). Consistent with these data, a recent overfeeding study found that a gain in fat mass was inversely related to the level of spontaneous physical activity (Levine *et al.* 1999). The authors call this activity non-exercise activity thermogenesis (NEAT).

Factors underlying variability in body weight

With the knowledge that approximately two-thirds of variance in BMI is genetically determined (Table 1; the remainder is due to 'sloth and gluttony'), we can divide the 67 % into 12 % for metabolic rate, 5 % for RQ and an estimated 10 % for spontaneous physical activity. This leaves another 40 % related to factors not measured in these studies, i.e. food intake. The latter has been very difficult to measure in humans. One can use precise methods in a laboratory setting, but results are not reflective of everyday life, or crude methods under free-living conditions that are not accurate enough. Therefore new techniques, such as positron emission tomography or functional magnetic resonance imaging (MRI), will help to uncover the genetic components underlying hyperphagia. In a recent study (Tataranni *et al.* 1999) we showed that in healthy men neuronal activity increases in the prefrontal cortex and decreases in the hypothalamus, insular cortex, orbital frontal cortex, thalamus and hippocampal formation, in response to a single meal. Another study using functional MRI confirmed that lean subjects demonstrate an inhibition of signals in the area of the paraventricular and ventromedial nuclei of the hypothalamus (Matsuda *et al.* 1999). Importantly, these authors showed that this inhibitory response was markedly attenuated and delayed in obese subjects when compared with lean volunteers. Using PET scans, one of our most recent studies raises the possibility that the brain's responses to a meal in pre-frontal areas (often associated with the inhibition of inappropriate response tendencies) and in limbic/paralimbic areas (commonly associated with the regulation of emotions) may reflect changes in the central autonomic network, which may be different between obese and lean subjects (Gautier *et al.*

1999, unpublished results). Such techniques, applied to post-obese subjects as well as patients suffering from eating disorders, will help identify the neurological pathways involved in hyperphagia, often found in obese subjects.

The search for obesity genes

Over the past 5 years genetic linkage studies have focused increasingly on complex traits such as obesity. Genome-wide scans have been completed in Mexican Americans (Comuzzie *et al.* 1997); Pima Indians (Hanson *et al.* 1998; Norman *et al.* 1998); a diverse population of whites and blacks (Lee *et al.* 1999); French Canadian families (Pérusse *et al.* 1999); and French families (Hager *et al.* 1998). From all these studies, major loci linked to obesity have been found on chromosomes 2, 5, 10, 11 and 20. Those areas of the genome will be studied further to possibly clone obesity susceptibility genes.

The Québec group (Pérusse *et al.* 1999) provides an annual update of the human obesity gene map. From association and linkage studies, the authors claim that putative loci affecting obesity-related phenotypes are found on all except chromosome Y of the human genome. It also seems that the number of genes and other markers that have been associated or linked with human obesity is increasing very rapidly, and now approaches 200.

With the upcoming partial publication of the Human Genome, it is likely that our understanding of the genetic basis and the identification of novel genes involved in obesity will be greatly improved. New pathways in the etiology of obesity will be uncovered, and in the more distant future individual identification of genetic variants will be possible, making individually targeted therapies available.

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