

# The Etiology of Obesity: Relative Contribution of Metabolic Factors, Diet, and Physical Activity

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Three major factors modulate body weight: metabolic factors, diet, and physical activity, each influenced by genetic traits. Despite recent advances in these areas, the prevalence of obesity in Westernized societies has increased. In contrast to monogenic animal models and rare human genetic syndromes, predisposition to common forms of obesity is probably influenced by numerous susceptibility genes, accounting for variations in energy requirements, fuel utilization, muscle metabolic characteristics, and taste preferences. Although recent increases in obesity prevalence cannot be explained by changes in the gene pool, previously "silent" genetic variants may now play important permissive roles in modern societies. Available data suggest that variations in resting energy expenditure, thermic effect of food, and fuel utilization exist but, by themselves, are unlikely to explain the onset of obesity. Regarding diet, the best available

trend survey data indicate that fat and energy intake have fallen, in this and other Westernized countries. Diverging trends of decreasing energy intake and increasing body weight suggest that reduced physical activity may be the most important current factor explaining the rising prevalence of obesity. Subsistence in modern societies requires extreme adaptations in previously useful energy-conserving diet and exercise behaviors. Recognizing the difficulties in sustaining energy-restricted diets in the presence of fast foods and social feasts, the current trend toward increasing body weight is not likely to be reversed solely through recommendations for further reductions in energy intake. In all likelihood, activity levels will have to increase in response to an environment engineered to be more physically demanding. *Am J Med.* 1998;105:145-150. ©1998 by Excerpta Medica, Inc.

In the past few decades, several advances have been made in our understanding of the factors that contribute to obesity, including the identification of a mutant gene causing obesity and the potential role of metabolic factors such as variations in energy expenditure and in patterns of fuel utilization. Despite these advances, the prevalence of obesity in the US adult population has increased by 31% from 1976 to 1991 (1). This upward trend is in sharp contrast to the US Public Health Service objective that there be no increase in the prevalence of obesity as outlined in *Healthy People 2000* (2).

Three major factors are believed to contribute to the etiology of obesity: metabolic factors, diet, and physical inactivity. In turn, each is influenced by genetic traits. For example, there is clear evidence from adoption (3-5) and twin studies (6,7) that there is a genetic component in human obesity. Both cross-sectional (8) and longitudinal studies (9) demonstrate familial resemblance in adipos-

ity. The purpose of this commentary is to examine the relative contribution of metabolic factors, diet, and physical inactivity to the development of obesity, and the underlying role of genetic influences. Our conclusion is that research and intervention efforts need to focus on physical inactivity as the major current factor contributing to the increasing prevalence of obesity in modern society.

## ROLE OF METABOLIC FACTORS

### *Energy Expenditure*

The three components of total energy expenditure include resting energy expenditure, thermic effect of food, and activity-related energy expenditure. Genetic influences appear to affect resting energy expenditure (10,11), thermic effect of food (11), and adaptive body fat changes to short-term overfeeding (12). The relative contribution of each component to daily energy expenditure is variable, the smallest coming from thermic effect of food, which accounts for about 10% of the total. Although several studies have reported that there is a blunted thermic effect of food response in obese persons, the potential energy "savings" is probably <25 kcal/day (13), an amount that would explain a total weight gain of less than 2 kg (14). Resting energy expenditure, which generally represents about 60% of daily energy expenditure, depends largely on body mass, especially fat-free mass, which is more metabolically active than fat tissue (15). On an absolute basis, resting energy expenditure is usually higher in obese persons because of their greater body size, including fat-free mass. However, when adjusted for

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differences in fat-free mass, resting energy expenditure values in obese and nonobese individuals tend to be comparable (10,13,15). Even after adjustment for body composition, there is variability in resting energy expenditure among individuals (16). Thus, relatively low resting energy expenditure values could be associated with weight gain. Several longitudinal studies have addressed this possibility. Seidell et al (17) found no association of baseline resting energy expenditure with weight change among 775 men during a 10-year period. In a study of 24 obesity-prone postobese women and 24 matched never-obese controls, Weinsier et al (18) found that resting energy expenditure did not predict weight gain in either group during a 4-year period of follow-up, though the obesity-prone women gained significantly more weight. Among 126 Pima Indians, Ravussin et al (16) reported that adjusted resting energy expenditure was lower in those individuals who subsequently gained >10 kg; however, a relatively low resting energy expenditure was not a significant predictor of the rate of weight gain during the 2 to 4 years of follow-up. They estimated that only about one third of the observed 15.7 kg weight gain could be attributed to a relatively low baseline resting energy expenditure. Recent data of Goran et al (19) indicated that initial resting energy expenditure level did not predict changes in fat mass in 75 children followed up annually for 4 years. Thus, normal variations in body composition-adjusted resting energy expenditure may affect daily energy requirements; however, available evidence suggests that such variations in resting energy expenditure have, at best, only a small impact on one's tendency to gain weight.

In contrast to resting energy expenditure, a relatively low total daily energy expenditure (measured in a metabolic chamber) has been found to be strongly correlated with the rate of weight gain ( $r = -0.39$ ,  $P < 0.001$ ) (16). These findings and subsequent data (20) suggest that reduced nonresting (ie, activity-related) energy expenditure may be the component of daily energy expenditure that predisposes to obesity, at least among the Pima Indians who were subjects of these studies. Moreover, spontaneous activity related energy expenditure represents about 30% of total energy expenditure and is the most variable component (21,22). For example, the total daily energy cost of physical activity varies about ninefold in the confines of a metabolic chamber, and about 30-fold in free-living conditions (23). Thus, although not all studies are confirmatory (19), the available evidence suggests that reduced activity-related energy expenditure is a potentially important contributor to the predisposition to obesity.

### *Fuel Utilization*

From data obtained in Pima Indians (24), a relatively high respiratory quotient, reflecting reduced fat oxida-

tion, has been suggested as a metabolic index that can predict weight gain (25). The Baltimore Longitudinal Study (17) also demonstrated that a higher resting respiratory quotient correlated with greater weight gain; however, this was only true among lean subjects. Conversely, a relatively low respiratory quotient did not predict subsequent weight loss. Larson et al (26) reported that 11 obesity-prone postobese individuals had significantly lower rates of fat oxidation (higher respiratory quotient) than control subjects despite similar energy requirements. In contrast, we have found that resting fat oxidation rates in 24 postobese women were not different from those of 24 never-obese controls, nor did fat oxidation rates predict 4-year weight gain patterns (18). Thus, the effects, if any, of fuel utilization on obesity are not established, nor is there evidence that reported variations in fuel utilization affect energy balance.

## **ROLE OF APPETITE AND DIETARY FACTORS**

In 1994 the leptin gene was described. Its product, leptin, acts via the leptin receptor to suppress food intake and to increase energy expenditure in animals (27). Evidence for genetic linkage of the leptin locus with human obesity has been reported, but only in extremely obese persons (28,29). Only two cases of leptin deficiency in humans have been reported, due in both cases to a homozygous frame shift mutation in the leptin gene. The subjects are two young cousins from a consanguineous family who are very obese and have barely detectable levels of an aberrant leptin molecule (30).

Contrary to early expectations that subnormal leptin synthesis may cause obesity in humans (eg, due to failure to suppress appetite), fasting serum leptin levels are elevated in obese patients and, in most cases, in proportion to the degree of obesity (31,32). These findings led some investigators to speculate that obesity may be due to leptin resistance (33). At present this is unconfirmed. Indeed, data in animals suggest that the appetite-suppressant effect of leptin may be overridden by access to highly palatable, energy-dense foods (34). The implication of these findings for human obesity seems obvious: enticing food advertisements and social eating behaviors may override leptin-induced satiety and cause weight gain.

Many studies have reported a relationship between dietary fat consumption as a percent of total caloric intake and adiposity, although the association appears to be highly variable (35). In contrast to such cross-sectional analyses, secular trend surveys can provide information about dietary and body weight patterns in large populations over time. According to the USDA Nationwide Food Consumption Survey, average fat intake in the United States decreased from 41% to 37% of calorie in-

take between 1977 and 1988 (36). (Another large survey, the National Health and Nutrition Examination Survey, NHANES, also examined food intake patterns over the same period of time; however, these data cannot be used to track changes in food intake because of revisions in survey methodology (37).) According to the Nationwide Food Consumption Survey, average total energy intake also decreased, by 3% in women and by 6% in men (36). Paradoxically, the reductions in average fat and energy intake were associated with a progressive increase in the prevalence of obesity in the US adult population (38). Similarly, surveys in Great Britain between 1970 and 1990 indicated that obesity has become more common while average recorded energy intake declined substantially (39). During the most recent 2 decades of the Bogalusa Heart Study, the prevalence of obesity among 10-year-old children rose, despite no change in energy intake and a decrease in fat intake (40). Finally, a preliminary report of 10-year-old French children studied in 1978 and again in 1995 indicated that obesity prevalence rose while energy intake fell (41). Admittedly, dietary patterns are difficult to measure accurately, and fat and calorie intake may have only *appeared* to decline in recent years, perhaps because of more underreporting, especially among obese persons (42). (Although a positive association has been found between adiposity and underreporting (43), another study found no relationship (44).)

Food industry efforts to promote the use of sugar-substituted, reduced-fat, and reduced-calorie food products have been highly successful in this country, as evidenced by a fourfold increase in the percentage of the US population consuming these items, from 19% in 1978 to 76% in 1991 (45). A nondigestible fat substitute (Olestra) has recently appeared on the market for use in select snack foods (46). Because of the popularity of these products, it is worth looking at their potential for controlling body weight. If, as is expected, the new fat substitute decreases average per capita daily fat intake by about 3 g, or 27 kcal per day, what is the likelihood that this potential energy "savings" will result in a substantial population-wide change in body weight? Assuming that a 7,700 kcal imbalance results in a 1 kg change in adipose tissue (47), clinicians often mistakenly project that even small energy imbalances such as 27 kcal/day (9,855 kcal/year) will result in large weight changes over time. In this instance, one might predict a weight change of about 1.3 kg a year (9,855 divided by 7,700) such that a 64-kg person could conceivably weigh nothing after 50 years, with no other diet or exercise modifications other than selection of the new fat-substituted snacks! The fallacy of this calculation is evident if one considers that a sustained reduction of 27 kcal/day (eg, from 2,027 to 2,000 kcal/day) cannot result in a person starving to death. A more realistic projection, taking into account changes in body composition and concurrent energy requirements as weight is gained or

lost (14), is that reduction of 27 kcal through use of the new snack products would produce a final weight change of less than 2 kg in about 5 years, after which a new weight plateau would be reached.

Although national survey data that describe divergent trends in energy intake and obesity prevalence do not permit conclusions about cause-effect relationships, it is evident that the increased use of the reduced-calorie food products and the concurrent reduction in fat and energy intake have not attenuated the rising prevalence of obesity. Thus, if these dietary intake data are correct, the average level of daily physical activity-related energy expenditure must be declining substantially (38).

## ROLE OF PHYSICAL INACTIVITY

There is an inverse relationship between physical activity and adiposity, with correlation coefficients in the order of  $-0.4$  (48,49). In a large population of adult Finns, the prevalence of overweight was found to be considerably higher in sedentary women (21%) and men (14%) than in physically active women (8%) and men (7%) (50). Exercise training also generally results in at least a moderate decrease in body fat (approximately 0.1 kg/week) (51). However, the amount of energy expended differs according to the type of physical activity chosen, and the energy economy of the activity (energy expenditure/work performed) is modified by its relative intensity, the muscle groups used, and the range of motion involved (52–55). For example, 22% more energy is required to perform the same amount of bicycle work at a high intensity than at a low intensity (56), and three times as much energy is required to perform one bench press at 80% of one's maximum compared with four bench presses at 20% of maximum (52). Thus, certain activities may be more beneficial than others in terms of their impact on energy balance.

In addition, people may not be equally predisposed to engage in physical activity, perhaps depending on their muscle fiber types and metabolic characteristics. Obesity-prone rats (57) and obese persons (58,59) have an increased proportion of fast-twitch (type IIB) muscle fibers, which have decreased oxidative capacity (60,61) and oxidize less lipid during steady-state exercise (59). Inherent differences in muscle oxidative capacity may influence the perceived level of fatigue and, hence, the ability or inclination to be physically active. Muscle fiber recruitment patterns might be responsible for the slow component of oxygen exchange kinetics during exercise, excessive oxygen cost, and, possibly, reduced exercise tolerance of certain individuals (62). Our preliminary data among obesity-prone women studied under controlled conditions suggest that a higher body weight is associated with greater physiologic stress of exercise, and a tendency

to spend less time in physical activity (63). Inherent differences in muscle fiber type ratios and function may predispose certain individuals to be less active and to gain weight (64).

Bouchard and Tremblay (11) have shown that the level of spontaneous physical activity may be influenced by genotype. Spontaneous activity related energy expenditure has not been well studied owing to measurement difficulties, but our preliminary data obtained from young sibling pairs suggest that nonresting energy expenditure is significantly correlated among siblings ( $r = 0.33$ ,  $P < 0.05$ ) (65). The impact of inherent differences in muscle characteristics on spontaneous activity levels is not known. However, available evidence supports the hypothesis that variations in muscle metabolic characteristics play a role in the etiology of obesity (59), and given an environment less demanding of physical activity, as typically found in this country, certain persons may be particularly predisposed to accept a sedentary lifestyle.

Systematic survey trend data on leisure-time physical activity in the US population were not collected until about 1985. Since that time, leisure-time physical activity appears to have changed very little, with 60% of US adults reporting that they are not regularly active and 25% reporting that they are not active at all (66). There are no epidemiological data on total daily physical activity, taking into account occupational and household activities, as well as leisure-time exercise. On the basis of survey data in Great Britain that show diverging patterns of energy intake and obesity prevalence, Prentice and Jebb (39) concluded that a modern inactive lifestyle must play an important, and perhaps dominant, role in the increasing prevalence of obesity. In support of this conclusion, we found that normal-weight, postobese women who reported being “nonexercisers” gained more than twice as much weight over 4 years of follow-up as “regular exercisers” (18). On a much larger scale, a 5-year prospective study of over 12,000 Finnish adults found that sedentary individuals were almost twice as likely to experience substantial weight gain as physically active men and women (50). By contrast, greater energy intake was associated with weight gain only among women. Thus, population-wide, the relationship of physical inactivity to weight gain appeared to be more consistent than the relationship of excess energy intake to weight gain.

## CONCLUSIONS

In contrast to the monogenic animal models of obesity and rare genetic syndromes of human obesity, the predisposition to common forms of obesity among humans is probably influenced by many susceptibility genes that may affect energy expenditure, fuel utilization, muscle fiber characteristics, and even taste preferences, all of

which could impact on our behavioral responses to the environment. Although the increase in obesity prevalence in the past few decades cannot be explained by changes in the human gene pool, genetic variants that were previously “silent” may be manifest. Current unprecedented environmental influences, together with genetic susceptibility, underlie the rise in obesity prevalence in this and other countries. Simply put, our genes permit us to become obese; the environment determines *if* we become obese.

Regarding metabolic factors, available data indicate that although there are variations in resting energy expenditure and in the thermic effect of food, there is little evidence that these variations contribute significantly to the observed trends in weight gain. The role of variations in fuel utilization is still unresolved, but if reduced fat oxidation were to contribute to the increased prevalence of obesity, it must be demonstrated to do so by affecting energy balance.

The reported patterns of decreasing fat and energy intake in Westernized countries have not prevented increases in body weight. These diverging trends do not mean that diet is not important in the development of obesity; obesity prevalence might have risen even faster if not for the apparent dietary restraint and availability of reduced-calorie food products. However, dietary factors do not appear to be the primary determinant of the increasing prevalence of obesity. By contrast, available longitudinal data point toward a potentially important contribution of reduced physical activity. Modern society may offer the perfect environment for expression of inherent differences in our muscle characteristics and proclivities for physical inactivity, making it easy to be inactive, especially when one is so predisposed. Indirect evidence from various national surveys supports this view and suggests that reduced total daily physical activity may well be the most important current factor contributing to the increase in body weight in Westernized countries. Efforts to exercise during leisure time appear to be offset by occupational and household activities that require less and less physical exertion.

Common forms of obesity may be viewed as disorders with genetic influences that occur most readily among individuals who are prone to energy-conserving behaviors when placed in environments that provide ready access to energy-dense foods and that are physically less demanding. These behaviors, which consist of preferential seeking of energy-dense foods and sedentary activities, are unlikely to be inherently maladaptive from an evolutionary standpoint since energy conservation represents an adaptive trait (67). Rather, subsistence in modern societies requires extreme adaptations in these previously useful dietary and activity behaviors—adaptations that are achievable by relatively few individuals. Survey data suggest that we have, in fact, adapted our dietary

behaviors reasonably well, even in the present climate of convenience foods, restaurants, and social feasts. However, recognizing the difficulties in sustaining energy-restricted diets, the current trend toward increasing body weight is not likely to be reversed solely through recommendations for further reductions in fat and energy intake. In all likelihood our daily activity level will have to increase in response to an environment that is engineered to be more physically demanding. To accomplish this goal, community, industry, and federal involvement will be needed to develop more physically demanding communities in the face of continued technological advances that reduce energy expenditure in activities of daily living.

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