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The role of high-fat diets and physical activity in the regulation of body weight

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The prevalence of obesity is increasing in westernized societies. In the USA the age-adjusted prevalence of BMI >30 kg/m² increased between 1960 and 1994 from 13 % to 23 % for people over 20 years of age. This increase in the prevalence of obesity has been attributed to an increased fat intake and a decreased physical activity. However, the role of the impact of the level of dietary fat intake on human obesity has been challenged. High-fat diets, due to their high energy density, stimulate voluntary energy intake. An increased fat intake does not stimulate its own oxidation but the fat is stored in the human body. When diet composition is isoenergetically switched from low to high fat, fat oxidation only slowly increases, resulting in positive fat balances on the short term. Together with a diminished fat oxidation capacity in pre-obese subjects, high-fat diets can therefore be considered to be fattening. Another environmental factor which could explain the increasing prevalence of obesity is a decrease in physical activity. The percentage of body fat is negatively associated with physical activity and exercise has pronounced effects on energy expenditure and substrate oxidation. High-intensity exercise, due to a lowering of glycogen stores, can lead to a rapid increase in fat oxidation, which could compensate for the consumption of high-fat diets in westernized societies. Although the consumption of high-fat diets and low physical activity will easily lead to the development of obesity, there is still considerable inter-individual variability in body composition in individuals on similar diets. This can be attributed to the genetic background, and some candidate genes have been discovered recently. Both leptin and uncoupling protein have been suggested to play a role in the prevention of diet-induced obesity. Indeed, leptin levels are increased on a high-fat diet but this effect can be attributed to the increased fat mass observed on the high-fat diet. No effect of a high-fat diet *per se* on leptin levels is observed. Uncoupling proteins are increased by high-fat diets in rats but no data are available in human subjects yet. In conclusion, the increased intake of dietary fat and a decreasing physical activity level are the most important environmental factors explaining the increased prevalence of obesity in westernized societies.

High-fat diet: Physical activity: Obesity: Fat oxidation

Obesity is becoming a major health problem in affluent societies. The incidence of obesity is increasing rapidly. In the USA the age-adjusted prevalence of BMI >30 kg/m² increased between 1960 and 1994 from 13 % to 23 % for people over 20 years of age. The overall prevalence of BMI >25 kg/m² was found to be 55 % (Flegal *et al.* 1998). In Europe, the most comprehensive data on the prevalence of obesity (BMI >30 kg/m²) comes from the World Health Organization MONICA study (Keil & Kuulasmaa, 1989). This study, for which data was collected between 1983 and 1986, shows that in only three out of thirty-eight participating centres was the prevalence of obesity below

10 %. In most European countries this prevalence is still rising (Seidell, 1995). In Australia, Canada and Brazil an increase in the prevalence of obesity has also been reported (Millar & Stephens, 1993; Boyle *et al.* 1994; Monteiro *et al.* 1995) and even the prevalence of obesity in developing countries (although still below 5 %) is increasing (Seidell & Rissanen, 1997). From these figures it can thus be concluded that the prevalence of obesity is increasing worldwide. The increase in the prevalence of obesity is often ascribed to the changing lifestyle in westernized societies, among which is the consumption of high-fat diets. In the last 20 years many food products have become

Abbreviation: FQ, food quotient.

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available that are cheap, palatable and high in fat content, and thus, dietary fat intake has increased rapidly. Since dietary fat is the most energy-dense macronutrient, with about 38 kJ/g (in comparison, carbohydrate and protein only provide about 17 kJ/g), an increase in dietary fat intake can easily promote an increase in energy intake and thus result in overconsumption. Epidemiological evidence for a relationship between fat intake and obesity comes from Lissner & Heitmann (1995), who reviewed data from thirteen studies examining the relationship between fat intake and obesity. In eleven out of thirteen studies a statistically significant relationship was found between energy-adjusted fat intake and one or more measures of obesity. Other evidence for a role of dietary fat intake in the increasing prevalence of obesity comes from studies examining the concurrent changes in obesity and fat intake over extended periods of time. For example, Sonne-Holm & Sorensen (1977) showed that the increase in obesity between 1945 and 1975 in Danish men was paralleled by an increase in fat intake. Together with the finding that the capacity of the human body to respond to an increased fat intake with an increased fat oxidation is limited (Blaak *et al.* 1994), and high-fat diets thus would preferentially lead to deposition of dietary fat into the fat stores, these results indicate that the consumption of high-fat diets seems to be a reasonable explanation for the increased prevalence of obesity in westernized societies. Recently, however, the impact of the level of dietary fat intake on human obesity has been challenged (Katan *et al.* 1997). The prevalence of obesity in the USA is still increasing, whereas the intake of fat is decreasing (Kuczmarski *et al.* 1994). Therefore, a decrease in physical activity has been proposed to be responsible for the increasing prevalence of obesity in westernized societies. Occupational work has been automated and this is not compensated for by an increase in physical activity during leisure time. Therefore, energy expenditure will be lower and thus a positive energy balance is likely to occur, even when energy intake does not change. A decreased physical activity might also therefore be responsible for the increased prevalence of obesity. In most data sets from the general US population, negative relationships between measures of physical activity (self-reports) and indices of obesity have been reported (Eck *et al.* 1992; Kuczmarski *et al.* 1994). However, accurate population-based records of trends in physical activity over time are lacking, which can be explained by difficulties in measuring physical activity in large populations.

Finally, in our westernized society there is still large individual variability in body weight even in people on similar diets. Thus, there seems to be an important interaction between dietary factors and genetic background. Indeed, adoption and twin studies show the impact of the interaction between environmental and genetic factors on body composition (Stunkard *et al.* 1986).

In this review, evidence will be presented for a role of high-fat diets in the development of obesity. The effects of high-fat diets on fat intake and fat oxidation will also be discussed. Furthermore, some evidence will be given for an interaction between high-fat diets and recently discovered, genetic determinants of obesity.

The effect of high-fat diets on energy intake

The development of obesity is characterized by an imbalance (temporal) between energy intake and energy expenditure. An increased energy intake, when not accompanied by an increased energy expenditure, will result in a positive energy balance and an increase in body weight. Since high-fat diets are characterized by a high energy density and high palatability they are often considered to increase energy intake (Miller *et al.* 1990; Prewitt *et al.* 1991; Klesges *et al.* 1992; Verboeket-van de Venne *et al.* 1996). In the Leeds (W. Yorks., UK) high-fat study there were nineteen times more obese subjects among the consumers of a habitual diet with a high fat content (>45 % of energy derived from fat) than among the consumers of a habitual diet with a low fat content (<35 % of energy derived from fat) (Blundell & Macdiarmid, 1997). Furthermore, numerous studies show that voluntary energy intake is higher on a high-fat diet (Lissner *et al.* 1987; Blundell *et al.* 1993; Lissner & Heitmann, 1995; Westerterp *et al.* 1996b). It has even been suggested that high-fat diets are more fattening than isoenergetic low-fat diets, i.e. independent of an effect on energy intake (Romieu *et al.* 1988; Miller *et al.* 1990). However, recent data clearly illustrate that the fat content of the diet influences body fat only when energy intake is also increased (Westerterp *et al.* 1996b). One explanation for the increased energy intake on high-fat diets is the higher palatability of high-fat diets compared with low-fat diets, stimulating voluntary food consumption. Another explanation for the increased energy intake on high-fat diets is that in commercially available food items, the percentage of energy derived from fat is highly correlated with energy density (Poppitt, 1995; Westerterp-Plantenga *et al.* 1996). Thus, when a similar volume of food is consumed, energy intake will be higher on high-fat diets compared with low-fat diets. It has therefore been suggested that it is simply the energy density of the diet instead of the dietary fat content that promotes over-consumption. Evidence for this is provided by Saltzman *et al.* (1997), who found no difference in voluntary energy intake between low-fat (20 % of energy derived from fat) and high-fat (40 % of energy derived from fat) diets when matched for energy density and palatability. This finding indicates that dietary advice to prevent the development of obesity should focus on a reduction of the consumption of energy-dense food items. However, although low-fat food items can also have a high energy density, in practice the fat content is the major determinant of energy density and the consumption of high-fat diets will therefore favour over-consumption, possibly leading to obesity.

The effect of dietary fat on fat oxidation

J. P. Flatt's two compartment model

As stated earlier, weight maintenance requires that, in the long term, energy intake is equal to energy expenditure. However, this also requires a close match between intake and oxidation for the separate macronutrients. Important work on this concept was done by Flatt (1987a,b, 1988). He described the features of body-weight maintenance with a

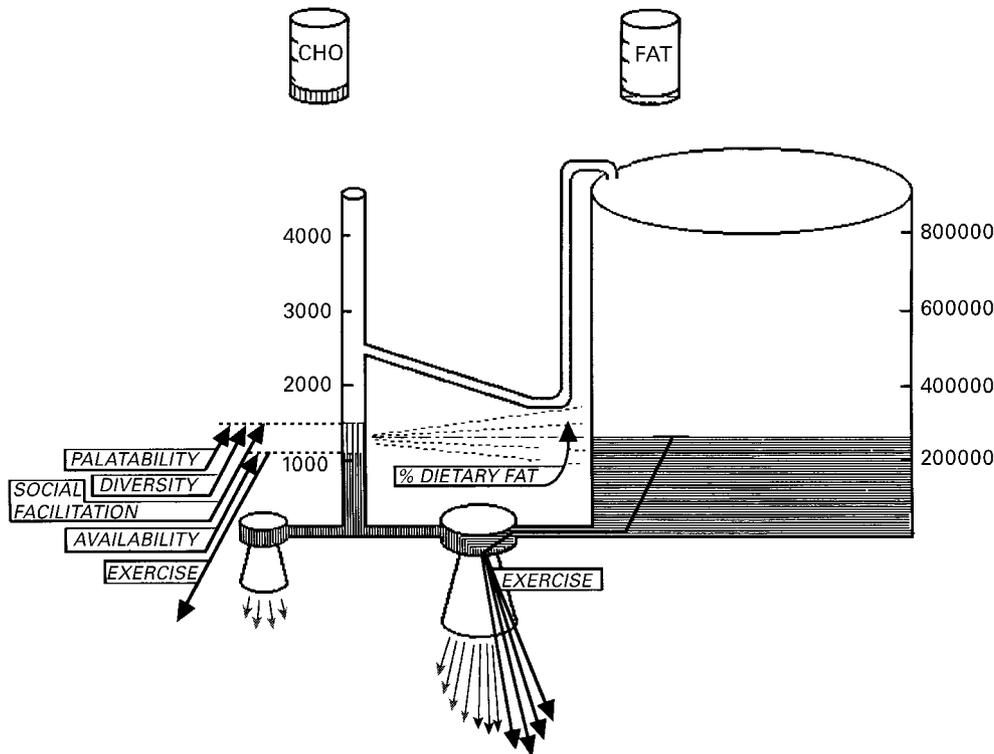


Fig. 1. Two-compartment model of J. P. Flatt, illustrating the effect of circumstantial and lifestyle factors on adiposity. The small and the large reservoirs represent the human body's limited capacity for storing glycogen and its large capacity for storing fat respectively (expressed as kcal; 1 kcal 4.184 kJ). The small turbine illustrates the exclusive use of glucose by the brain. The relative proportions of glucose and fatty acids used by the large turbine are assumed to be influenced by the levels to which the two reservoirs are filled at a given time. Reproduced, with permission, from Flatt (1987a).

two-compartment model (Flatt, 1987a; Fig. 1). The small reservoir is representative for the carbohydrate stores in the human body, which can vary between 200 and 800 g glycogen. The large reservoir represents the capacity of the human body to store fat, which is huge when compared with the glycogen stores. The relative size of the two reservoirs determines the composition of the fuel being oxidized. Expansion of one reservoir will lead to an increased influx from this reservoir and a greater contribution to the fuel mix oxidized. Addition of a fixed quantity (carbohydrates) to the small reservoir will lead to an increase in the contribution of carbohydrates to the fuel mix oxidized (rise in RER), whereas addition of an isoenergetic quantity (fat) to the large reservoir will only result in minor changes in the fuel-mix oxidized. Furthermore, the model predicts that one of the driving forces for food intake is a physiological requirement to maintain glycogen stores at a certain level. With this model, the effect of the fat content of the diet on substrate metabolism can be predicted. Addition of a fat supplement to the diet will not stimulate fat oxidation and, in the long term, fat mass will increase. When diet composition is isoenergetically switched from low-fat to high-fat, the model predicts that an expansion of the large reservoir (fat mass) or a decrease in the small reservoir (glycogen stores) is required to allow an increase in fat oxidation. Since, according to the model, man will voluntarily eat to maintain glycogen stores, a higher amount of energy will be ingested when dietary

composition is high in fat (and thus low in carbohydrate). Therefore, consumption of high-fat diets will lead to a positive fat balance and thus an increase in fat mass will occur. This increase in the fat mass is then accompanied by increased fat oxidation, thereby compensating for the high fat intake on the high-fat diet. Thus, the model gives a possible explanation for the suggested link between dietary fat and obesity observed in western society. With the model it can be explained that physical activity might prevent the development of obesity when high-fat diets are consumed, by lowering glycogen stores and thus increasing fat oxidation. Since physical activity seems to influence food preferences, with active subjects consuming carbohydrate-rich diets (Westerterp *et al.* 1996a), and exercise results in a short-term reduction of energy intake (Westerterp-Plantenga *et al.* 1997), lowering of the glycogen stores by physical activity does not necessarily lead to a drive to increase food intake. Therefore, the model predicts an overall positive effect of intensive (i.e. glycogen lowering) physical activity on the development of obesity.

Apart from the theoretical explanation for the effect of high-fat diets on body-weight regulation given by the two-compartment model, several studies have examined the effect of fat content of the diet on substrate oxidation. In these studies, two approaches have been used: the effect of fat supplements in excess of energy requirements, or the effect of isoenergetic high- and low-fat diets, supplied in energy balance.

Table 1. The effect of fat supplements on fat oxidation

Study	Subjects	n	Fat in diet (%)	Size of fat supplement (g)	Duration of diet (h)	Fat oxidation (g/h)		Fat balance (g)	
						Mean	SD	Mean	SD
Flatt <i>et al.</i> (1985)	Lean	7	11	50	9	4.2	1.6	-32	18
			50		9	4.6	1.6	+7	10
Schutz <i>et al.</i> (1989)	Lean	7	35	106	24	6.3		-43	
			52		24	6.0		+75	
Bennett <i>et al.</i> (1992)	Lean	8	30	50	18	3.9	1.8	+34	26
			37		18	4.0	2.0	+72	24
Dallosso & James (1984)	Lean	8	30	135	7 × 24	NA		+14	25
			50		7 × 24	NA		+163	27
Thomas <i>et al.</i> (1992)	Lean	11	37	56	7 × 24	4.4		NA	
			52		7 × 24	4.8		NA	
	Obese*	10	38	59	7 × 24	5.3		NA	
			52		7 × 24	6.2		NA	

* NA, not available.

Obesity was defined as a BMI >30 kg/m².

The effect of fat supplements on fat oxidation

Flatt *et al.* (1985) investigated the effect of dietary fat on postprandial substrate utilization and nutrient balance in seven young men, 1 h before and 9 h after the ingestion of two different breakfasts. Subjects were given a low-fat breakfast (11 % of energy derived from fat) or a low-fat breakfast with a 50 g fat supplement. As predicted by his model, substrate oxidation was not influenced by the surplus fat. After the low-fat breakfast (9 h) fat balance was negative, whereas after the fat supplement a positive fat balance was reached. Similar results were obtained by Bennett *et al.* (1992). Adding 50 g fat to a standard breakfast did not increase fat oxidation during an 18 h period following the breakfast and therefore it was concluded that all surplus fat was stored. Schutz *et al.* (1989) studied the effect of a dietary fat surplus on substrate oxidation in a respiration chamber over 60 h intervals. After a 12 h run-in period, subjects consumed a mixed diet (35 % of energy derived from fat) in the first 24 h and were in energy and fat balance. Adding 106 g fat to the diet in the next 24 h did not change energy expenditure or substrate oxidation, leading to the conclusion that the total fat surplus was stored. Fat balance and energy balance were closely correlated. The effect of 1 week fat-overfeeding on 24 h substrate oxidation was studied by Dallosso & James (1984). They found that the fat overfeeding had no effect on fat oxidation and the surplus fat (50 % of normal energy intake) was stored. To study the influence of diet composition on the regulation of body weight, Thomas *et al.* (1992) fed eleven lean and ten obese subjects (body fat > 25 % for men and > 30 % for women) *ad libitum* with low-fat and high-fat diets for 1 week. On day 7 on each diet, 24 h substrate oxidation was measured using a respiration chamber. Voluntary energy intake was higher on the high-fat diet compared with the low-fat diet. On day 7 of the low-fat diet, carbohydrate intake was positively related to carbohydrate oxidation, indicating that carbohydrate intake stimulated its own oxidation, and carbohydrate balance was reached. After 7 d on the high-fat diet, fat intake was related to fat oxidation, but only in the lean subjects. Furthermore, even the lean subjects were not able to stimulate fat oxidation to an

extent sufficient to match fat intake, and a positive fat balance was reached.

The results of these studies (Table 1) clearly show that, both in the short as well as in the long term, fat intake does not stimulate its own oxidation, when dietary fat is given in excess of energy requirements. The excess dietary fat is stored in the adipose tissue and energy balance is closely correlated with fat balance. However, the question remains whether similar effect would be observed if subjects were not overfed by adding fat to the diet, but by adding carbohydrates. To test this, Horton *et al.* (1995) overfed isoenergetic amounts (50 % above energy requirements) of fat and carbohydrate (for 14 d each) to lean and obese men. It was found that 14 d carbohydrate overfeeding produced a rapid increase in carbohydrate oxidation (2-fold), whereas 14 d fat overfeeding had no effect on fat oxidation at all. Furthermore, during carbohydrate overfeeding more of the excess energy was oxidized and less stored in the body when compared with fat overfeeding. As a result, positive fat balance was much more pronounced after carbohydrate overfeeding compared with fat overfeeding.

These results thus illustrate that an excess fat intake does not stimulate its own oxidation and therefore promotes the development of a positive fat balance and thus obesity.

The effect of isoenergetic high- and low-fat diets on fat oxidation

Another approach for studying the effect of diet composition on substrate metabolism is the comparison of isoenergetic high- and low-fat diets with energy contents equal to the individuals' energy requirements. In these studies RER is compared with food quotient (FQ). The RER is the ratio of CO₂ produced to O₂ consumed by the body (VCO₂:VO₂). Since the amount of CO₂ produced and O₂ consumed is dependent on the substrate metabolized, RER is used to measure substrate oxidation. In case of carbohydrate-only oxidation, RER is equal to 1.0, whereas with fat-only oxidation, RER equals 0.7. The FQ is the theoretical RER when all dietary carbohydrates, fat and protein would be completely oxidized.

Abbott *et al.* (1990) studied the acute effect of such

high-fat (65 % of energy derived from fat) and low-fat (20 % of energy derived from fat) diets on 24 h substrate oxidation in Pima Indians. On the high-fat diet, 24 h RER was similar to FQ whereas on the low-fat diet RER was significantly less than FQ. McNeill *et al.* (1988) studied the long-term effects (6 d) of diet composition on fasting RER in eleven healthy women. Fasting RER was lower after a diet with normal composition (41 % of energy derived from fat) compared with a high-carbohydrate diet (31 % of energy derived from fat) and the difference in RER was similar to the difference in FQ between the diets. Similarly, Hurni *et al.* (1982) studied the long-term (7 d) effects of low-fat (4 % of energy derived from fat) and medium-fat (37 % of energy derived from fat) diets on substrate metabolism in lean subjects. RER (24 h) was lower on the low-fat diet compared with the high-fat diet. Hill *et al.* (1991) studied lean subjects after 3 and 7 d on high-fat (60 % of energy derived from fat) and low-fat (20 % of energy derived from fat) diets. On day 3, RER was shifted in the direction of FQ on both diets, and no further changes in RER between day 3 and day 7 were observed.

Several studies were performed to study the effect of diet composition on substrate metabolism in groups with different susceptibility to obesity. Lean & James (1988) studied the acute effect of isoenergetic low-fat (3 % of energy derived from fat) diet and high-fat (40 % of energy derived from fat) diets on 24 h substrate oxidation in lean, obese (BMI >32 kg/m²) and 'post-obese' (previously obese with BMI >32 kg/m², and at least 6 months weight-stable with BMI <25 kg/m²) women. The lean and obese women responded to the high-fat diet by increasing fat oxidation, whereas in the post-obese women the increase in fat oxidation in response to the high-fat diet was blunted. This might indicate a diminished capacity for fat oxidation in post-obese (and predisposed) subjects. Similar results were obtained by Astrup *et al.* (1994). They studied whether subjects with a predisposition to obesity (post-obese) respond differently to changes in dietary composition compared with controls. Subjects consumed a low-fat (20 % of energy derived from fat) or high-fat (50 % of energy derived from fat) diet for 3 d at home and subsequently for 24 h in a respiration chamber. In the lean subjects the high-fat diet stimulated fat oxidation and substrate balance was reached. However, the post-obese subjects were not able to stimulate their fat oxidation sufficiently to match fat intake. Verboeket-van de Venne *et al.* (1994) studied the effect of 3 d low-fat (10 % of energy derived from fat), medium-fat (30 % of energy derived from fat) or high-fat (50 % of energy derived from fat) diets on 24 h substrate oxidation in restrained and unrestrained eaters. On the low-fat and medium-fat diets RER was lower than FQ, whereas on the high-fat diet RER was equal to FQ. However, the restrained eaters, who are considered to have higher susceptibility to becoming obese, responded with a smaller increase in fat oxidation on the high-fat diet than the unrestrained eaters.

The studies reported earlier indicate that isoenergetic low- or high-fat diets influence substrate oxidation, with RER shifting in the direction of FQ. Moreover, some of the studies mentioned earlier indicate that RER is lower than FQ on a low-fat diet, which is in contrast with the notion

that carbohydrate intake rapidly stimulates carbohydrate oxidation. However, this can be explained by the fact that many of the studies on the effect of isoenergetic high- and low-fat diets on fat oxidation have difficulties in achieving energy balance and the results are confounded by energy imbalance. While in the respiration chamber, energy requirements are often based on (a percentage of) energy intake measured on a 'weight-maintenance diet' or on predicted (or measured) resting metabolic rate multiplied by a factor for physical activity inside the chamber. We recently showed that the day-to-day variance in energy expenditure in a respiration chamber, especially when the level of activity is controlled for, is limited (Schrauwen *et al.* 1997c). Therefore, when energy expenditure is measured on 1 d, energy intake can be adjusted to energy requirements and subjects can be fed in energy balance. We used this approach to study the effect of diet composition on substrate oxidation when subjects were shifted from a low-fat diet (30 % of energy derived from fat) to a high-fat diet (60 % of energy derived from fat), while staying in the respiration chamber for 7 d. Subjects showed a close balance between energy expenditure and energy intake and FQ was equal to RER after 2 d on the low-fat diet. On the high-fat diet we found that RER shifted in the direction of FQ but that only after 7 d was RER equal to FQ (Schrauwen *et al.* 1997a).

Taken together, the results from these studies (Table 2) indicate that isoenergetic high- and low-fat diets influence substrate oxidation, with RER shifting in the direction of FQ. However, the adjustment of RER to FQ on a high-fat diet is slow and requires several days. Thus day-to-day variability in dietary fat intake is not accompanied by rapid changes in fat oxidation and therefore positive fat balance will occur. It might be that these cumulative positive fat balances will, over time, lead to the development of obesity. Furthermore the results suggest that a diminished fat oxidation capacity might be a predictor for the development of obesity.

The results discussed earlier strongly suggest an important role for the dietary fat content in the development of obesity. However, a decreased physical activity has also been proposed to be responsible for the increasing prevalence of obesity (Saris, 1996).

Physical activity as a determinant of energy and substrate metabolism

The development of obesity is, by definition, characterized by an energy intake exceeding energy expenditure. Therefore, it seems logical that physical activity could prevent the development of obesity. However, studies examining the effect of physical activity on obesity are scarce, due to methodological problems in quantifying the amount of physical activity. The doubly-labelled water method allows the measurement of average daily metabolic rate, i.e. the total of energy expended during 24 h. If this measurement is combined with the measurement of BMR, energy expenditure for physical activity can be calculated from the difference between BMR and average daily metabolic rate. With this method, it was shown that energy expended during physical activity is negatively correlated with body

Table 2. Food quotient (FQ) and RER in isoenergetic high- and low-fat diets

Study	Subjects	n	Fat in diet (%)	Duration of diet (d)	FQ	RER		RER-FQ
						Mean	SD	
McNeill <i>et al.</i> (1988)	Lean and obese*	6 and 5	31	6	0.88	0.85	0.03	-0.03
			41	6	0.85	0.82	0.03	-0.03
Abbott <i>et al.</i> (1990)	Pima Indians	20	20	1	0.91	0.88	0.01	-0.03
			42	1	0.83	0.84	0.01	0.01
Hurni <i>et al.</i> (1982)	Lean	11	4	7	0.95	0.88	0.01	-0.07
			37	7	0.85	0.80	0.01	-0.05
Hill <i>et al.</i> (1991)	Lean	8	20	7	0.92	0.86	0.01	-0.06
			60	7	0.77	0.75	0.01	-0.02
Lean & James (1988)	Lean	6	3	1	0.96	0.87	0.01	-0.09
			40	1	0.85	0.82	0.01	-0.03
	Obese*	10	3	1	0.96	0.87	0.01	-0.09
			40	1	0.85	0.82	0.01	-0.03
Schrauwen <i>et al.</i> (1997a)	Lean	12	30	2	0.88	0.88	0.01	0.00
			60	7	0.80	0.80	0.01	0.00
Verboeket-van de Venne <i>et al.</i> (1994)	Unrestrained	7	10	3	0.94	0.90	0.01	-0.04
			50	3	0.82	0.82	0.00	0.00
			10	3	0.94	0.91	0.00	-0.03
	Restrained‡	7	50	3	0.82	0.83	0.00	0.01
			10	3	0.94	0.91	0.00	-0.03

FQ, food quotient.

* Obesity was defined as a BMI >30 kg/m².

† Post-obesity was defined as previously obese with BMI >32 kg/m², and at least 6 months weight-stable with BMI <25 kg/m².

‡ Restrained eating was defined as a score >15 on the Herman-Polivy restraint scale.

fat percentage in males (Westerterp & Goran, 1997). Schulz & Schoeller (1994) combined data from a large number of doubly-labelled water studies and found a negative correlation between body fat percentage, both in males and females. Furthermore, training studies showed that after a 40-week training programme previously untrained subjects had an increase in fat-free mass and decrease in fat mass (Westerterp *et al.* 1994). These studies suggest a positive effect of physical activity in the prevention of obesity due to an elevation of daily energy expenditure. Apart from the elevation in energy expenditure during physical activity, it has been suggested that physical activity also increases resting energy needs. One of the most important determinants of resting metabolic rate is the fat-free mass (Ravussin *et al.* 1986) and endurance training increases the latter. Whether endurance training influences resting metabolic rate after adjustment for body composition is still controversial. Some studies have shown an increase in resting metabolic rate, adjusted for fat-free mass and fat mass, in response to training (Tremblay *et al.* 1986; Poehlman *et al.* 1988), whereas others did not (Davis *et al.* 1983; Schulz *et al.* 1991; Westerterp *et al.* 1994). However, there is agreement that in the short term, energy expenditure is elevated above resting metabolic rate for several hours following exercise, a phenomenon called excess post-exercise O₂ consumption. Interestingly, the type of physical activity could have an influence on the amount of excess post-exercise O₂ consumption. Some studies have shown that high-intensity exercise has a more pronounced effect on post-exercise energy expenditure compared with low-intensity exercise (Gore & Whither, 1990; Smith & Naughton, 1993; Phelain *et al.* 1997), whereas others found no difference (Sedlock *et al.* 1989; Sedlock, 1991). Treuth *et al.* (1996) showed

that average daily metabolic rate was elevated by 0.6 MJ/d after a 60 min high-intensity interval exercise session compared with an equal amount of work performed in a 60 min low-intensity exercise session.

These results suggest that physical activity might be helpful in the prevention of obesity by elevating average daily metabolic rate. However, this does not mean that a decreased physical activity is the sole reason for the increasing prevalence of obesity in westernized societies. In a recent review it was illustrated that obese subjects were not less physically active when compared with normal-weight subjects (Westerterp, 1999).

Beyond the effects of physical activity on energy metabolism, physical activity has been used as a tool to promote fat oxidation. It is well known that at low exercise intensities fat oxidation is responsible for the major part of the energy demands and that with increasing exercise intensity the contribution of carbohydrate oxidation increases. It has been shown that maximal fat oxidation is achieved between 40 and 65 % of maximal power output (W_{max}) (Romijn *et al.* 1993). Therefore, for a long time low-intensity exercise has been considered the most beneficial for the treatment of obesity. However, high-intensity exercise has been suggested to have a more pronounced impact on post-exercise fat oxidation (Tremblay *et al.* 1994) and low glycogen levels could be involved in the high post-exercise fat oxidation. According to the model of Flatt (1987a,b, 1988), fat oxidation can be raised to match fat intake on a high-fat diet by maintaining lower glycogen levels. As discussed earlier, the consumption of a high-fat diet, while in energy balance, leads to a gradual increase in fat oxidation. One explanation for the latter is that declining glycogen stores, indicated by a negative carbohydrate balance (as RER>FQ) on the first days of a

high-fat diet, are responsible for the gradual increase in fat oxidation. Therefore, the hypothesis was tested that acute lowering of the glycogen stores, by high-intensity exercise, would lead to a rapid increase in fat oxidation. It was found that lean and obese subjects were capable of adjusting fat oxidation to equal fat intake within 1 d when glycogen stores were low (Schrauwen *et al.* 1997b, 1998). Since most people do not consume high-fat diets for several days in a row but have a large day-to-day fluctuation in fat intake, most people will not adjust their fat oxidation to their fat intake and cumulative positive fat balances might occur. Therefore, lowering of the glycogen stores (by high-intensity exercise) might prevent cumulative positive fat balances, and thus eventually the development of obesity. Therefore, (high-intensity) exercise can counterbalance the increasing intake of fat in our westernized societies and might prevent the development of obesity.

Apart from the effect of physical activity on energy and substrate metabolism, regular physical activity might have an effect on food intake preferences. Subjects with a higher spontaneous activity level consumed more carbohydrate (Westerterp *et al.* 1996a), and exercise resulted in a short-term reduction in hunger and energy intake (Westerterp-Plantenga *et al.* 1997).

Together these results suggest that regular physical activity might be an important strategy in the prevention of diet-induced obesity. Apart from an effect on energy intake, high-intensity physical activity, leading to lowering of the glycogen stores, might be a good strategy for obese people to enhance their fat metabolism. The combination of (high-intensity) exercise and a low-fat diet might be a helpful tool in the treatment of obesity. However, obese subjects are not less active compared with normal-weight subjects and thus decreased physical activity can not be the sole explanation for the increasing prevalence of obesity in our westernized societies.

Mechanisms behind the effect of high-fat diets on fat oxidation

As discussed earlier, an increased dietary fat content does not stimulate its own oxidation. However, it is not clear why the adaptation of fat oxidation to fat intake is slow. To examine this, whole-body fat oxidation should be studied in more detail and be divided into the oxidation of fat derived from plasma, intramuscular triacylglycerol or VLDL-triacylglycerol. Using labelled fatty acids, plasma-derived fatty acid oxidation can be distinguished from the oxidation of intramuscular triacylglycerol–VLDL-triacylglycerol. We used this approach to study the effect of a high-fat diet (60 % of energy derived from fat) for 7 d on the contribution of different fat compartments to total fat oxidation. In seven healthy lean subjects, we measured total fat oxidation using a respiration chamber and determined plasma fatty acid oxidation using infusion of ^{13}C -labelled palmitate. Total fat oxidation increased slowly on the high-fat diet and this increase in fat oxidation was accounted for by an increase in non-plasma fatty acid oxidation (Schrauwen *et al.* 2000). This suggests that the oxidation of VLDL-triacylglycerol or intramuscular triacylglycerol is increased on a high-fat diet. It has previously been shown

that after consumption of a high-fat diet intramuscular triacylglycerol concentration was elevated in healthy subjects (Kiens *et al.* 1987; Starling *et al.* 1997) and it can be suggested that an increased intramuscular triacylglycerol concentration allows an increased intramuscular triacylglycerol oxidation. After switching from a low-fat to a high-fat diet, intramuscular triacylglycerol concentration will gradually increase and this might result in the gradual increase in fat oxidation. On the other hand, lipoprotein lipase activity, the enzyme responsible for releasing fatty acids from the lipoproteins (VLDL) is increased after consumption of a high-fat diet (Kiens *et al.* 1987) and a relationship between lipoprotein lipase activity and whole-body fat oxidation has been shown (Ferraro *et al.* 1993). The increased lipoprotein lipase activity on a high-fat diet might facilitate the uptake and storage of VLDL-triacylglycerol by the muscle, explaining the increase in intramuscular triacylglycerol concentration on a high-fat diet. However, part of the fatty acids released from VLDL-triacylglycerol might also be directly oxidized in the muscle, especially in the post-absorptive state. More studies are required to establish the role of either intramuscular or VLDL-triacylglycerol oxidation in the adaptation of fat oxidation to a high-fat intake. A role for intramuscular triacylglycerol concentration and oxidation in the adaptation to a high-fat diet is interesting because a relationship between intramuscular triacylglycerol concentration and insulin sensitivity has been shown (Philips *et al.* 1996; Pan *et al.* 1997). Thus, high intramuscular triacylglycerol concentrations are correlated with a low insulin sensitivity. These findings might provide the link between high-fat diets, obesity and insulin resistance. However, more information on the role of intramuscular triacylglycerols in the development of obesity and insulin resistance is required.

Genetic determinants of obesity

Apart from environmental factors, obesity is also determined by genetic factors. Estimates of the heritability of body composition suggest that 40–70 % of the variation in body composition is genetic (Stunkard *et al.* 1990). In recent years, the discovery of two previously unknown genes, the *ob* gene, encoding for the adiposity hormone leptin, and the uncoupling protein-2 and uncoupling protein-3 genes, encoding for uncoupling proteins, renewed the interest in genetic determinants of obesity.

In 1994, the *ob* gene, encoding for the *ob* protein (leptin) was discovered by Zhang *et al.* (1994). In a strain of extremely obese mice, (*ob/ob*), leptin is absent due to a mutation in the *ob* gene, and administration of leptin to these mice led to an increase in food intake and a decrease in body weight. Another strain of extremely obese mice (*db/db*) have a mutation in the gene encoding for the leptin receptor and therefore leptin can not exert its effects. In human subjects, in a few families only, mutations in the leptin (receptor) gene have been found which resulted in extreme obesity (Montague *et al.* 1997; Clément *et al.* 1998; Strobel *et al.* 1998). Therefore, research has focused mainly on the normal regulation of leptin concentrations. Increasing evidence suggests that leptin exerts its effect

through the hypothalamus. The synthesis of hypothalamic neuropeptide Y, a potent stimulator of food intake, is inhibited by leptin (Stephens *et al.* 1995). Evidence is also accumulating for an effect of leptin on lipid metabolism. In cell cultures, leptin directly reduces intracellular lipid concentrations by inhibiting fatty acid and triacylglycerol synthesis and increases lipid oxidation (Shimabukuro *et al.* 1997). Recently Wang *et al.* (1998) showed that hyperlipidaemia and hyperglycaemia resulted in increased leptin expression in white adipose tissue and, interestingly, also in skeletal muscle. This finding might unveil an important link between increased nutrient availability and leptin expression. However, most of the variability in leptin expression is explained by the size of the adipose tissue stores. In obese human subjects, leptin levels are elevated in close relation to the body fat mass, eliminating a causal role for (low) leptin levels on obesity, although in Pima Indians low leptin levels predispose to future weight gain (Ravussin *et al.* 1997). Leptin might play a role in the interaction between genetic and environmental factors since it was shown that consumption of a high-fat diet led to an increase in leptin levels in rats (Frederich *et al.* 1995; Masuzaki *et al.* 1995) and this effect could possibly explain the variability in body composition between individuals on similar diets. However, the increase in leptin levels was best explained by the increase in fat mass. In accordance, isoenergetic low- and high-fat diets had no effect on leptin concentrations, but leptin levels were correlated with body fat percentage, as was described earlier (Schrauwen *et al.* 1997d). This suggests that leptin does not play a role in the prevention of diet-induced obesity and can not explain why some subjects become obese on high-fat diets whereas others maintain normal weight.

In brown adipose tissue an uncoupling protein, uncoupling protein-1, is responsible for the thermogenic effect of this tissue (Nicholls *et al.* 1978). Uncoupling proteins are able to uncouple O₂ consumption from ATP production, thereby dissipating energy as heat. In rodents, brown adipose tissue is involved in the cold-induced and diet-induced thermogenesis. When overfed on a high-fat diet therefore, rodents can maintain energy balance by increasing brown adipose tissue activity (equal to uncoupling protein activity) and thus expending a large part of the excess energy. However, brown adipose tissue is limited in adult man, and therefore the role of uncoupling proteins in human obesity has long been controversial (Lean *et al.* 1986). In 1997, two novel uncoupling proteins, uncoupling protein-2 (Fleury *et al.* 1997; Gimeno *et al.* 1997) and uncoupling protein-3 (Boss *et al.* 1997), which are widely expressed in human tissues, were cloned. Recently, we found that in Pima Indians, who have a predisposition to obesity, the mRNA levels of uncoupling protein-3 were positively correlated with sleeping metabolic rate. This suggests that low uncoupling protein-3 levels, and thus low heat production, would result in a low sleeping metabolic rate (Schrauwen *et al.* 1999). Interestingly, high-fat feeding upregulates the expression of uncoupling protein-2 (Fleury *et al.* 1997) and uncoupling protein-3 (Matsuda *et al.* 1997) in rats, due to an effect of free fatty acids on uncoupling protein-2 and uncoupling protein-3 expression (Weigle

et al. 1998). It was observed in obesity-resistant mice, which do not become obese when fed a high-fat diet, that uncoupling protein-2 was upregulated by high-fat feeding whereas in obesity-susceptible mice high-fat feeding had no effect on uncoupling protein-2. Therefore, uncoupling proteins might play a role in diet-induced obesity, and high expression of uncoupling proteins would be beneficial in preventing obesity.

These results indicate that genetic factors might be important in the development of obesity, but even in subjects with a genetic predisposition to obesity, environmental factors are the most important determinants of body weight and/or composition. This interaction between environmental and genetic determinants was shown by Ravussin *et al.* (1994), who studied two populations with a similar genetic background (Pima Indians) living in different environments. The Pima Indians who live in Mexico have a traditional lifestyle, with a low-fat diet and high levels of physical activity. The mean BMI of these Mexican Pima Indians is 7–10 kg/m² below the mean BMI of the Pima Indians living in the USA, who have a westernized lifestyle. Therefore, a high-fat diet, in combination with low physical activity, seems to be the most important determinant of the increased prevalence of obesity in our westernized society.

Conclusion

In the present review evidence has been presented that high-fat diets play an important role in the increased prevalence of obesity. Due to their high energy density, high-fat diets will stimulate voluntary energy intake. This increased intake of dietary fat will not stimulate fat oxidation but the excess fat intake will be stored in the adipose tissue, so there is a close correlation between energy balance and fat balance. Even when isoenergetic high- and low-fat diets are compared, high-fat diets will lead to a positive fat balance in the short term due to the lack of adjustment of fat oxidation to fat intake. In the long term, cumulative positive fat balances could lead to weight gain. The lack of adjustment of fat oxidation to a high-fat intake can be counteracted by performing physical activity, leading to lowering of the glycogen stores.

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