

Obesity

What is obesity?

Obesity is defined as an excessive amount of body fat, rather than just excessive weight, and is a potentially serious health problem. Some individuals are obese because of an underlying medical condition, many more because of a sedentary lifestyle and high food intake in combination with a genetic predisposition towards obesity.

Someone is considered to be obese when their body mass index (BMI, defined as body weight in kg divided by the square of their height in metres) exceeds 30. Such people have a markedly higher risk of early death compared with someone of the same age and normal weight, owing to the link between obesity and diabetes, hypertension, atherosclerosis, gall bladder disease, osteoarthritis and some cancers.

Obese women have 12 times the risk of developing type 2 diabetes compared to women who are not overweight. More than 85 per cent of patients diagnosed with type 2 diabetes are obese.

Apart from the risk of disease, obesity leads to poor physical functioning and reduced quality of life. Symptoms of chronic low back pain are clearly related to massive overweight, and there are obvious economic and individual implications. Obese people miss far more work days through illness than people with normal body weight. Whereas all medical consequences of obesity qualify as medical disorders, obesity in itself is only considered a risk factor.

Who does obesity affect?

Generating statistical figures on obesity prevalence in Europe is somewhat difficult, as these tend to be based on self-reporting data which are conducted each year in some, but not all, European states. Only a few countries measure both height and weight. In many countries, obesity has reached epidemic proportions. Its medical relevance on a global scale is surpassing that of malnutrition.

During the past 20 years, the prevalence of obesity in the EU has risen tremendously. In the Netherlands, the numbers have doubled, and data from Denmark, Sweden, and Norway show a similar pattern. The prevalence of obesity in most Western European countries is high (15-25 per cent in women; 10-20 per cent in men) and growing in most countries. In Eastern Europe, the prevalence of obesity in women is even higher, in the area of 30 to 40 per cent.

In conclusion, obesity constitutes an important health hazard throughout Europe. As increased affluence coincides with middle age and exercise tends to fall away, it is becoming a major problem. The increasing prevalence of obesity among children is also a concern.

In many European countries, the most rapid growth in obesity is seen in children at the age of six. Within countries, there is a great variation in the prevalence of obesity between different sub-populations. In addition to social class, ethnicity also plays a role: compared to Central European children, children of immigrant parents have twice the prevalence of obesity.

Obesity is when someone has too much body fat. It can lead to serious health problems such as diabetes and raised blood pressure. More and more people are suffering from it. Despite this there are currently only two medicines available to treat obesity. However, there are several others being researched by the pharmaceutical industry.



Present treatments

Anti-obesity treatment is recommended for selected patients in whom lifestyle modification is unsuccessful. Despite the widespread nature of the problem, only two medications are currently licensed for long-term use in the EU.

One compound, a gastrointestinal lipase inhibitor which, taken in combination with a fat-controlled diet, acts within the stomach and small intestine to prevent breakdown and absorption of dietary fats, thereby reducing weight by around ten kilogrammes on average in six months and decreasing progression to diabetes in high-risk patients. The other product is a monoamine-reuptake inhibitor which results in mean weight losses of 4–5 kg, but is associated with increases in blood pressure and pulse rate.

What's in the development pipeline?

Several of the medicines in development for obesity act centrally in the brain.

A molecule, also indicated for the prevention of epileptic seizures, has been shown to cause significant loss of weight over six months or more of treatment. This compound is currently in Phase 3 trials. A further compound, a selective antagonist of dopamine D-1 and D-5 receptors, has also reached Phase 3 trials.

Two additional lipase inhibitors are being studied. One is in clinical Phase 2, the other in clinical Phase 1.

A further anti-obesity medication under investigation first attracted attention as it caused unintended weight loss when given to overweight patients with Parkinson's or Alzheimer's disease. The compound works by inhibiting the neurotransmitters noradrenalin, dopamine, and serotonin in the brain, suppressing the feeling of hunger.

Another approach being explored is the so-called "hunger hormone" ghrelin which is known to increase when a person has no intake of food. Fasting causes ghrelin to be produced in the gastrointestinal tract, and the hormone then plays a role in sending hunger signals to the brain. Research groups have suggested that blocking the body's response to ghrelin signals might be one way to help control weight by decreasing food intake and increasing energy expenditure.

Although there are now a significant number of compounds under investigation for use in weight reduction, the approach of the approving authorities is likely to remain cautious and directed towards patients whose obesity places them at genuine medical risk, rather than at those for whom weight loss is primarily a cosmetic consideration.

The longer-term future

Feelings of hunger and fullness are regulated by peptide hormones secreted by the gut, acting on the brain. One of these, cholecystokinin (CCK), dispels the feeling of hunger, and there is a compound in Phase 1 trials that acts at CCK-A receptors.

Furthermore, a naturally occurring gut peptide, PYY3-36, signals the brain to stop feeling hungry after a meal and might therefore be a new treatment avenue for obesity. Exploratory investigation showed that intravenous infusion of the peptide leads to remarkable reduction in calorie intake.

Another natural anorectic could be a fatty acid, oleylethanolamide (OEA), which in an animal model reduced hunger, promoted weight loss and decreased blood levels of cholesterol and triglycerides. The action of OEA is dependent on its binding to the receptor PPAR-*alpha*, which might become a target for the development of a new therapy.

An alternative long-term approach is to develop medicines that raise the metabolic rate and burn off excess calories. Two of these are under investigation in Phase 1 trials.

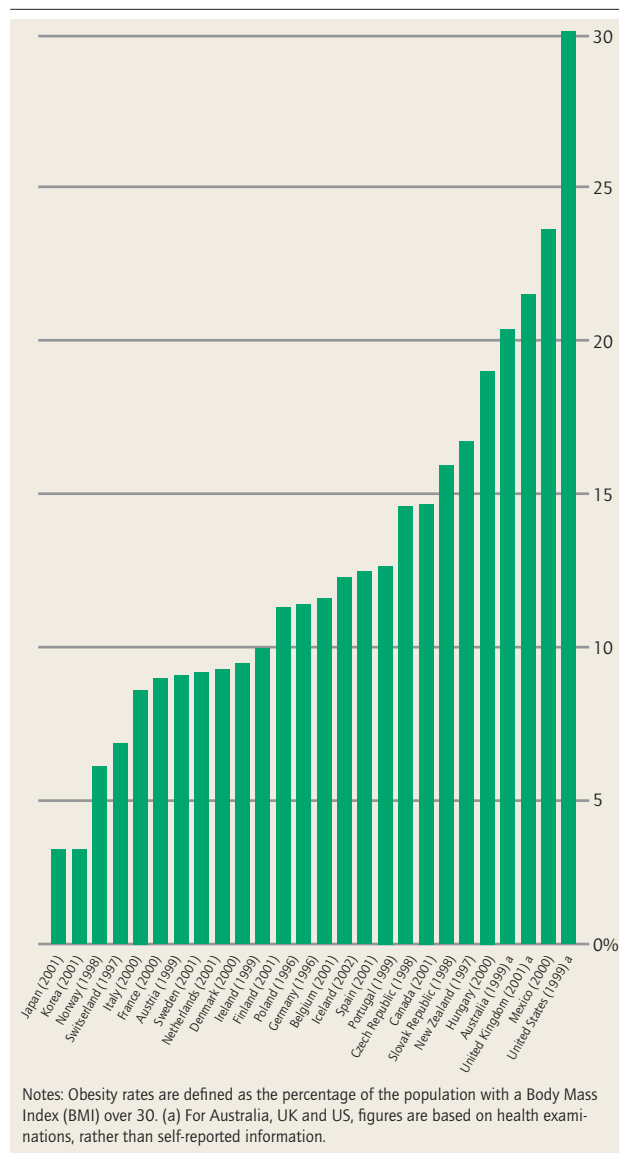
According to recent research reports, newly discovered mutations of the melanocortin 4 receptor (MC4R) gene are implicated in obesity from overeating, making MC4R a candidate gene for the control of eating behaviour. Several investigators are exploring the MC4R as target for anti-obesity medicines.

Appetite and energy balance are regulated by the hypothalamic region of the brain, and considerable progress has been made in defining the underlying neural circuitry involved. Today, scientists believe that these feeding circuits are not firmly "hardwired" but rather exhibit remarkable plasticity, even in adults.

There is the surprising observation that a neurotrophic factor that induces sustained weight loss in adult mice does so by the proliferation of hypothalamic neurons. Using medicines in the inhibition of this nerve growth compromises the capacity of that factor to induce long-term weight loss. Hypothalamic plasticity thus adds another potentially important layer of complexity to the regulation of body weight.

There is also a genetic predisposition towards obesity. Variation in the fat mass and obesity-associated (FTO) gene has provided the most robust associations with common obesity to date. However, the role of FTO variants in modulating specific components of energy balance is still unknown. Recently, researchers have shown that the FTO variant rs9939609 may have a role in the control of food intake and food choice, suggesting a link to a phenotype with uncontrolled eating or a preference for energy-dense foods.

With such a range of potential new medicines under investigation, clinicians can hope for a wider range of treatments for the growing problem of obesity, with the potential to prevent many future cases of obesity-related diseases.



Obesity rates among the adult population, latest year available

Source: OECD Health Data 2003

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Editing Board - Dr. Robert Geursen (Chief Editor), Bill Kirkness, Dr. Jean-Marie Muschart and Marie-Claire Pickaert (Coordinator).

Photocredits & Illustrations - ABPI, Allergan, AstraZeneca, EFPIA/Lander Loeckx, Damian Foundation, Dermatology Group Practice (Brussels), Galderma, Hilaire Pletinckx, Roche, sanofi-aventis, sanofi-pasteur

Design & Production - Megaluna

Last update: July 2009