Aetiology of obesity

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Obesity is not a single disorder but a heterogeneous group of conditions with multiple causes each of which are ultimately expressed as an obese phenotype. Fatness does run in families, but the genetic component does not follow simple Mendelian principles and the influence of the genotype on the aetiology of obesity may be attenuated or exacerbated by non-genetic factors. Body weight is ultimately determined by the interaction of genetic, environmental and psychosocial factors acting through the physiological mediators of energy intake and expenditure.

Aetiological determinants of obesity

Endocrine and hypothalamic disorders

A number of endocrinological disorders may contribute to obesity, although these represent only a very small proportion of the total cases. The endocrinological determinants of obesity have recently been reviewed\(^1\). The most common single disorder in this group is hypothyroidism in which weight gain occurs primarily as a consequence of decreased energy expenditure. Others include Cushing's syndrome and disorders of corticosteroid metabolism, where weight gain is accompanied by characteristic patterns of fat deposition in the truncal region, sex hormone disorders including hypogonadism in men and ovariectomy in women, insulinoma and growth hormone deficiency. Here weight gain is believed to occur predominantly due to increases in energy intake. The polycystic ovarian syndrome of Stein–Leventhal is commonly associated with obesity which may be related to altered ovarian function or hypersensitivity of the hypothalamic-pituitary-adrenal axis.

Hypothalamic tumours or damage to this part of the brain as a consequence of irradiation, infection or trauma may also lead to obesity, apparently due to a defect in appetite control and subsequent hyperphagia. However, altered hypothalamic control of the autonomic nervous system may also reduce energy requirements in these patients. A
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hypothalamic disorder is also believed to be the origin of a number of congenital abnormalities which result in obesity, e.g. Prader–Willi syndrome.

Genetic considerations

**Heritability** At a population level, the genetic component of obesity is expressed in terms of heritability. This refers to the proportion of the total variation in a character which is attributable to genetic factors. The heritability of obesity may be considered either in terms of the total fatness of an individual or the distribution of body fat.

Numerous studies in different ethnic groups suggest that the familial correlation in total body fatness, expressed as body mass index, (BMI; kg/m^2) from parent to offspring is about 0.2 and for sibling–sibling relationships about 0.25^2. As would be expected, studies of twins show a much higher correlation, particularly for monozygotic pairs. However, these findings do not segregate the independent effects of genetic transmission and a shared environment. Further studies of twins reared apart attribute 50–70% of the difference in BMI in later life to genetic factors^4,5. Adoption studies, where an individual is compared both to their biological and adopted parents, have also demonstrated the importance of genetic influences. There is a strong relationship between the BMI of the adoptee and their biological parents across the entire range of fatness, but no relationship between the adoptee and their adoptive parents^6,7.

Studies of fat distribution have considered both the ratio of subcutaneous to total fat mass and the distribution of subcutaneous fat in the trunk relative to the limbs. Data from the Quebec Family Study suggest that the size of the internal fat stores are more strongly influenced by genetic factors than subcutaneous fat depots^2. Familial clustering analysis suggests that genetic factors may account for 37% of the variance in the trunk to extremity skinfold thickness ratio^8.

The combined evidence from these genetic analyses suggests that obesity is a polygenic disorder and that a considerable proportion of the variance is non-additive. This would explain the higher correlations between siblings than those between parent and offspring, and the 2-fold greater correlation between monozygotic than dizygotic twins. These genetic influences seem to operate through susceptibility genes; the occurrence of the gene increases the risk of developing a characteristic but is not essential for its expression nor is it, in itself, sufficient to explain the development of the disease.
Animal models of obesity  Animal models of obesity may derive from lesions in the ventro-medial hypothalamus, the paraventricular hypothalamus or the amygdala. Alternatively, there are autosomal recessive gene defects, of which the best known are ob/ob or db/db mice and falfa rats and a few less well-known polygenic models, such as the Japanese mouse. There are also models of dietary-induced obesity, which can be precipitated by feeding high carbohydrate diets (e.g. Spiny mouse), high fat diets (Osborne–Mendel rat) or cafeteria diets (e.g. Sprague–Dawley rat).

There is currently particular interest in the gene defect in the ob/ob mouse. This has been shown to be responsible for a failure to produce the hormone, leptin. Injections of recombinant leptin lead to reductions in body weight, percent fat, serum glucose and insulin. Injections into the lateral ventricle or third ventricle of the brain suggest there may be a central site of action, probably by reducing the concentration of neuropeptide-Y. The leptin receptor has now also been cloned. In man, the ob gene has 84% overall homology with that of the mouse but, in adipose tissue of obese subjects, ob mRNA is present at high levels and there are much higher serum concentrations of leptin in obese than normal weight humans. It is possible that obese humans have a relative insensitivity to leptin or decreased transport into the CSF. However, no structural or functional defects of the leptin-effector system in humans have yet been identified. The effects of the ob gene are mediated through effects on both energy intake and energy expenditure. The mice are hyperphagic and constantly search for food. They also have a defect in thermogenesis, mediated through the activity of the sympathetic nervous system and have low levels of spontaneous physical activity.

Candidate genes  Unlike animal models, where a number of single gene defects can lead to obesity, no human obesity gene has yet been characterised, but the heterogeneous nature of human obesity does not preclude the identification of small numbers of individuals with a single gene defect which leads to obesity. A number of so called candidate genes have been identified which are associated with the obese phenotype: these include the β3 adrenergic receptor, lipoprotein lipase, dopamine receptor D2, glucocorticoid receptor, TNF and apolipoprotein B, D and E genes.

In man, a number of genetically determined conditions result in excess body weight or fatness (e.g. Prader–Willi syndrome or Bardet–Biedl syndrome), but these cases account for only a very small proportion of the obese population.
Gene–environment interactions The susceptible gene hypothesis implies that environmental factors play a key role in unmasking latent genetic tendencies to develop obesity. This has been investigated in studies in which pairs of twins have been exposed to periods of positive and negative energy imbalance. Here, the within pair differences in the rate of weight gain, the proportion of weight gained as fat and the sites of fat deposition showed greater similarity than the between pair differences. This suggests that differences in genetic susceptibility within a population may determine which individuals are most likely to become obese in any given set of environmental circumstances. These effects may be mediated by changing the individual’s sensitivity to environmental exposures. Putative mechanisms for such effects may include altered sensitivity to gastrointestinal or neuro-peptides which control appetite and satiety, specific taste preferences, sympathetic nervous system (SNS) activity or differences in patterns of spontaneous physical activity. Studies of gene–environment interactions which may determine human obesity are complicated by the fact that the clinical features of obesity may be modulated over time and that there is a time-lag between environmental exposures, lifestyle choices and weight gain. There are also substantial inter-individual differences which need to be explained.

Physiological mediators

Energy expenditure

Studies in animals have suggested that during overfeeding a significant increase in metabolic rate may dissipate the excess energy thus reducing the rate of weight gain below theoretical values. Genetically obese animals gain more weight than their lean controls even when they are pair-fed, implying a greater metabolic efficiency. One possible mechanism for this effect is a decrease in diet-induced thermogenesis which is attenuated in animal models of obesity due to a decrease in the sympathetic activation of brown adipose tissue. These unequivocal effects on energy expenditure in obese animals contrast with the paucity of evidence in humans. Nonetheless, in obese humans, there have been persistent reports of abnormally low energy intakes which indirectly imply that there must be a defect in energy expenditure. There are three principal components to energy expenditure which have each been the subject of detailed research.
Basal metabolic rate  Basal or resting metabolic rate is the energy expended by an individual at rest, following an overnight fast and at a comfortable environmental temperature in the thermoneutral range. Numerous studies of basal metabolic rate have conclusively demonstrated that obese subjects have an increased BMR relative to their lean counterparts\textsuperscript{21}. Figure 1 shows data from a recent analysis\textsuperscript{22} of basal energy expenditure in 319 obese subjects in which the BMR of the women with a BMI less than 25 kg/m\textsuperscript{2} is only $5.71 \pm 0.54$ MJ/day compared to $8.23 \pm 1.21$ MJ/day in those with a BMI $> 35$ kg/m\textsuperscript{2}. The increase in BMR is predominantly due to an increase in the fat-free mass which increases alongside fat mass.

Approximately 80\% of the inter-individual variance in BMR can be accounted for by age, fat-free mass, fat mass and gender\textsuperscript{23}. Nonetheless, this still leaves some potential for inter-individual differences in BMR which may predispose individuals with a relatively low BMR to become obese. Longitudinal studies of the Pima Indians suggest that the risk of gaining 10 kg in the subsequent 4 year follow up was 7-fold greater in those in the lowest tertile of relative BMR than those in the highest tertile\textsuperscript{24}. However, it predicts only about 40\% of the weight gain, and the increase in body weight is in itself still associated with an increase in resting metabolism which normalises BMR. Similar observations have also been made in infants and in children\textsuperscript{25}. Putative mechanisms for these effects include differences in SNS activity or skeletal muscle metabolism. However, this is not a consistent predictor in other populations. For example Seidell et al. found no association between BMR and

\textbf{Fig. 1} Influence of body weight on basal metabolic rate in women (open circles) and men (closed circles) analysed by BMI category (< 25, 25.0–29.9, 30–34.9, > 35 kg/m\textsuperscript{2}). Reproduced with permission from Prentice et al.\textsuperscript{22}
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10 year weight gain in 775 men and women and others have also questioned the validity of this putative association.

Studies of resting energy expenditure in post-obese subjects matched to never-obese controls have usually found no difference in BMR, although a recent combined analysis of 11 published studies of energy expenditure in the post-obese concluded that there was a 5% decrease in resting energy expenditure, which would be too small to be statistically significant in many of the individual studies with small groups of subjects.

Diet-induced thermogenesis A number of studies have suggested that the post-prandial increase in energy expenditure is attenuated in obese subjects, perhaps due to decreased SNS activity (for example). Similar effects have also been demonstrated in the post-obese. However, this is not a consistent finding, even among studies from the same laboratory. A recent review has identified 28 studies in favour of a defect in thermogenesis in humans and 17 against. This variability may be due in part to methodological issues, since this is the least reproducible component of energy expenditure. However, since thermogenesis accounts for only a fraction of total energy expenditure (approximately 10%), the potential for a significant effect on total energy expenditure is small.

It has been suggested that the capacity for facultative thermogenesis may explain the differential propensity to weight gain during periods of overfeeding, a process described as luxus consumption. Although there was considerable support for this in the 1960s, the most recent studies, under carefully controlled conditions and with rigorous measurement techniques, do not suggest any significant role for this process in the modulation of energy balance during overfeeding. It is imperative to make accurate measurements of changes in body composition during overfeeding, since differences in nutrient partitioning between lean and fat tissue will lead to differences in absolute weight gain for a similar energy excess because of the differences in the energy density of tissue gained. Data from the Minnesota study, in which 32 subjects were underfed for 24 weeks and then progressively re-fed, show that the proportion of weight gained as protein (p-ratio) during refeeding was strongly correlated with the p-ratio during weight loss. Moreover, in a multiple regression analysis, the p-ratio was strongly correlated with the magnitude of the decrease in thermogenesis during weight loss.

Physical activity The most variable component of energy expenditure is physical activity which may represent 20–50% of total energy expenditure. Studies of fidgeting movements in Pima Indians within a whole-body calorimeter have shown significant inter-individual variations.
in the daily energy cost of these actions from 400–3000 kJ/day, with low levels predictive of subsequent weight gain at least in males but not females. However, in free-living conditions, the freedom to undertake conscious physical activity or exercise increases the inter-individual variability even further.

Research in this area has been hampered by imprecision in the methods to measure physical activity which have included various actometers, heart rate monitoring, activity diaries and direct observation. However, a stable isotope technique, the doubly-labelled water method, allows accurate measurements of habitual total energy expenditure (TEE) over a 10–20 day period. The ratio of TEE/BMR gives the physical activity level (PAL), an index of the physical activity of the subjects. When analysed in relation to BMI, the PAL is similar in groups of subjects with a BMI <20, 20–25 and 25–35 kg/m² in both men and women, suggesting similar levels of habitual activity. The PAL ratio is reduced in grossly obese subjects (BMI >35 kg/m²) where it seems reasonable to assume that their size becomes physically incapacitating. Although these measurements were made in subjects with established obesity, it is unlikely that they have become increasingly active as their weight has increased; so it appears that, during the dynamic phase of weight gain, there is little evidence that obese people were less active than their lean counterparts.

**Total energy expenditure** The energy requirements of an individual reflect the sum of basal expenditure, thermogenesis and physical activity. Total energy expenditure can be measured under experimental conditions using a whole-body calorimeter. Studies of age and sex matched pairs of lean and obese women clearly demonstrate that, whilst following an imposed activity schedule, the energy expenditure of obese subjects is consistently higher than their lean pair (Fig. 2). Energy expenditure measured at home during everyday activities using doubly-labelled water shows a similar elevation, although when corrected for differences in body size there is no significant difference between lean and obese women. The analysis of total energy expenditure in 319 obese subjects clearly demonstrates a significant increase in energy expenditure with increasing body weight such that individuals with a BMI in excess of 35 kg/m² have an energy expenditure approximately 30% higher than those with a BMI less than 25 kg/m² (Fig. 3).

The outstanding difficulty with these studies is that the increase in energy expenditure seen in obese subjects as a consequence of their increased body size may conceal pre-existing metabolic defects in the pre-obese state which predisposed the individual to excessive weight gain. However, in experimental overfeeding studies, there is no significant difference in the rate of weight gain between lean and obese
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Fig. 2  Energy expenditure measured over 37 h in a whole-body calorimeter in lean (broken line) and obese women (solid line). Reproduced with permission from Prentice et al. 21

Fig. 3  Influence of body weight on total energy expenditure in women (open circles) and men (closed circles) analysed by BMI category (< 25, 25.0-29.9, 30-34.9, > 35 kg/m²). Reproduced with permission from Prentice et al. 22

Subjects when matched for their excess energy intake 30. Studies of total energy expenditure in post-obese subjects have been less conclusive; some studies show no difference in energy expenditure in the post-obese relative to never-obese controls 36, whilst others show a modest suppression of energy expenditure 37. However, the magnitude of the effect is small and may reflect either metabolic or behavioural differences between the groups.
Overall, there is little evidence to support the hypothesis that human obesity may be due to a specific defect in energy expenditure in predisposed individuals. However, advocates of a metabolic basis to obesity argue that only very small differences in energy expenditure are required to produce sustained weight gain over many years, and this difference may be below the limits of precision of even the most sophisticated methodology.

Substrate oxidation  Energy balance can also be considered as the sum of individual macronutrient balances. For subjects in energy balance, the fuel oxidised will have a similar composition to that consumed. Thus, changes in the composition of the diet can have a profound influence on substrate oxidation in the absence of changes in total energy expenditure. Calorimetry studies, with constant diets, suggest that the modulation of substrate oxidation may take 3–5 days to re-establish macronutrient balance\(^{38}\). In free-living situations where the composition of day-to-day food intake is more variable, the previous day’s diet composition exerts a strong influence on the subsequent day’s substrate oxidation. This has the potential to produce artefactual results in studies in which antecedent diet is not carefully controlled.

Flatt has proposed that the positive fat balance associated with the aetiology of obesity reflects a failure to increase fat oxidation to match dietary fat intake\(^{39}\). In support of this hypothesis, Astrup et al. have demonstrated that post-obese subjects (who have previously demonstrated a predisposition to obesity) have an impaired ability to increase the rate of fat oxidation when challenged by a high fat diet\(^{40,42}\). They have suggested that the development of obesity may represent a mechanism to compensate for this defect and to facilitate increases in fat oxidation to match the amount of fat consumed. This may be achieved through higher circulating concentrations of non-esterified fatty acids and insulin resistance which favours fat oxidation. However, this would imply a self-limiting mechanism, which is clearly not always the case.

Longitudinal studies in the Pima Indian population have shown that subjects with a relatively high 24 hour respiratory quotient (RQ; reflecting a high ratio of carbohydrate to fat oxidation) are at 2.5 times the risk of gaining > 5 kg than those with a lower RQ\(^{43}\). Moreover, 28% of the variance in RQ can be explained on the basis of familial associations, which may partly explain the aggregation of obesity in families. In the Quebec Family Study, the heritability of RQ was assessed to be 20%\(^{44}\). Given the effects of antecedent diet on measured RQ, these similarities could have resulted from similar habitual diets. However, when diet was controlled within a 100 day overfeeding study in identical
twins, the within-pair resemblance in RQ was greater than the between-pair effects. The mechanism of a putative genetic determinant in fuel selection is unclear although there is evidence that it may be mediated via plasma concentrations of triiodothyronine (T₃) and androstenedione, SNS activity, or the activities of key enzymes in the β-oxidation pathway. It has also been hypothesised that skeletal muscle may be an important site of differences in fuel selection, either through the effects of insulin sensitivity or muscle fibre type. Type I muscle fibres have a higher capacity for substrate oxidation and thus a low ratio of Type I to Type II fibres may predispose to low fat oxidation and obesity. Wade found an inverse relationship between body fatness and the proportion of type 1 muscle fibres, but other studies have found no significant relationship and have suggested that the link may be an artefact of different levels of physical fitness. This remains an important area of research.

Energy intake

The failure to identify a defect in the metabolic control of energy expenditure, and the contrary observation of high levels of energy expenditure in obese subjects has led to a focus on food intake to explain the aetiology of obesity. The increase in energy expenditure associated with the development of obesity should automatically help to prevent continued weight gain, hence the failure of this auto-regulatory system suggests that there must be a considerable error in the regulation of food intake. Furthermore, habitually lean individuals are able to regulate intake to match energy requirements over a wide range of energy requirements yet those who become obese seem unable to achieve this balance.

Under-reporting of food intake Progress in understanding the role of energy intake in the aetiology of obesity has been seriously confounded by the profound under-reporting which is now widely recognised as a feature of obesity. Comparisons of energy intake and energy expenditure show consistent shortfalls in self-reported intake, averaging approximately 30% of energy requirements in obese subjects. This phenomenon also extends to post-obese subjects and to others who may be very weight conscious. Figure 4 shows the comparison of reported energy intake with measured energy expenditure for individual subjects. In the obese group, the mean under-reporting was -36% and in the post-obese group -27%. There may be a number of causes of under-reporting. It is common for individuals to change their eating habits as a consequence of the pressure of recording their food intake. This is usually associated with a reduction

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in intake as subjects consciously or sub-consciously adopt a self-imposed ‘diet’. Thus they may accurately report their intake for that week, but it is not representative of their habitual diet. Other causes of under-reporting may include forgetfulness, underestimation of portion size and inadequate knowledge of food composition. However, it is probable that there are also instances of self-deception or deliberate manipulation of dietary records. Under-reporting is such a reproducible bio-behavioural observation in obese people that it may in itself represent part of the aetiological syndrome of obesity through a failure to acknowledge true food intake.

**Appetite control** Recent research into the appetite control system has identified a network of synchronous interactions which govern eating behaviour. These effects are mediated through the central nervous system particularly the hypothalamus, where a number of neuropeptides appear to regulate feeding behaviour via effects on hunger and satiety. Laboratory studies of feeding behaviour have suggested that, following a covert energy preload, obese subjects may be less able to accurately compensate for the energy content of the preload at a subsequent meal than lean subjects. However, these studies are usually of short duration in laboratory settings and may not accurately reflect eating behaviour in a naturalistic setting, where knowledge of foods consumed and conditioned learning may invoke other regulatory processes.

**Macronutrient selection** There is abundant evidence that the individual macronutrients (protein, fat, carbohydrate and alcohol) exert different effects on eating behaviour, predominantly due to their effects on
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Satiety

Experimental studies of manipulated foods and retrospective analyses of dietary records suggest that protein is the most satiating\textsuperscript{54,55}. Carbohydrate is also an efficient inhibitor of later food consumption, at least in the short term, meal-to-meal context\textsuperscript{56}. A variety of carbohydrates suppress subsequent intake roughly in proportion to their energy content\textsuperscript{57}. The evidence in relation to the effects of dietary fibre is less clear.

Fat appears to have a weak satiating capacity\textsuperscript{58}. Subjects readily overeat in response to high fat foods\textsuperscript{59}. This effect seems to occur within a single meal and has been described as high fat hyperphagia or passive overconsumption. However since fat has twice as much energy per gram as protein or carbohydrate, this may simply be a consequence of energy density and not a specific property of dietary fat \textit{per se}\textsuperscript{60}. Studies in which lean individuals were confined to a whole-body calorimeter for 7 days and allowed to eat \textit{ad libitum} from a diet providing 20, 40 or 60\% energy as fat, on three separate occasions, ate significantly more energy on the high fat diet and gained weight\textsuperscript{61}. However, when the energy density of the three diets was constant, the high fat hyperphagia was abolished\textsuperscript{62}.

Alcohol has been claimed to have appetite stimulating effects. In free-living circumstances, alcohol consumption with meals is associated with higher energy intakes, but this may also reflect the fact that alcohol is more likely to be consumed on special occasions which in themselves are associated with increased food intake\textsuperscript{63}. In experimental circumstances, a preload of alcohol has a similar effect to carbohydrate, suppressing subsequent intake and partially, but not completely, compensating for its energy content\textsuperscript{64}.

Sensory preferences

The sensory perception of palatability may influence the amount and type of food consumed. This might be expected to exert its effects predominantly within a meal, by prolonging the duration of eating and quantity of a particular food consumed. Hence, sensory properties may have acute effects on energy intake and thus energy balance, but these effects may be rather more limited in the long term.

There have been numerous reports of sensory preferences for particular food groups in association with obesity, but inter-subject variability is so great as to obscure any underlying obese–lean differences\textsuperscript{65}. Experimental studies of taste preferences have moved beyond classical taste tests to more complex food-like stimuli. Drewnowski has identified a relationship between the relative taste preference for fat versus sugar and BMI. Anorectic, low BMI women expressed a preference for foods with a high sugar to fat ratio and obese women the reverse, i.e. increasing overweight was associated with...
enhanced preference for fat\textsuperscript{66}. Unfortunately, simple measures of liking for specific foods do not necessarily correspond to actual dietary intake behaviour. Dietary surveys reveal few, if any, relationships between specific food selections and relative body weight. In community-based studies, the inter-subject variability in preferences was greater than the obese-lean differences\textsuperscript{67}.

It is plausible to suggest that individuals predisposed to obesity may be hyper-sensitive to the hedonic properties of food (see externality). A recent study has demonstrated that post-diet weight regain in women was associated with preferences for high fat-high sugar desserts\textsuperscript{68}.

\textbf{Eating frequency} Some epidemiological studies have suggested that individuals who report eating a greater number of small meals have a lower relative weight than those eating fewer meals and it has been inferred that the consumption of large meals may be a risk factor for obesity. However, a recent review of the literature failed to find any significant association\textsuperscript{69}. Research in this area is confounded by under-reporting of intake in obese subjects and by post-hoc changes in eating habits as a consequence of obesity and attempts at weight control. Measuring eating frequency in subjects with established obesity is an unreliable guide to the eating practices involved in its aetiology.

The putative mechanisms whereby frequent feeding episodes may modulate energy balance are unclear. Some studies\textsuperscript{70} have suggested a higher thermic effect of food associated with ‘gorging’ relative to ‘nibbling’, but measurements made over a 24 h period do not support this hypothesis\textsuperscript{71}. It is more likely that any effects are mediated through changes in appetite and hence energy intake. Studies of the effect of variation in feeding frequency during voluntary dieting have not observed any effect on the rate of weight loss\textsuperscript{69}.

\textbf{Environmental factors} Environmental factors may play a critical role in the development of obesity by unmasking genetic or metabolic susceptibilities. Examples of this come from the Naura in Micronesia, and Polynesians in Western Samoa. There has been a dramatic change in diet and lifestyle in these communities over a very short period of time, resulting in an age standardised prevalence of obesity in men and women of 60\% or more\textsuperscript{72}. There are also a number of migrant studies, where populations with a common genetic heritage now live under very different environmental circumstances. Pima Indians living in the US average 25 kg heavier than comparable subjects living in Mexico\textsuperscript{73}. A recent study of migrant
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Africans living in the Caribbean or US showed a significant increase in the prevalence of obesity in comparison to their native countries of Nigeria or Cameroon. In Nigeria, the mean BMI was $21.7 \pm 3.6$ kg/m$^2$ in men and $22.6 \pm 4.7$ kg/m$^2$ in women, whereas in the US, the average was $27.1 \pm 5.5$ kg/m$^2$ and $30.8 \pm 7.7$ kg/m$^2$, respectively. The increased prevalence of obesity is also associated with an increase in adverse health consequences, such as hypertension, which ranges from only about 15% in those living in Africa to over 30% among those in the US.

Environmental influences must act via an increase in energy intake and/or a decrease in energy expenditure and there is a substantial body of evidence which has investigated these effects both within and between populations. Cross-cultural dietary studies have failed to show a consistent relationship between nutritional factors and relative weight, although within populations there is some evidence that high fat diets are associated with an increased risk of obesity. These studies are frequently confounded by under-reporting of dietary intake, which may be a particular problem if the bias is unevenly distributed across the different populations. To some extent, this can be minimised by considering the proportion of dietary energy derived from each macronutrient. For example, in the Scottish arm of the MONICA study, there is a positive association between the proportion of dietary fat and BMI and a negative association with the proportion of carbohydrate (particularly simple sugars), for both men and women. When expressed as the fat to sugar ratio, there is a 3-fold difference in the prevalence of obesity in men and a 2-fold difference in women in the upper and lower quintiles of macronutrient intake. Although such studies have formed the basis of the hypothesis that dietary fat is an aetiological determinant of obesity, this has not been conclusively demonstrated by the more rigorous prospective studies. This may be due in part to the difficulties of making reliable estimates of energy and macronutrient intake. The metabolic evidence presented above, that dietary fat may undermine appetite regulation, continues to make this a plausible hypothesis.

Cross-cultural studies of physical activity and BMI, have shown that there is a 7-fold increased risk of overweight (BMI > 2.5 kg/m$^2$) in those with a PAL ratio of < 1.8 and within developed countries there is a relationship between low levels of physical activity and an increased likelihood of becoming obese. In a large study in Finland ($n = 12,669$), those reporting physical exercise three or more times per week had, on average, lost weight since a preceding survey 5 years earlier, whilst those with little physical activity had gained weight and had twice the risk of gaining in excess of 5 kg than the physically active subjects. Other studies have examined the relationship of obesity to sedentary behaviours per se, notably TV viewing (an almost invariably totally
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Fig. 5  Secular trends in diet (left) and exercise (right) in relation to obesity in Britain. Reproduced with permission from Prentice and Jebb.

inactive pursuit). Among children in the US, the relative risk of obesity was 5.3 times greater for children who watched more than 5 h TV per day compared with those who watched less than 2 h, even after correcting for a wide range of socio-economic variables.

In the UK, a study has combined data on energy intake and physical activity in relation to the secular increase in obesity in which the proportion of clinically obese subjects has increased from <2% in 1930 to 15% in 1994. This shows that there has been no relationship between either total energy intake or fat consumption and the prevalence of clinical obesity over the last 60 years, whilst proxy measures of physical inactivity (TV viewing and car ownership) are closely related (Fig. 5). A study analysing trends in energy intake and expenditure in recent years, as part of the Finn Monica study suggests that these changes are now becoming less marked. Between 1982 and 1992, the prevalence of obesity (BMI > 27 kg/m²) increased from 39% to 43% in men and 33% to 34% in women. During this time, energy intake declined in both groups but, when suspected under-reporters were excluded, the decrease was only 519 kJ/day in men and 347 kJ/day in women. Physical activity at work and in transport declined, although there was a significant increase in leisure time activity. Overall, the net energy cost of physical activity in women was unchanged and in men decreased by 3%. These data suggest that, in recent years, the apparent
secular decrease in energy intake may be largely due to an increased prevalence of under-reporting and that increased leisure time activity may at least partially offset the decline in manual occupations.

In spite of the epidemiological evidence that environmental factors are playing an important role in the aetiology of obesity, it is a fact that within a population there are also a significant number of people who are able to control their weight. Analysis of the prevalence of obesity by socio-economic status shows a strong social class gradient, especially in women, in the UK ranging from 10.7% in social class I (high) to 2.5% in social class V (low)\(^8^2\). There is evidence that although the types of foods consumed across the social groups may be very different, total energy and fat intake is remarkably constant\(^8^0\). However, there are marked differences in measures of physical activity. UK national surveys show that those in social classes IV and V spend significantly more time watching TV and are more likely to define themselves as inactive compared to those in social class I. However, in a stepwise multiple regression analysis, the social class gradient in obesity in women persisted even after correction for physical activity and other lifestyle variables such as smoking and alcohol consumption\(^8^3\). This implies that there may be other individual factors which have not been considered that play an important role in modulating the risk of obesity, such as the cognitive control of food intake.

**Psycho-social influences**

Studies of the aetiology of human obesity are complicated by the potential for voluntary or cognitive factors to over-ride many physiological regulatory systems. Cultural factors operating through gender, ethnic, socio-economic or familial hierarchies provide a powerful determinant of body weight by setting moral and social connotations to body weight and defining attitudes to eating and exercise behaviours. Against this background, a number of specific individual characteristics may place individuals at increased risk of obesity.

**Externality**

The ‘externality theory’ of obesity was first described by Schacter to explain the observation that, relative to lean controls, eating behaviour in obese humans appeared to be more sensitive to external cues, such as the time of day, sight or smell of food or the presence of others, than to internal cues of hunger or satiety\(^8^4\). Subsequent research suggested that
externality was closely related to dietary restraint, but recent studies using improved psychometric measures of externality have shown a correlation of externality with BMI, even after controlling for restraint. The effects of palatability on food consumption have recently been explored in the context of this theory. In most experimental studies, preferred foods are consumed in greater quantities than less preferred foods, but the magnitude of this effect is greater in obese subjects. It seems probable that multiple aspects of 'externality' require further analysis as potential contributors to obesity.

Restraint

There is suggestive, but inconclusive, evidence for the role of restrained eating in the aetiology of obesity. Studies of eating behaviour show that restrained eaters report more food cravings and binge eating. One of the characteristic features of dietary restraint is a tendency towards disinhibited eating in particular circumstances. In experimental situations, intake at a test meal is inversely related to the energy content of a preload in unrestrained eaters but, paradoxically, restrained eaters show a positive relationship between the size of the preload and subsequent intake. This disinhibition may be a cognitive effect; restrained eaters given the same preload on two separate occasions ate more after the preload was identified as high energy rather than low energy. This effect might suggest that restrained eaters may be more susceptible to the availability of highly palatable foods, which act as a stimulus for excess food consumption. However, it is also possible that a degree of cognitive dietary restraint is necessary in order to protect against overconsumption in an environment with an excess supply of affordable and palatable foods.

Psychological disturbances

A number of specific psychological syndromes have been identified in obese subjects, but whether these represent a cause or consequence of obesity is unclear. Evidence of improvements in emotional well-being following successful treatment are indicative that many emotional disorders are secondary to obesity.

Binge eating in association with obesity was first described in 1959, but it has only recently been classified as a specific disorder, occurring when an individual consumes objectively large amounts of food with subjective sensations of a loss of control, on at least two occasions per
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week for 6 months\textsuperscript{90}. One epidemiological study has shown that in women presenting for treatment, the onset of binge eating preceded the onset of obesity or dieting\textsuperscript{91}. Some studies have linked binge eating to emotional distress. There is evidence of a higher level of both personality disorders and depression in binge eaters but, in many cases, the eating disorder precedes the development of other co-morbidity.

Many other obese subjects do not fulfill the strict classification for binge eating but, nonetheless, report being more likely to overeat at times when they are in a negative emotional condition. This is the basis of Kaplan’s psychosomatic theory of obesity which hypothesises that obesity may be the consequence of early childhood experiences in which food was continually associated with comfort. However, there is little evidence in support of this beyond clinical case histories and no convincing evidence of an association between obesity and any particular personality type.

Stress

There is some evidence that stress, and more specifically an individual’s capacity to control their stress levels, may play a role in the aetiology of obesity. Some studies report that stress is associated with the consumption of high fat foods and a community based study has linked stress to weight gain\textsuperscript{92}. Bjorntorp has proposed a metabolic basis to this theory, particularly in the modulation of abdominal obesity, through the effects of stress on the hypothalamic-pituitary-adrenal axis and cortisol overproduction\textsuperscript{93}.

Conclusions

Obesity is probably one of the most complex diseases in respect to its aetiology. At its simplest, obesity will only develop when energy intake exceeds energy expenditure over a prolonged period, but this overview conceals the multiple influences on energy intake and expenditure and ignores the potential for a genetic predisposition. Accordingly, there is unlikely to be a single unifying theory to explain the aetiological basis of obesity. However, a better understanding of the aetiological determinants in individual subjects will provide a basis for more rational interventions to both prevent and treat this recalcitrant public health problem.
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