Obesity

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Prevalence

In its recent world health report,[1] the World Health Organization stated that:

> *We are facing a worldwide epidemic of obesity, a key risk factor in type 2 diabetes, cardiovascular diseases, high blood pressure and stroke, as well as various types of cancer. More than one billion adults worldwide are overweight, and at least 300 million of these are clinically obese.*

Obesity prevalence is 14–20% in industrialised countries, but the fastest increases, particularly in childhood obesity, are seen in developing countries such as Chile and China.[2] Worldwide, 22 million children under the age of five are overweight; 10% of US preschool children are obese, half of whom are likely to have impaired glucose tolerance.[3] In Europe, England and Wales have seen one of the most rapid increases in prevalence of overweight and obesity. There has been an increase from 6% and 8%, respectively, for men and women in 1980 to 8% and 12% in 1990, and to over 21% for both in 2000 (Fig 1). More than 50% of adults are overweight (body mass index (BMI) ≥25).

Aetiology

Lifestyle

There are complex causes for this increasing prevalence, involving secular changes in lifestyles affecting both energy and energy expenditure (Table 1). Analysis of food intake data and proxy measures of exercise and activity suggest that the recent rise in overweight and obesity in England can be attributed more to inactivity than to food intake.[4] Worldwide, the adoption of industrialised western society lifestyles (urbanisation, western foods, increased sedentariness and car ownership) is associated with increasing obesity. In countries adopting these lifestyles there appears to be a particularly rapid increase in childhood obesity; for example, in Chile, Peru and Mexico 25% of children are overweight and obese.

Genetics

At the same time, there is increasing evidence for a genetic predisposition to obesity. Studies in adopted children in the 1980s showed a strong correlation between the weight class (thin, median weight, overweight or obese) and the BMI of the biological parents (for mothers $p<0.0001$, for fathers $p<0.02$), but no correlation with the BMI of their adoptive parents.[5] In a study in South-West American Indians, energy expenditure correlated with the rate of change in body weight over a two-year follow-up period. Also, in 94 siblings from 36 families, 24-hour energy expenditure aggregated in families.[6]

Genetic factors are estimated to explain 30–50% of the heritability of obesity. The human obesity gene map[7] is now complex. Currently identified are:

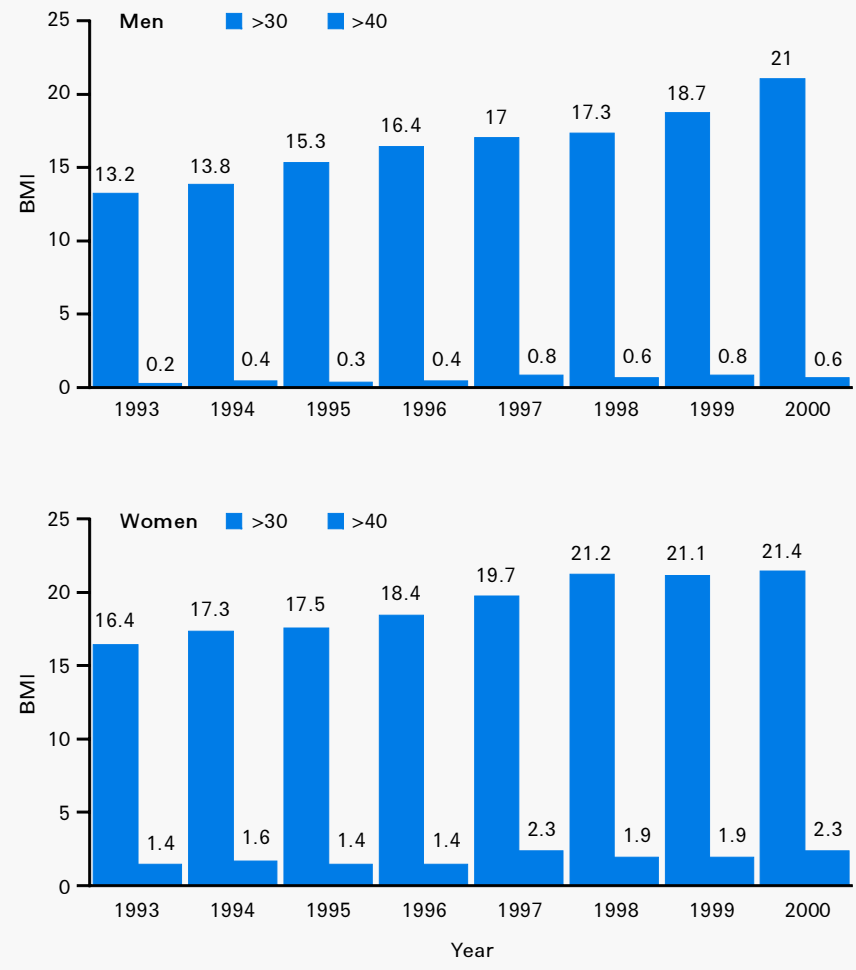

Fig 1. Prevalence of different degrees of obesity in England and Wales (data from Health Survey of England and Wales, 1993–2000) (BMI = body mass index). These graphs allow the prescription of an individually tailored weight-reducing diet providing a 600 kcal (2.5 MJ)/day deficit to men and women of varying degrees of body weight, according to sex (assuming mild to moderate activity level) with a minimum energy prescription of 122 kcal (5 MJ)/day.

Table 1. Examples of changes in energy intake (diet) and energy expenditure (physical activity and exercise) over the past 50 years.

Energy intake	Energy expenditure
Cheaper food	Increased ownership of cars
Greater availability of food: • Supermarkets • Freezers • Fast food outlets	Change in work practices: • Construction machines • Production lines • Computers
Change in diet composition: • Increased fat • Increased refined sugars • Less complex carbohydrates • More alcohol	Labour-saving devices: • Washing machines • Dishwashers • Remote controls • Cordless phones
Change in eating patterns: • More snacks • Fewer 'family' meals • Increased portion sizes	Sedentary relaxation: • Television • Computer games • Lifts • Escalators
Children: • Targeted by food industry • Greater autonomy • Greater spending power	Children: • Push chairs • Fewer walk to school • Decreased sport at school

- six single gene mutations
- 25 Mendelian disorders with map location
- 48 candidate genes
- 33 human quantitative trait loci, and
- 48 other human linkages.

Clearly, the human gene pool has not changed over the past 50 years during which the prevalence of obesity has increased, thus pointing to the importance of gene–environment interactions.

Health risks

The health risks of overweight are well defined (Fig 2). They increase with greater degrees of obesity as well as with central or visceral fat accumulation (clinically assessed by the waist circumference). This relationship has been particularly well defined for type 2 diabetes mellitus (Fig 3)[8] and highlights the need to assess both BMI and waist circumference in the clinical evaluation of the obese patient (Table 2). Different criteria are proposed for non-European ethnic groups (eg adult Asians: overweight BMI >23, obesity >25).[9] In addition, obesity impairs quality of life, increases morbidity and leads to premature mortality.

Treatment

Lifestyle interventions

Treatment aims to produce clinically valuable weight loss (5–10%) (Table 3)[10,11] that is maintained long-term. Lifestyle modification remains a cornerstone of obesity treatment, combining dietary modification, increased activity and exercise, behavioural and cognitive therapy. Therapy is often delivered to groups of patients who need to be 'ready to change', and able and willing to spend time working on learning and practising new skills.

Current dietary management commonly advises on healthy eating principles and a fixed caloric deficit of 600 kcal

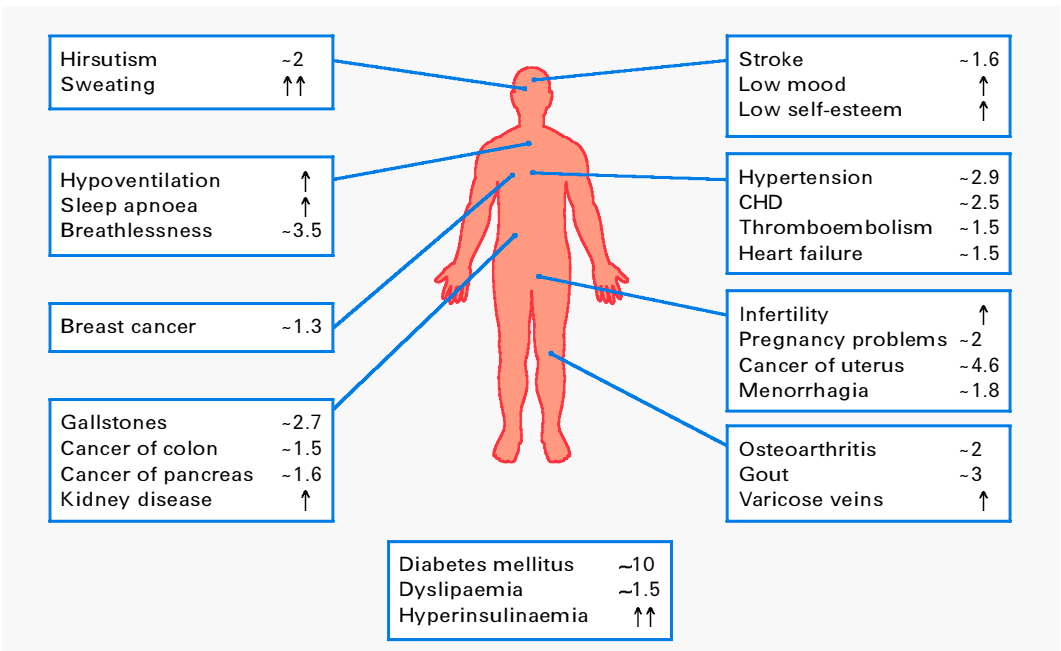

Fig 2. Schematic representation of some of the major complications of overweight and obesity and their approximate relative risks for body mass index greater than 27–30 (CHD = coronary heart disease).

(2.5 MJ) from the calculated energy expenditure (Fig 4). If complied with, such diets reliably predict a loss of 0.5 kg/week. The short-term use of liquid, very low calorie diets (ca 800 kcal (3.4 MJ)) can be an effective strategy to produce initial weight loss, but requires adjunctive treatment for longer-term weight maintenance.

Pharmacological interventions

Two drugs are currently licensed for use in the UK:

- orlistat, a pancreatic and gastric lipase inhibitor that produces about 30% fat malabsorption
- sibutramine, a centrally acting monoamine uptake inhibitor that enhances satiety and possibly attenuates the fall in metabolic rate that occurs with weight loss.

Both drugs have been approved by the National Institute for Clinical Excellence (NICE).[12,13] They have slightly differing prescribing guidance, precautions and adverse events (Table 4). Both drugs achieve an approximate 10% weight loss that reaches a maximum after six months which is almost totally maintained for two years. Patients losing weight successfully with either drug will show improvement in metabolic factors such as fasting glucose, lipids and urate. There is no evidence that combining the drugs is worthwhile.

Fig 3. Age-adjusted incidence rates of type 2 diabetes cross-classified according to quintile of body mass index (BMI) and waist circumference.

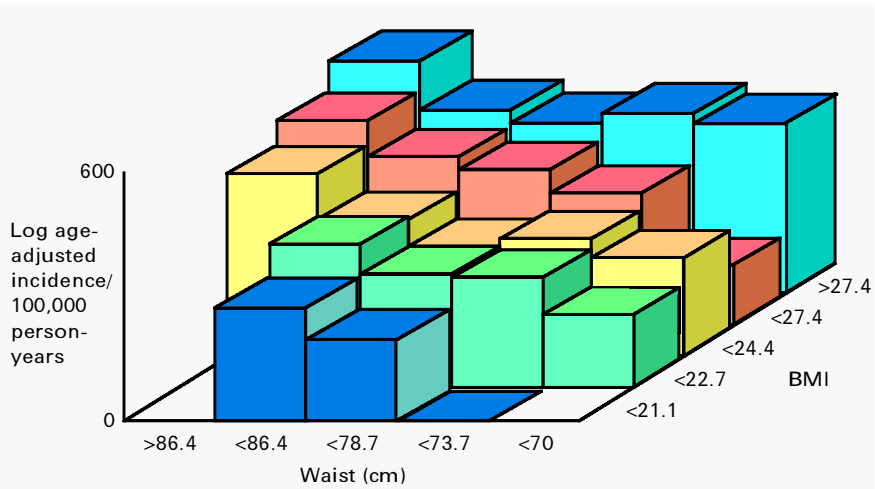

Table 2. World Health Organization definitions of obesity, amended to take account of fat distribution assessed by waist circumference.

Classification of obesity	BMI	Obesity class	Disease risk* Men <102 cm Women <88 cm	Disease risk* Men ≥102 cm Women ≥88cm
Underweight	<18.5			
Normal	18.5–24.9		Average	Average
Overweight	25.0–29.9		Increased	High
Obesity	30.0–34.9	I	High	Very high
Obesity	35.0–39.9	II	Very high	Very high
Extreme obesity	>40	III	Extremely high	Extremely high

* relative to normal weight and waist circumference.
BMI = body mass index.

Table 3. Benefits of a 10 kg weight loss (based on data from Scottish Intercollegiate Guidelines Network).[10]

Mortality

Reduction:
>20% total mortality
>30% diabetes-related deaths
>40% obesity-related cancer deaths

Blood pressure

Reduction:
10 mmHg systolic
20 mmHg diastolic

Diabetes

Reduction:
50% fasting glucose

Lipids

Reduction:
10% total cholesterol
15% LDL
30% triglycerides

Increase:
8% HDL

Respiratory

Reduced sleep apnoea

Decreased breathlessness

Gynaecological

Improved ovarian function and fertility in POS

HDL = high-density lipoprotein;
LDL = low-density lipoprotein;
POS = polycystic ovary syndrome.

Key Points

Obesity is reaching pandemic proportions due to environmental changes affecting both sides of the energy balance

Modest weight reduction of 10% achieves medically important outcomes

Pharmacotherapy can be a useful adjunct to lifestyle modification to achieve medically worthwhile weight loss

Bariatric surgery should be considered in those with a body mass index above 35 and comorbidities

KEY WORDS: diet, energy balance, exercise, leptin, lifestyle modification, orlistat, sibutramine, waist circumference

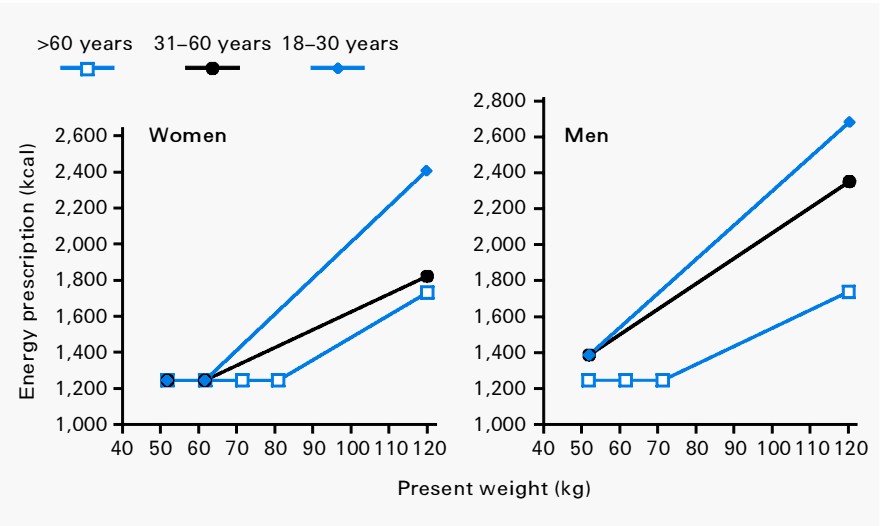

Fig 4. An individually tailored weight reducing diet providing a 600 kcal (2.5 MJ)/day deficit, with a minimum energy content of 1,200 kcal (5 MJ)/day.[10]

The recent XENDOS trial of orlistat (presented at the International Congress on Obesity, September 2002) showed a 6.9 kg loss after four years compared with 4.1 kg on placebo and was associated with a 37% relative risk reduction of progression to diabetes.[14]

Newer pharmacological targets focus on the complex central/hypothalamic control of obesity through either leptin/neuropeptide Y/melanocortin pathways or vagally-mediated afferent pathways from the gastrointestinal tract (cholecystokinin, glucagon-like peptide). Leptin replacement therapy is highly effective in the handful of children with mutations leading to leptin deficiency (Fig 5), acting as a proof of principle that disorders of body weight regulation exist. However, most obese subjects have high circulating leptin levels (as a consequence of increased fat mass), augmentation of which has proved disappointing in clinical trials so far.

Surgery

Operations to produce gastric restriction, with or without a degree of malabsorption, are highly effective at producing weight loss and weight loss maintenance (30–40%) and are approved by NICE.[16] Current operations include:

- purely restrictive procedures (eg vertical-banded gastroplasty (laparoscopic or open surgery), gastric banding (laparoscopic)), or
- restrictive and malabsorptive procedures (eg gastric bypass).

There are no controlled comparative trials, but weight loss may be greater after gastric bypass (30–40%) than following restrictive procedures (25–35%). Considerable investment in facilities, surgical, anaesthetic and medical skills is required to support bariatric surgical programmes which are aimed at patients with a BMI above 40, or above 35 when there are comorbid complications.

Table 4. Comparison of prescribing/National Institute for Clinical Excellence guidance for sibutramine and orlistat.

	Sibutramine	Orlistat
Indications	BMI >27 with significant comorbidity BMI >30 Inadequate response (<5% loss) to previous 'serious' attempts to lose weight Age 18–65 years	BMI >27 with significant comorbidity BMI >30 2 kg weight loss in 4 weeks with diet before starting orlistat Age 18–65 years
Continued prescribing	2 kg loss at 4 weeks 5% loss at 12 weeks	5% loss at 12 weeks 10% loss at 24 weeks
Monitoring	BP and pulse 2-weekly, then monthly for 24 weeks	
Duration of treatment	1 year	1 or 2 years
Contraindications	Include: antidepressants, antipsychotics, inadequately controlled hypertension or significant cardiovascular or peripheral vascular disease, prostatic hyperplasia, hyperthyroid	Chronic malabsorption syndromes, pregnancy, breast-feeding
Side effects	Blood pressure and heart rate increase, dry mouth, constipation, insomnia, sweating	Gastrointestinal
Metabolic benefits	20–30% increase in HDL cholesterol, improved HbA1c in diabetics	Decreased total cholesterol, BP 37% fewer patients progress from IGT to diabetes over 4 years

BMI = body mass index; BP = blood pressure; HbA1c = glycated haemoglobin; HDL = high-density lipoprotein; IGT = impaired glucose tolerance.

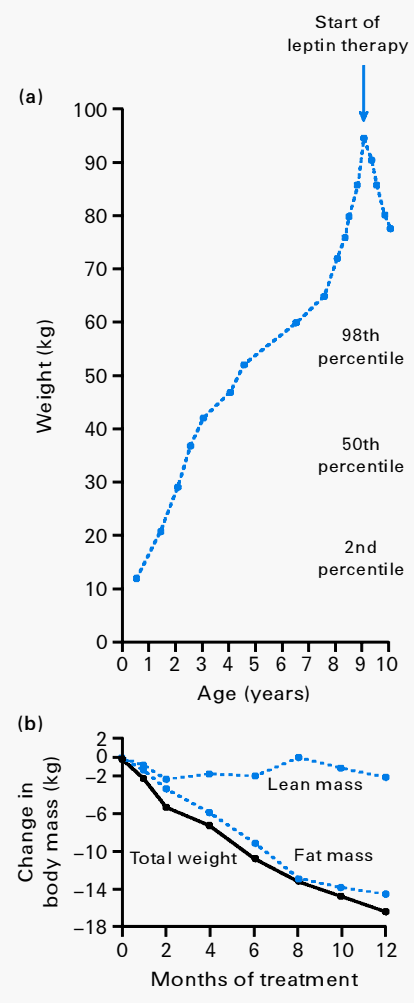

Fig 5. Weight in a girl with congenital leptin deficiency before and in response to leptin treatment: (a) changes in weight from birth to the age of 10 years, showing the 2nd, 50th and 98th percentiles for weight among girls; **(b)** changes in body composition during treatment (reproduced from Ref 15).

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