

YOU ARE WHAT YOU EAT?

Evidence for dietary phenotypes and implications for weight management.



ESTELLE LAMBERT

BSc (Phys Ed), MS
(Exercise Physiology), PhD
(Physiology)

Professor

Department of Human
Biology
Faculty of Health Sciences
University of Cape Town

Estelle Lambert is a member of the UCT/MRC Research Unit for Exercise Science and Sports Medicine. Her areas of research include obesity and metabolism, physical activity and health, early origins of adult disease and the aetiology of fatigue during exercise. She is author or co-author of more than 65 peer-reviewed scientific publications and currently acts as an expert consultant to the World Health Organization on issues related to physical activity guidelines in developing countries.



JULIA H GOEDECKE

BSc (Physiology), BSc
(Med) Hons Nutrition and
Dietetics, PhD (Exercise
Science)

Senior Lecturer

Department of Human
Biology
University of Cape Town

Julia Goedecke is a registered dietician who is currently an MRC Career Development Awardee. Her research focuses on understanding the mechanisms underlying the association between obesity and the manifestation of the metabolic syndrome, specifically examining the role of the adipose tissue compartments.

Conventional wisdom gives rise to the adage 'you are what you eat', both in terms of portions and composition. When we think of this axiom, we conjure visions of ample food portions, rich in energy, high in fat, and associated with persons of equally ample body size proportions and body fat composition. However, these relationships are more complex than they may appear at first glance. The physical, physiological and behavioural manifestation of the complex interaction between genetics and environment is known as a phenotype. The extent to which the environment can have an impact on the expression of the phenotype is known as plasticity. If the environment can strongly influence the phenotype, this is regarded as a high level of phenotypic plasticity (Fig. 1).¹

Therefore, for a given genotype, depending on environmental cues and exposures, any number of phenotypes may develop. As a result the obesity 'phenotype' is likely to be, in fact, not one but many phenotypes or subgroups, based on a number of interactions between genotype and environment.

EVIDENCE FOR DIETARY AND METABOLIC OR OXIDATIVE PHENOTYPES: IMPLICATIONS IN OBESITY

One such environmental determinant that has been implicated in the aetiology of obesity is dietary fat intake. There is substantial epidemiological evidence to suggest that increased dietary fat intake is positively associated with increased body fat composition and the prevalence of obesity. This has been shown in population-based adult studies, in a variety of countries and settings, using both cross-sectional and longitudinal study designs.² The proposed underlying mechanisms for this association have been the palatability and energy density of the high-fat diet, leading to overconsumption, which is not matched by increased fat oxidation. Despite this, there is also evidence to suggest that behavioural or dietary phenotypes exist, reflected by persons who can select a diet that is relatively high in fat, maintain a BMI within the normal range and successfully increase whole body rates of fat oxidation.^{2,3}

It has been argued that in order to remain weight stable, and to prevent unhealthy weight gain, the substrate or fuel mix, in terms of macronutrient intake, must be matched by levels of oxidation.³ Failure to match intake and oxidation is implicated in obesity. This line of reasoning is supported by studies that have demonstrated an inverse association between body fat content and rates of fat oxidation compared with carbohydrate (as measured by the respiratory exchange ratio (RER)).⁴ Moreover, a low ratio of fat-to-carbohydrate oxidation has been shown to predict future weight gain in a group of obese-susceptible individuals.⁵ In a study of over 150 non-diabetic Pima Indians, those who had an overall lower rate of fat oxidation on entry into the study at year 1 were 2.5 times more

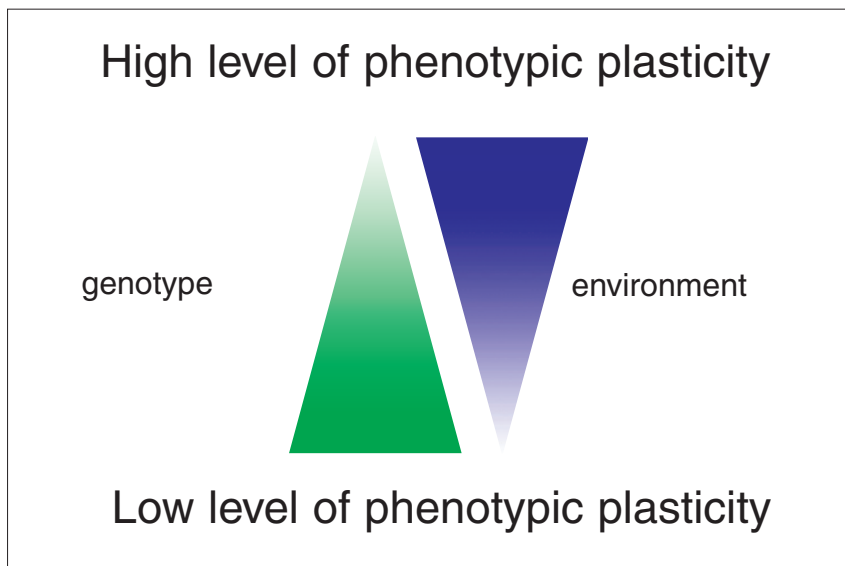


Fig. 1. Phenotypic plasticity suggests that environment can play a significant role in the development of the phenotype.

likely to gain weight (> 5 kg) over a 3-year follow-up period. Marra *et al.*⁶ found a similar association between low ratios of fat-to-carbohydrate oxidation and subsequent weight gain in non-obese women followed up over a 3-year period. Taken together, these data suggest that the inability to increase fat oxidation in response to dietary fat predisposes individuals to an increased risk of obesity. At a functional level, this observation has been corroborated by studies in which obese persons, under controlled conditions, have been provided with *ad libitum* access to high-fat foods. These subjects were unable to increase the overall rate of fat oxidation over a 7-day period, and were in positive energy and fat balance.⁷ Therefore, a mismatch between fat intake and oxidation in some people may be causatively associated with obesity.

However, as mentioned above, several cross-sectional studies in healthy, normal-weight, male university students have described high- and low-fat dietary phenotypes. In the low-fat group, < 35% of ingested energy was comprised of dietary fat compared with > 43% in the high-fat group. It is remarkable that those with the higher fat intake have a significant and concomitantly higher resting energy expenditure, a higher rate of fat oxidation in the fasted state, and are better able to oxidatively dispose of fat in response to a high-fat meal (Fig. 2).^{8,9}

These groups not only differed in their oxidative metabolism, but also in their behavioural response to feeding. For example, in terms of meal size, when presented with *ad libitum* high-fat and low-fat meals, the high-fat phenotype group consumed a similar weight of food each time, and therefore had a

higher energy intake with the high-fat meal. Conversely, the low-fat phenotype group ate according to energy content, and as a result had less of the more energy-dense, high-fat meals. The high-fat group also experienced a much higher hunger rating before eating, and eating resulted in a more effective suppression of hunger in this group. The low-fat group, on the other hand, had a very flat response to appetite before and in response to eating.

These studies provide only a cross-sectional snapshot of what may be a dynamic process of metabolic compensation for a behavioural phenotype. We do not know, for example, if these individuals will be placed at increased risk for obesity when exposed to a high-fat diet over a period of time (Table I).

Longitudinal studies are needed to determine whether the increased levels of fat oxidation will protect this lean, high-fat phenotype group from weight gain. Similarly, it is unclear whether or not the low-fat phenotype individuals would be able to prevent weight gain in the face of increased dietary fat intake or a decrease in activity levels.

FACTORS INFLUENCING THE DIETARY OR METABOLIC PHENOTYPE: IS THIS PHENOTYPE MUTABLE?

Dietary change

Dietary fat intake may be influenced, in part, by external environmental factors such as the relatively low cost per

Table I. Behavioural or dietary phenotypes, protective factors and factors which may place them at risk for obesity in the long term^{8,9}

Phenotype	Risk factors	Protective factors	Risk for weight gain
High fat	High-fat diet ↑ Total energy intake ↑ Sedentary behaviour	↑ RMR ↑ Night-time EE ↑ Fat oxidation	Further ↑ in sedentary behaviour Maintenance of a high-fat diet
Low fat	↓ RMR ↓ Fat oxidation	Low-fat diet ↓ Daily energy intake ↓ Daily activity	Introduction of high-fat foods or occasional high-fat binges Less active

RMR = resting metabolic rate; EE = energy expenditure

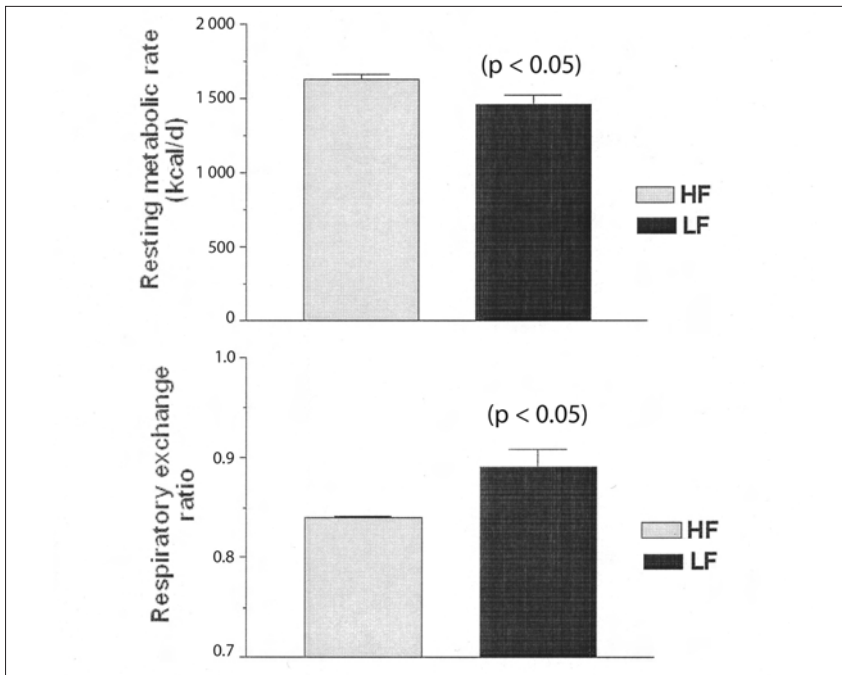


Fig. 2. Resting metabolic rate and respiratory exchange ratio in high-fat and low-fat consumers. A lower respiratory exchange ratio denotes a higher rate of fat oxidation.^{8,9}

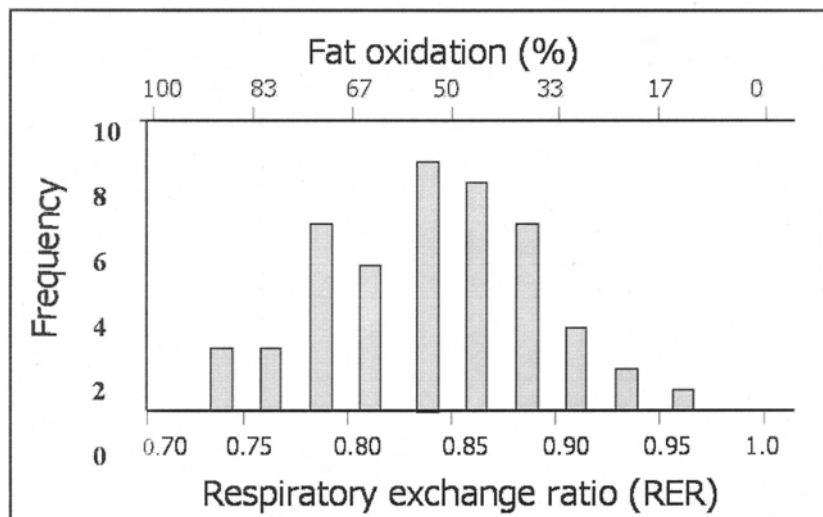


Fig. 3. Individual variability in fat and carbohydrate oxidation in the fasted, rested state in well-trained cyclists is highlighted by this frequency distribution.¹³

MJ of foods rich in added fat and sugar, which are energy-dense and highly palatable.¹⁰ In addition, the social norms for portion sizes have steadily increased over the past 2 decades,¹¹ with restaurants and fast food outlets serving meals and a la carte items that are 2 - 3-fold greater in weight or energy than previously. However, food energy intake as well as dietary preferences and dietary

macronutrient selection may also be influenced by genetic susceptibility. It has been said that 'genes load the gun and a permissive environment pulls the trigger'.²

Exercise training

There is evidence that exercise and/or endurance training is associated with an increased fat oxidative capacity, and for a given energy output there is an increased rate of fat oxidation.¹²

On the other hand, there are data to suggest that even well-trained individuals present with a wide range of metabolic or substrate phenotypes, with fat oxidation at rest accounting for as little as 20% of overall energy expenditure to as much as 80% of oxidative metabolism¹³ (Fig. 2). Therefore, just how mutable or changeable is the fuel mix?

We know that the ratio of fat-to-carbohydrate oxidation tends to aggregate in families,¹⁴ is determined in part by age, gender, dietary fat content,^{13,14} and indirectly by muscle glycogen content.¹³ In healthy, non-obese persons, increased fat oxidation at rest has been positively associated with increased prevalence of type I muscle fibres,¹⁵ as well as increased activity of key enzymes involved in β -oxidation.¹⁶ Theoretically, exercise training should increase the overall reliance on fat as an oxidative fuel. However, in studies of obese and post-obese individuals, training results in little or no change in 24-hour fat oxidation.¹⁷ However, if obese persons exercise in conjunction with a high-fat diet, fat balance is more readily achieved, probably in response to reduced glycogen stores and an overall increased rate of fat oxidation.¹⁸ Thus, fat oxidation can adjust to fat intake when glycogen stores are reduced through prior exhaustive exercise, even in the obese phenotype.

Weight loss

Indirect evidence remains to suggest that the metabolic phenotype is causally associated with obesity. For example, post-obese women and restrained eaters have higher RERs (and thereby lower ratios of fat-to-carbohydrate oxidation) than either their lean or freely eating counterparts. Moreover, the muscle enzyme profile of post-obese women reflects a lower capacity for fat oxidation compared with weight-matched, never-obese women, and similar to that of obese women before weight loss. Therefore, a lower capacity for fat oxidation imparts risk for obesity, particularly in the face of increased dietary fat.

IMPLICATIONS FOR INTERVENTIONS

There is compelling evidence that there are specific metabolic subgroups, or dietary and metabolic phenotypes, seen in people whose diets are relatively higher or lower in dietary fat or who appear to have a greater or lesser ability to oxidise dietary fat. The question remains as to whether people with a high-fat diet, without a concomitant increase in fat oxidation, are predisposed to obesity. Does this, or should this, change our existing public health recommendations for prudent dietary guidelines?

Current public health guidelines continue to recommend that dietary fats comprise less than 20 - 35% of energy intake¹⁹ and that dietary carbohydrate sources are rich in fibre, such as fruits, vegetables and whole grains. Even though dietary fat is one of the factors that may promote fat oxidation in some individuals, this has not been well demonstrated in obesity-prone persons. In fact, these persons present with a mismatch between fat intake and oxidation. Therefore, the current dietary recommendations make empirical sense.

These recommendations are, however, further corroborated by results of intervention studies in which dietary fat intake was reduced, either alone or in combination with an overall reduction in energy intake. In a recent meta-analysis, an *ad libitum*, low-fat, high-carbohydrate diet was effective in inducing weight loss at an average rate of ~ 1.8 kg/month. Moreover, the low-fat diet resulted in greater reported satiety and less caloric compensation, leading to an overall lower food energy consumption. It was estimated that a 10% reduction in dietary fat energy was associated with a weight loss of 32 g/day,² highlighting this approach as an effective intervention strategy. If subjects who are predisposed to obesity have some impairment or reduced capacity to oxidise fat compared with carbohydrate this provides further impetus for a reduced fat intake.

There is increasingly popular support for diets, such as the Atkins diet, which are generally low in carbohydrate and relatively higher in protein and fat content. Despite this, there is little scientific evidence evaluating the long-term success of these diets in controlled clinical trials. Recent studies suggest that weight losses in the short term may be better, but after 12 months the low-carbohydrate diets fare no better than any other dietary method, and are perhaps not as effective for long-term adherence compared with their low-fat counterparts. What is often not considered is the fact that nutritional individuality, or the presence of various obesity subgroups or phenotypes, may contribute to the variability of responses to dietary and exercise regimens.

METABOLIC FLEXIBILITY AND MANAGEMENT OF OBESITY

Currently, there has been a tendency to adopt a one-size-fits-all approach to the management of obesity, without consideration of the possible behavioural and metabolic phenotypes that underpin this condition. Perhaps another way of looking at the obese state is to consider the concept of metabolic flexibility, which has been defined as 'a clear capacity to utilise lipid and carbohydrate fuels and to transition between them'.²¹ Indeed, dysfunction or failure in metabolic flexibility leads not only to the obese state, but also to the associated metabolic consequences of insulin resistance and the metabolic syndrome. For example, a loss of metabolic flexibility may be manifest by an absence of the cephalic-phase insulin response in anticipation of a meal. This has important implications for suppressing the release of fatty acids from adipose tissue or glucose output from the liver. Another example of loss of metabolic flexibility may be related to a reduced mitochondrial size or density in the obese, type 2 diabetic individual, with an associated decrease in the capacity for oxidative disposal for fat and reduced insulin sensitivity.

Both conservative management and pharmacotherapy must take into consideration potential targets such as reducing dietary fat intake or increasing energy expenditure and fat oxidation, with the expressed purpose of matching dietary intake with relative oxidative disposal of macronutrients. Moreover, characteristics of the obese phenotype may not be reversed simply as a result of weight loss, and thus may further predispose an individual to weight gain. Finally, as an individual loses weight, changes his/her diet or increases levels of physical activity, he/she becomes a moving target from a metabolic perspective, and as such, treatment strategies may need to be revised.

References available on request.

IN A NUTSHELL

A phenotype is the physiological, structural and behavioural manifestation of a genetic and environmental interaction.

There are likely to be many subgroups or phenotypes of obesity, with many predisposing environmental and behavioural precedents.

There are some individuals, with a lean phenotype, who consume a high level of dietary fat, with a concomitantly high level of fat oxidation. However, obesity is in part due to a mismatch between dietary fat intake and fat oxidation.

There is evidence that obese individuals have a reduced capacity to oxidise fat, and a reduced proportion of type I muscle fibres, and tend to select a diet higher in overall fat energy.

Exercise helps to restore fat balance by increasing fat oxidation, in particular when glycogen stores are limited.

Current dietary recommendations for a low-fat diet are still valid, even for various obesity phenotypes.

A failure of metabolic flexibility, or a capacity to utilise both lipid and carbohydrate fuels, and to move appropriately between them may be implicated in obesity and associated morbidity.