Obesity

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Excess bodyweight is the sixth most important risk factor contributing to the overall burden of disease worldwide. 1·1 billion adults and 10% of children are now classified as overweight or obese. Average life expectancy is already diminished; the main adverse consequences are cardiovascular disease, type 2 diabetes, and several cancers. The complex pathological processes reflect environmental and genetic interactions, and individuals from disadvantaged communities seem to have greater risks than more affluent individuals partly because of fetal and postnatal imprinting. Obesity, with its array of comorbidities, necessitates careful clinical assessment to identify underlying factors and to allow coherent management. The epidemic reflects progressive secular and age-related decreases in physical activity, together with substantial dietary changes with passive over-consumption of energy despite the neurobiological processes controlling food intake. Effective long-term weight loss depends on permanent changes in dietary quality, energy intake, and activity. Neither the medical management nor the societal preventive challenges are currently being met.

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Hippocrates wrote "Corpulence is not only a disease itself, but the harbinger of others", recognising that obesity is a medical disorder that also leads to many comorbidities. This association is profoundly important for the affected individuals, but the associated morbidity is also economically damaging for society. The number of deaths per year attributable to obesity is roughly 30 000 in the UK[1] and ten times that in the USA,[2] where obesity is set to overtake smoking in 2005 as the main preventable cause of illness and premature death.[3]

WHO[4] describes obesity as one of the most blatantly visible, yet most neglected, public-health problems that threatens to overwhelm both more and less developed countries. The problems of overweight and obesity have achieved global recognition only during the past 10 years, in contrast to underweight, malnutrition, and infectious diseases, which have always dominated thinking. WHO now accepts a body-mass index (BMI) of 25·0 kg/m^2 or higher as abnormal; the overweight category is classified as obese when the BMI is 30·0 kg/m^2 or more. The risks of diabetes, hypertension, and dyslipidaemia increase from a BMI of about 21·0 kg/m^2, thereby reducing life expectancy and greatly increasing the health and societal economic burden;[5] excess bodyweight is now the sixth most important risk factor contributing to the overall burden of disease worldwide.[6]

Figure 1 shows the average regional prevalence of obesity (not overweight) by age and sex in the sub-regions of the world. These estimates, based on measured BMI in appropriate population samples, show that the only region in which obesity is not common is sub-Saharan Africa as a whole. However, the prevalence in South Africa is high, especially among the poorest women, and reflects the general worldwide finding that obesity is linked to poverty,[7] particularly when a country's GDP exceeds about US$5000 per year.[5,8] At all ages and throughout the world, women are generally found to have a higher mean BMI and higher rates of obesity than men, for biological reasons.[5] The International Obesity TaskForce estimates that at present at least 1·1 billion adults are overweight, including 312 million who are obese. With the new Asian BMI criteria of overweight at a lower cut-off of 23·0 kg/m^2, the number is even higher (1·7 billion people).[9] Optimum waist circumferences are lower for Asians: 90 cm for men and 80 cm for women,[10] compared with 102 cm and 88 cm suggested for white people.[4] These data have now been incorporated into new proposals by the International Diabetes Federation on the metabolic syndrome,[11] but the limits for Europid, as distinct from American, white people are 94 cm for men and 80 cm for women, These values and the limits for Japanese, Chinese, and other ethnic groups are based on different criteria and estimates.[12]

Life expectancy

Even 50 years ago, men and women taking out insurance policies were known to be likely to die early if they were overweight and especially if they were obese when young.[13] Obesity has more recently been shown to decrease life expectancy by 7 years at the age of 40 years.[14] The increase in risk of death with each unit increase in BMI declines progressively with age but remains substantial until the age-group of 75 years and

Search strategy and selection criteria

Studies of interest were identified by systematic searches of MEDLINE and EMBASE for all 191 countries of the world with the keywords "BMI", and "obesity" each paired with "cardiovascular disease", "hyperlipidaemia", "cholesterol", "stroke", "ischaemic heart disease", "osteoarthritis," "diabetes mellitus type 2", "cerebrovascular disease", and in combination with each country's name. We contacted WHO Regional Officers for help with searches and governments and individuals in searches for unpublished data. Cochrane reviews, meta-analyses, and other systematic reviews were preferentially used.

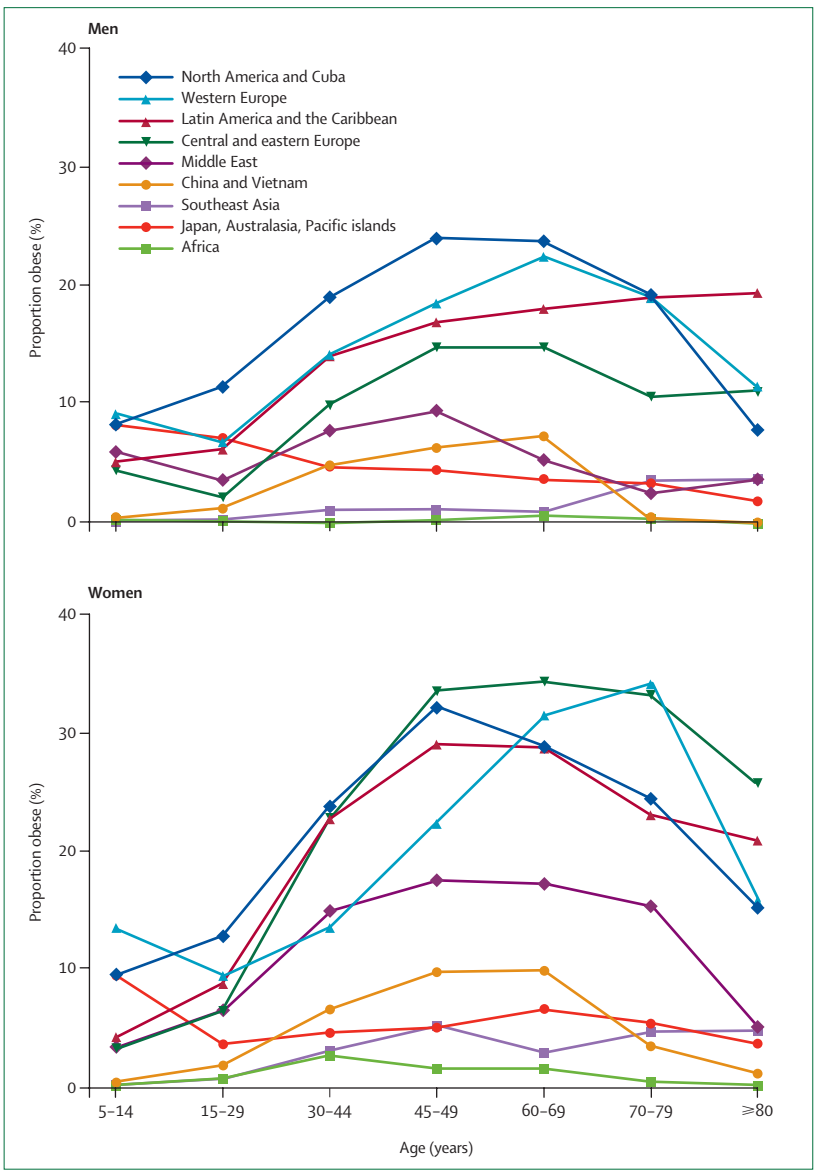

Figure 1: **Prevalence of obesity worldwide by age and sex**
Derived from James and colleagues,[5] where the full list of countries included in each subregion is the same as in the main WHO analysis.[6]

older.[15] Thus, the UK Government now estimates that a BM`I of 25·0 kg/m^2 decreases the life expectancy of English men by 2 years and, given the progressive epidemic of obesity, the effect will increase to 5 years by 2050.[16] What is not yet confirmed, however, is whether intentional weight loss in obese individuals prolongs life as well as reducing risks. Preliminary evidence suggests a 30–40% reduction in diabetes-related mortality with moderate (less than 10% of bodyweight weight loss.[17] People with newly diagnosed diabetes who lost 10 kg in their first year of management were found to have gained a further 4 years of life.[18]

Disease burden from excess weight in adults

Detailed estimates of the years of ill health and lives lost between the ages of 30 years and 75 years because of excess weight are shown for the subregions of the world in figure 2. These predictions are based on detailed estimates of the prevalence of various disorders and deaths from them, the prevalence of high BMI according to age, and the proportion of the disease burden attributable to the excess weight.[5] Cardiovascular disease dominates, followed by diabetes and some cancers, especially in women. Again, the burden of disease is high in eastern Europe and Latin America, but the Asian countries have a surprisingly high burden in view of their lower obesity rates. This finding relates to the higher absolute risk of diabetes and probably cardiovascular disease among Asian,[5,19] Hispanic,[20] and perhaps African populations, partly because they are more prone to abdominal obesity with its excess risks.

Fat distribution

Many of the comorbidities of obesity are reflected in the so-called metabolic syndrome, originally defined arbitrarily by WHO on the basis of insulin resistance with other features of obesity[21] or pragmatically in the USA[22] on the basis of three of five features: large waist circumference, abnormal concentrations of triglycerides, HDL cholesterol, and fasting glucose, and hypertension. Lower waist circumference cut-off points for Asian populations have been used in Asian analyses of the metabolic syndrome,[23] but now the International Diabetes Federation[11] has proposed a universal system in which an ethnically specific waist circumference is the first requirement with abnormalities in two of the other four (triglycerides, HDL cholesterol, fasting blood glucose, and blood pressure) as in the latest criteria.[22] The INTERHEART findings,[24] from 52 countries on the predictive importance of the waist/hip ratio rather than waist or BMI measures alone, imply that the early emphasis on waist/hip ratios might have to be reapplied even though the waist measurement is simpler to use in clinical practice.

Currently, up to 30% of middle-aged people in more developed countries have several features of the metabolic syndrome.[25] The prevalence is as high as 60% among individuals in the seventh decade of life. Only an estimated 30% of adults have no features at all.

Insulin resistance is induced by fat deposited intracellularly and the secretory products of the expanded adipocyte mass, which is the body's most prolific endocrine organ. These products include cytokines such as interleukins 1 and 6 and tumour necrosis factor α. The latter also has a paracrine suppressive effect on the secretion of adiponectin, a powerful insulin sensitiser which is secreted less as the adipocyte mass expands.[26,27] The infiltration of fat into

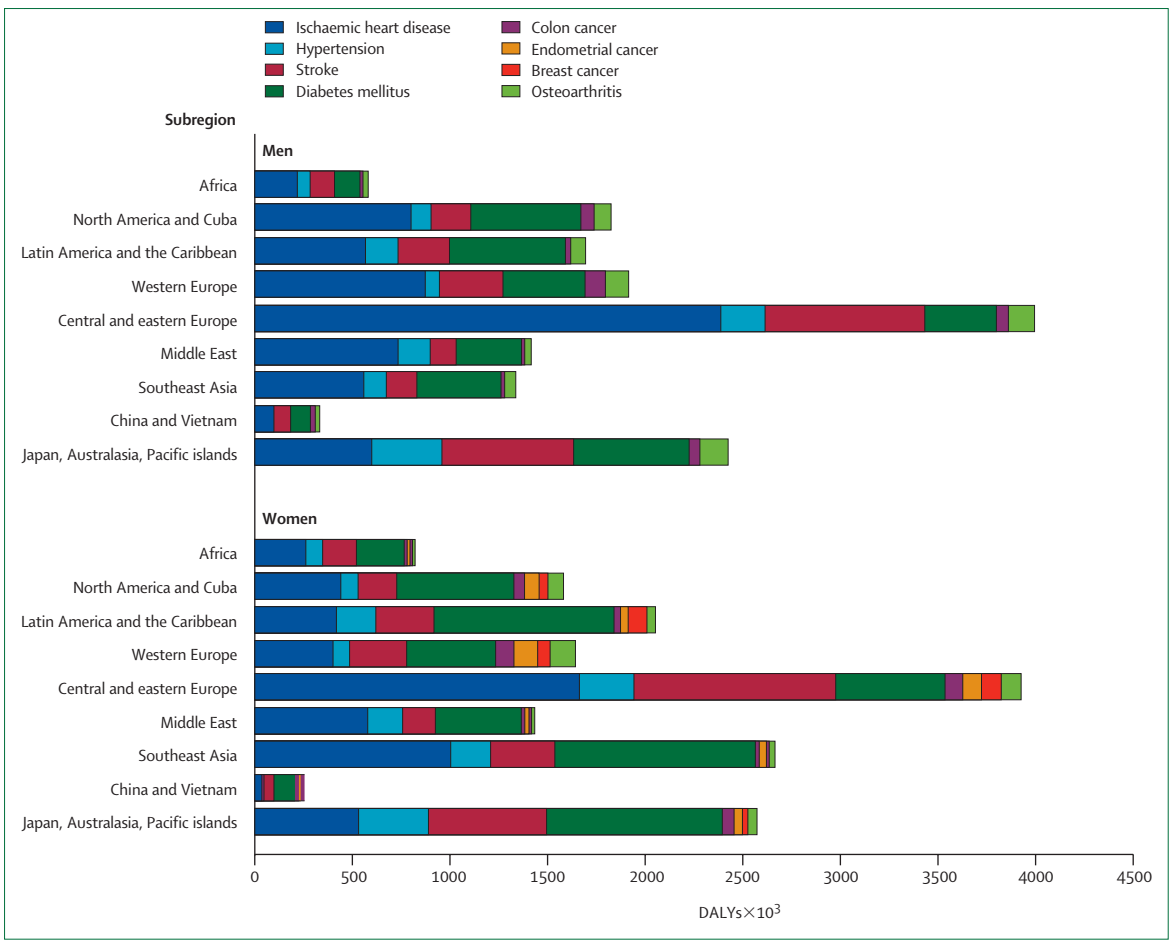

Figure 2: **Disability-adjusted life-years (DALYs) lost as a result of obesity in men and women worldwide**
Derived from James and colleagues.[5]

the pancreatic islet cells amplifies the age-related decline in the islets' capacity to maintain the increased insulin output demanded by insulin resistance, so glucose intolerance and premature type 2 diabetes readily develop.

Abdominal obesity accentuates the problem, probably because of the unusually high influx of portal fatty acids, cytokines, and hormones into the liver from omental adipocytes that normally are almost devoid of fat. The resulting distortion of hepatic metabolism includes increased synthesis of apolipoprotein B and VLDL and greater release of insulin to enter the general circulation. The effects of cytokines on the peripheral tissues with increased intracellular lipid also lower cellular insulin sensitivity; the surge in lipids promotes proliferation of the vasa vasorum of the arterial media and apoptosis by the medial macrophages, with a further release of cytokines. These changes help to explain the role of obesity as a promoter of intracellular inflammatory pathophysiological processes by inflammatory mechanisms with resulting arterial damage.[28]

Hypertension

The risk of hypertension is up to five times higher among obese people than among those of normal weight,[29] the variability in response reflecting differential genetic susceptibility as well as dietary factors. Up to two-thirds of cases of hypertension are linked to excess weight,[30] and cross-sectional population surveys[31] suggest that more than 85% of hypertension arises in individuals with BMI values above 25 kg/m^2. The increase in blood pressure with excess weight gain arises partly because of the release from adipocytes of angiotensinogen (a precursor of angiotensin that has well-known effects on blood pressure), an increase in blood volume associated with the greater body mass, and in response to a rise in blood viscosity. The change in blood viscosity is induced by the release of profibrinogen and plasminogen activator inhibitor 1 from adipocytes with a fall in plasminogen activator.[32]

Diets conducive to weight gain independently amplify blood pressure. Dietary fats, especially saturated fats, induce a rise in systolic and diastolic blood pressures as well as hypercholesterolaemia, as shown in the Dietary

	Change in systolic blood pressure (mm Hg)		Change in diastolic blood pressure (mm Hg)	
	Normotensive	Hypertensive*	Normotensive	Hypertensive*
Increase intake of fruit and vegetables by 200 g/day†	−0·8	−7·2	−0·3	−2·8
Decrease fat intake by10% of energy†	−2·7	−4·1	−1·8	−2·6
Decrease daily salt intake from 10 g to 4 g†	−1·6	−7·6	Average −3·5	
Total weight-independent dietary benefit†	−7·1	−11·5	Average −4·5	
Increase intake of free sugars to 152 g/day	6·9		5·3	
Reduce weight	Average −6·1‡		Average −3·7§	

*⩾140 mm Hg systolic, ⩾90 mm Hg diastolic. †Data from the DASH trial[31,35] with some values inferred from the graphs. The sucrose effect is taken from Raben and colleagues' paper[34] and the effect of weight loss from Avenell and colleagues' systematic review.[37] ‡For loss of 10% of bodyweight. §For 10 kg loss.

Table: **Measured and estimated changes in blood pressure from weight-independent dietary changes in relation to weight-loss-induced changes in adults with normal or high blood pressure**

Approaches to Stop Hypertension (DASH) trials.[33] Energy-dense diets rich in fats and refined sugars promote weight gain,[34,35] and high sugar intakes also induce increases in blood pressure of 6·9 mm Hg (systolic) and 5·3 mm Hg (diastolic).[36] Energy density is reduced by higher intake of fruit and vegetables, which the DASH trial also showed lowered blood pressure. The challenge, therefore, is to assess the contribution of weight gain as distinct from that attributable to dietary factors including salt.[37] Data from the DASH trial (table) suggest that blood pressure can be lowered independently of weight change, especially in people with hypertension, and the overall effect is equivalent to that achieved with a reasonably potent blood-pressure-lowering drug. In adults in North Karelia, Finland, during a 15-year period in which vegetable consumption trebled there was a substantial fall in intake of total fat and saturated fat accompanied by a 15% decrease in total serum cholesterol concentrations[38] and a substantial decline in salt intake. These changes were accompanied by an increase, rather than a decrease, in the average BMI of the population. Thus, the combination of these intervention studies on volunteers and an unwell population suggests that dietary changes are more important than weight loss in lowering blood pressure especially in people with hypertension.[33] Avenell and colleagues' Cochrane analysis[39] could not distinguish between the effect of weight loss per se and the accompanying changes in diet leading to the weight loss.

Coronary artery disease and strokes

Dyslipidaemia progressively develops as BMI increases from 21 kg/m^2 with a rise in proatheromatous, dense, small-particle-sized LDL. This change increases the risk of coronary heart disease by 3·6 times. With low HDL concentrations, as well as high concentrations of triglycerides, CHD risk increases.[40] The combined effect of dietary saturated and *trans* fatty acids on plasma lipids is amplified by the lack of n-3 long-chain fatty acids, which have complex competitive effects with the more pervasive n-6 polyunsaturated fatty acids on prostanoid synthesis, cellular function, and thrombosis.[41] There is also an interaction with abdominal obesity; the influence of abdominal weight gain and external sources of infection as well as endogenous inflammation on the development of the metabolic syndrome, dyslipidaemia, and diabetes can now be quantified.[42] Findings from the Asia-Pacific Cohort Collaboration Study involving 26–33 cohorts and more than 300 000 adults followed up for almost 7 years found for each unit change in BMI a 9% difference in ischaemic-heart-disease events and a change of about 8% in hypertensive deaths and ischaemic strokes.[5] A surprising finding, given the clear relation with hypertensive deaths, was the closer relation of BMI to ischaemic than to haemorrhagic stroke. This finding could reflect the importance of weight-independent dietary factors such as salt in determining death rates from haemorrhagic strokes.

Left-ventricular hypertrophy occurs in 70% of women with both obesity and hypertension, and around 14% of cases of heart failure in women (11% in men) are attributable to obesity.[43] The effect of obesity on heart function is probably due to a combination of factors including hypertension, dyslipidaemia, diabetes mellitus, increased fat mass and left-ventricular mass, endothelial dysfunction, and atherosclerosis.

These epidemiological inferences are paralleled by intervention studies, which have shown that weight loss improves the lipid profile as well as hypertension. Extensive Cochrane analyses[39] suggest that a weight loss of 10 kg will induce a reduction in total cholesterol concentration of about 0·25 mmol/L (about 5%). Again, however, a distinction should be made between the immediate effect of weight loss and the longer-term effects of maintaining a lower weight by eating an appropriate diet. The observed hazards of weight loss in people with existing heart failure[44] show the probable importance of further losses of lean body mass, including cardiac muscle, in older patients who have already replaced much of their lean body mass with fat.

Diabetes

The relation between obesity and type 2 diabetes is so close that Sims and co-workers coined the term "diabesity" in the 1970s, when they showed that in young men with no family history of diabetes who were overfed for 6 months BMI increased to 28·0 kg/m^2 and there were reversible rises in fasting concentrations of insulin, glucose, and triglycerides, and impaired glucose tolerance.[45] Stevens and colleagues[46] showed that around 90% of individuals who develop type 2 diabetes have BMI higher than 23·0 kg/m^2, the risk of diabetes being greatly increased by early weight gain,[47] especially in childhood and in people with a family history of diabetes, with abdominal obesity, and whose mothers who had gestational diabetes. In Japan, the risk of diabetes is greatly increased by excess weight in older people; 50% of 70-year-old Japanese with BMI of 28·0 kg/m^2 have diabetes.[5]

Imprinting of metabolic control in fetal life and early childhood

Worldwide analysis of diabetes shows that four of the five countries with the most cases are in Asia,[48] with the risks of diabetes increasing from very low BMI. Clinicians must therefore be more proactive and alert to the possibility of impaired glucose tolerance and diabetes even at BMI values of around 23·0 kg/m^2 when there is even slight abdominal obesity. In the most deprived areas of India, 14% of adults have diabetes and further 18% have glucose intolerance; on the basis of Chinese studies, the latter group have an annual probability of 11% of developing diabetes within 5 years.[49]

These ethnic differences seem to be imprinted by generations of fetal and postnatal malnutrition, combined with recent rapid childhood weight gain, which seems particularly conducive to the development of insulin resistance and the metabolic syndrome.[50] In experimental models, poor maternal feeding leads to profound changes in development of hepatic and pancreatic tissue in the offspring with altered expression of various metabolic pathways and changes in telomere length accompanied by substantial differences in the lifespan of the progeny.[51,52] There seem to be clear parallels with the concept of a disjunction in nutritional experience having profound effects in both animals and people.

Nevertheless, the development of diabetes is substantially preventable in both white and Asian people by small weight losses with dietary change and moderate exercise.[50,53,54]

Respiratory effects

People with pre-existing respiratory disease can be severely handicapped by weight gain: resting metabolic rates and movement costs are higher, but the physical effect of thoracic and abdominal fat restricts vital capacity and can be severely debilitating. Respiratory complications such as atelectasis and infection readily occur after anaesthesia. Whether obesity specifically induces bronchospasm is less clear, but overweight patients with asthma are further burdened, and their clinical condition can become evident only after weight gain, perhaps induced by steroids. The mechanical effects of bulky fatty tissue around the neck induce an obstruction to breathing, particularly during sleep, leading to sleep apnoea. A neck circumference of 43·0 cm or more in men or 40·5 cm or more in women is associated with episodes of disrupted breathing, recurring up to 30 times a night. Observers describe loud snoring, followed by a pause of 10 s or longer in breathing, then a loud grunt and resumption of normal respiration. About 3% of middle-aged people in more developed countries are affected, with a male to female ratio of four to one.[55] Sleep apnoea can lead to pulmonary hypertension, right heart failure, drug-resistant hypertension, stroke, and arrhythmias, but the main risk is accidents caused by daytime somnolence, for example when driving.

Cancers and reproductive abnormalities

Obesity is one of the most important known preventable causes of cancer. About 10% of all cancer deaths among non-smokers are related to obesity. The WHO International Agency for Research on Cancer[56] estimated that overweight and inactivity account for a quarter to a third of cancers of the breast, colon, endometrium, kidney, and oesophagus. The underlying mechanisms are difficult to define. Acid reflux, due to abdominal bulk, contributes to oesophageal cancer, and colon cancer has been linked to hyperinsulinism. Breast cancer seems to be related to the abnormally high concentrations of free oestrogen in postmenopausal obese women caused by peripheral conversion of sex hormones in adipose tissue by aromatase, together with a fall in the concentrations of plasma sex-steroid-binding globulin. These changes probably also explain the propensity to endometrial cancer and could be relevant to the suggested link between overweight and prostate cancer.

The excess oestrogen concentration also interferes with the feedback regulation of the hypothalamo-pituitary axis, disrupting normal reproductive function and causing irregular, commonly anovulatory cycles; the greater the degree of obesity, the more profound the effect on ovarian function, and obesity probably now accounts for 6% of primary infertility.[57] In men, similar changes are now recognised as leading to impotence and increasing infertility, with abdominal obesity again a particular risk.[58]

These disturbances in sex hormones are also commonly accompanied in women by hirsutism and development of the polycystic ovary syndrome, characterised by substantial insulin resistance, androgen production from oestrogens partly resulting from the greater adipocyte aromatase activity in obesity. This poorly defined syndrome[59] responds to weight loss[60] and changes in intake of essential fatty acids,[61] however, as well as treatments for the insulin resistance.

Obesity-related changes in hormone concentrations adversely affect pregnancy; the risk of admission to hospital is four to seven times higher than for non-obese women. The US Surgeon General's obesity report[62] highlighted an increase of three to ten times in the risk of pre-eclampsia, more common gestational diabetes, difficulties in labour and delivery, and higher rates of caesarean deliveries with more maternal and infant deaths. Infants are at greater risk of neural-tube defects and macrosomia.

Arthritis

That obesity leads to joint pain and arthritis of the knees and hips is not surprising, but the involvement of the carpometacarpal joints of the hand[63] implies a metabolic

Panel 1: **Criteria for common eating disorders**[64]

Binge eating syndrome
Large meals, eaten rapidly, without control
Three or more of: rapid eating, solitary or secretive eating, eating despite fullness, eating without hunger, self disgust, guilt, depression
Striking distress while eating
If vomiting is part of the disorder, classify as bulaemia
No compensatory features—eg, excess exercise, purging or fasting
>2 days/week for 6 months

Night eating syndrome
Evening hyperphagia; >50% of daily intake after evening meal
Guilt, tension, and anxiety while eating
Frequent waking and more eating
Morning anorexia
Consumption of sugars and other carbohydrates at inappropriate times
Persistent for longer than 2 months

contribution. Hyperuricaemia and gout are well-recognised features of both weight gain[65] and the metabolic syndrome.

Non-alcoholic steatohepatitis

The prevalence of non-alcoholic steatohepatitis is increasing rapidly in more developed countries as part of the obesity epidemic. It is set to become one of the most common causes of end-stage liver failure in more developed countries, because it progresses from benign fatty changes to cirrhosis, portal hypertension, and hepatocellular carcinoma.[66] The changes in liver histology seen in alcoholic disease are also typical of non-alcoholic steatohepatitis, but the aetiological factors are obesity, diabetes, hyperlipidaemia, and hypertension. The disorder is generally asymptomatic, although some patients describe tiredness and abdominal discomfort; hepatomegaly occurs in up to 75% of patients, but other signs of liver disease are rare. The finding of raised concentrations of γ-glutamyl transpeptidase and alanine aminotransferase, and to a lesser extent aspartarte aminotransferase and alkaline phosphatase, can be the first indication of non-alcoholic fatty liver disease; these findings can be associated with an abnormally echogenic white or bright appearance of the liver on ultrasonography. CT and MRI can show gross hepatic steatosis, but liver biopsy is the gold-standard diagnostic test, revealing identical features to alcoholic liver disease. The prevalence of non-alcoholic steatohepatitis in the general population is between 2% and 9%. 50% of patients with the disorder develop fibrosis and 30% cirrhosis, and 3% will develop liver failure and need transplantation.

There is a strong connection between gallbladder disease, especially gallstones, and obesity, due to supersaturation of bile with cholesterol. In women, the risk is three times higher with BMI of 32·0 kg/m^2 or above and seven times higher with BMI of 45·0 kg/m^2 or above than in those with lower BMI. There is a particular risk in patients who lose weight rapidly; gallstone formation after bariatric surgery has been reported to affect 38% of patients.

Psychological features of obesity

Obesity was a sign of wealth and wellbeing in the past and still is in many parts of Africa, particularly since the HIV epidemic began. Care is needed to distinguish the social from the pathophysiological consequences of weight gain. In affluent societies and many Asian countries, slenderness is now the ideal, so individuals gaining weight, especially women, feel increasingly unacceptable and become anxious and depressed and can develop obsessive behaviours as they attempt to deal with their excess weight. Discrimination is rampant; obese individuals are less acceptable marriage partners, are handicapped in job promotions, and earn less.[67]

In US women, obesity increases the risk of being diagnosed with major depression by 37%, whereas obese men have a 37% lower risk of depression than men of normal weight. In men, underweight is associated with significantly higher risks of depression and suicide, although whether the association is causal, or whether depressed men smoke more heavily, for example, is unclear.

Two eating disorders are linked with both depression and obesity: binge eating disorder (a subgroup of bulimia nervosa) and night eating syndrome (panel 1). These disorders affect a substantial proportion of patients attending obesity clinics; recognition of the characteristics is important, because psychological assessment and counselling are essential.

Weight gain despite good physiological control of intake

Despite the obesity epidemic, individuals have extraordinarily fine control of their food intake on a weekly if not daily basis. Although there are unpredictable variations in daily intake in response to social events, and smaller fluctuations in energy output from changes in physical activity, body energy stores remain fairly constant. A weight gain of 0·5–1·0 kg in a year amounts to 3500–7000 kcal (14·6–29·3 MJ), implying an error in the regulation of food intake of less than 0·5% of average daily consumption. Subconscious mechanisms, including gastrointestinal hormones, such as ghrelin PYY$_{3–36}$, gastric inhibitory peptide, and cholecystokinin, and other complex neuroendocrine systems are therefore effective in controlling adjustments to appetite and intake in the short, medium, and long term. These mechanisms are surpassed only by the multi-

faceted processes that come into play when people are deprived of food. Those processes enable deliberately overfed young but not older volunteers to return spontaneously to normal bodyweights over a few months.[68]

In the light of this surprisingly good control of energy balance, why do people become overweight and obese as they become middle aged? Genetic factors are well recognised to influence who gains weight, and the magnitude of weight gain, as shown by overfeeding studies in twins.[69] Statistical analyses suggest that 50% or more of the variation between individuals in BMI has a genetic basis,[70] but these effects are dominated by polygenic environmental interactions that reflect many genetic influences affecting spontaneous physical activity, twitchiness, basal metabolic rate, propensity to synthesise diurnally lean rather than fat tissues, and appetitive behaviour. Monogenic mutations, of leptin secretion or receptor activity for example, are very rare but single base changes in the gene for the hypothalamic melanocortin receptor, normally involved in appetite suppression, explain about 5% of obesity in children if it is severe early in life.[71]

These genetic influences cannot explain the population's public-health problem of obesity. The adult phase of weight gain (figure 1) corresponds to a substantial fall in leisure-time sports for men. Women tend to gain weight once they cohabit and begin to share meals with men, who have intrinsically higher energy needs and commonly take more exercise.[72] Oral contraceptives could provide further physiological and social conditions conducive to weight gain; repeated pregnancies certainly do so.[73] The well-documented progressive fall in physical activity with age means that the less effective mechanisms downregulating food intake are under severe strain as energy needs decline. Before major changes occurred in use of cars, mechanical aids, television, and computers in the 1960s to 1980s, the fall in total energy output from age 25 years to 75 years in the Baltimore ageing study[74] amounted in men to 1200 kcal (5·02 MJ) per day. To avoid any gain in body energy would therefore have required a progressive fall in intake of about 270 kcal (1·13 MJ) daily, each decade, throughout adult life. Now the environment is deliberately designed to promote inactivity, even children are sedentary, especially when both parents work and they are confined indoors or at school.

Accompanying the documented secular and age-related declines in physical activity are changes in food habits that might originally have been responses to reduced energy needs. Social historians describe the three or four large meals a day taken by hard-working people, amounting to 3000–4500 kcal (12·5–18·8 MJ) per day to cope with physical demands at work and in the home. As working conditions and household aids apparently improved, meals became smaller; breakfast was omitted or reduced, sandwiches or single, smaller courses were eaten in the middle of the day, and the evening meal became the main meal of the day. In the 1960s and 1970s in more developed countries rates of overweight and obesity were of little immediate concern; however, by 1983 the potential public-health problem of obesity was being highlighted.[75] What can explain the huge rise in obesity rates?

Physical inactivity

Many studies have shown the relation between sedentary lifestyle and weight gain, but reliable direct measures of physical activity are only just emerging.[76] Nevertheless, the secular decline in physical activity is obvious. Morris and colleagues showed more than 50 years ago[77,78] that vigorous exercise was crucial to cardiovascular health, but highly sedentary adults now derive benefit from even slight exertion.[79] Exercise has many benefits, from psychological to physical, independent of its contribution to weight stability. However, the recent emphasis on weight maintenance has highlighted the importance of total energy output—60–90 min per day of walking,[80] 10 000 steps monitored on a pedometer, or 15 000 steps in individuals attempting to maintain weight loss. Such activity is difficult nowadays without redesigning cities to necessitate more walking and spontaneous movement. Gyms tend to be attended by more affluent and motivated individuals. Physical activity is helpful in weight loss, and essential for limiting the progressive decline in lean tissues with age, but its main importance in bodyweight is in maintaining rather than increasing a 5–10% weight loss.

Changes in daily food intake patterns

Short-term regulation of food intake is readily overcome by sudden increases in the energy density of food, for example by fat-rich evening meals that allow no compensatory adjustments until the next day.[81] Sugar-rich drinks also circumvent the meal-based regulation of appetite.[82] Foods with higher energy density—those rich in fats, extracted sugars, and refined starches—are unwittingly consumed in greater amounts, the density rather than the macronutrient content being the determinant of intake.[83–86] Nevertheless, the urge to eat sugary and salty foods is driven by selective taste buds and neuronal projections to the limbic pleasure centres, and the combination of the fats and sugars, rare and precious in our early evolution, is especially alluring. When displayed in larger portions, the visual impact of food dominates appetitive regulation in adults and children older than about 4 years so they consume more.[87] Food companies have long known the commercial benefits of promoting larger portion sizes. Given the fixed energy requirements of a population, the only ways to promote sales involved provision of products with higher content of fats, sugars, and salt, in larger portions, making them available everywhere, and promoting drinking and eating on the move since this distracts the normal appetite regulatory responses.

Eating outside the home also restricts the ability to control the composition and quantity of food. Targeting of children from infancy to generate brand loyalty, which distorts dietary patterns,[88] and expansion of sales to the huge potential markets of less developed countries are the only means seen by food companies for maintaining expansion, profits, and shareholder value. Contrary to initial estimates[89] that the dominant factor precipitating the obesity epidemic in the UK was a decline in physical activity rather than excessive intake,[90] recent evidence from secular trends and obesity rates in 36 countries shows rising intakes.[91] Similarly, national studies of BMI of different groups[92] show that intake is now the dominant determinant with lower physical activity following, rather than preceding, weight gain in some cases.[93] Thus, a decline in activity was probably a particular feature of the 1960s to 1980s, but the transformation of our food habits in response to intense industry competition is now the main amplifier of the epidemic.[94]

Drugs

An increasing number of drugs are now being documented as causing weight gain (panel 2).[95]

Assessment and management

Despite the plethora of diet books and heavily promoted schemes for effortless and rapid weight loss, the escalating epidemic of obesity shows the failure of these approaches. The medical issue is now how to help transform patients' lives in the long-term when they are constantly distracted and disheartened by the claims for miracle cures. Patients need to create a micro-environment as a buffer against the all-pervading toxic environment, and the greater the genetic contribution to the individual's obesity the more abnormal their micro-environment must be.

Although there is plenty of evidence clearly proving the relation between obesity and disease, this relation is rarely apparent to affected individuals. An obese person's health might not be as obviously compromised as that of someone with asthma or chronic pain, unless comorbidities have already developed. Most people are unaware of the underlying development of the sinister early signs of the metabolic syndrome, which helps to explain the lack of motivation for change of many obese individuals. Motivation depends on the acceptance and recognition that obesity is a medical disorder; since many clinicians do not, this is asking a lot of a patient. Recognition depends on improving the patient's understanding, which also involves increased public awareness of obesity in a medical context and therefore depends on more coherent views being set out by government, the medical profession, schools, and the media as well as by the food, advertising, and retail industries. Until that happens, clinicians have to tackle the obesity problem one person at a time.

Many obese individuals are already being monitored in chronic disease clinics, but the preliminary assessment of the patient's excess weight is commonly neglected. Immediate and complete assessment need not be undertaken in a busy time-constrained clinic by a stressed clinician but should be arranged for an early date. The assessment environment needs to be appropriate, friendly, and unthreatening with large enough chairs and suitable equipment such as large blood-pressure cuffs at hand. A full history should be taken, with particular attention to symptoms of comorbidities, such as sleep apnoea, that might be unrecognised. Emphasis should be given to a family history of diabetes, including gestational diabetes, and cardiovascular disease as well as the obesity itself. Successful and unsuccessful attempts at weight loss, a social history including work and leisure activities, and the availability of a support network is as important for long-term care as enquiries about smoking and alcohol intake. Motivation should be assessed because it is essential for a favourable outcome and can be encouraged in different ways. A new symptom or other triggers, such as the arrival of a baby or grandchild or the death or illness of a friend or relative, can precipitate a determination to cope with long-term weight management. The estimated proportion of people who are sufficiently motivated to accept treatment is believed to be less than 20%, and in many cases treatment is essential but needs to be set out as a facet of comorbidity management in patients who deny their weight problem. Efficient use of resources is to focus on individuals who are most motivated. Lack of motivation is a massive barrier to change. However, the presence of motivation is powerful and should be harnessed by continuing support, encouragement, and follow-up by a weight-management team, which needs to be developed for effective long-term care.

Clinical examination should be undertaken; height, weight, and waist circumference should be measured,

***Panel 2:* Drugs that can cause weight gain**

Antipsychotics, especially olanzepine
Antidepressants: tricyclics, selective serotonin-reuptake inhibitors, monoamine oxidase inhibitors, mirtazepine, lithium
Corticosteroids
Oral contraceptive and progestagenic compounds
β blockers
Oral hypoglycaemic agents: glitazones (peripheral rather than visceral gain), sulphonylureas
Insulin
Anticonvulsants: phenytoin, sodium valproate
Antihistamines: many antihistamines, though weight gain is greater with older agents
Pizotifen, used as a prophylactic migraine treatment

and BMI calculated. Hypertension should be excluded with the use of a large arm cuff for blood-pressure measurement. Simple investigations should be done to identify markers of the metabolic syndrome and comorbidities, to provide a baseline for future readings to map improvements, and to show to patients that their blood tests indicate no reason, hormonal or otherwise, why they should not lose weight.

Measurement of blood glucose after overnight fasting is essential; if the concentration is raised, further tests for diabetes mellitus will be needed, including glucose tolerance testing, measurement of haemoglobin A_{1c}, and screening for microalbuminuria. Measurement of blood concentrations of lipids, particularly triglycerides and HDL cholesterol as well as total cholesterol, allows an objective calculation of the probability of cardiovascular events.[96–98] Care is needed when extrapolating risk scores to patients with diabetes, for whom the UK Prospective Diabetes Study scoring system is more appropriate.[99] The validity of these scoring systems in non-white ethnic groups (eg, south Asians[100]) is still uncertain, and adjustments to the scoring system might be needed.[101]

The value of simple measures of physical fitness[102] rather than formal exercise testing should also be considered.[103] Non-alcoholic steatohepatitis should be assessed by liver function tests and renal function by measurement of plasma urea and electrolytes. Thyroid function should be tested to exclude myxoedema and electrocardiography undertaken to detect possible left-ventricular hypertrophy. Other tests will depend on the individual as dictated by history and initial assessment. Chest radiographs might be appropriate, as well as screening for obesity-related cancers, hormone profiling in suspected polycystic ovary syndrome or infertility, and measurement of uric acid concentrations in serum in gout. Disorders such as sleep apnoea should be carefully investigated; the cardinal symptoms are too readily assigned simply to excess weight.

When the patient's weight is stable, physical activity should be recorded, preferably with a pedometer, and intake assessed by mean of a systematic food diary—a far more reliable guide to food habits than history taking. A non-judgmental approach is crucial to helping and negotiating with patients their options for long-term change. Symptom control for a related disorder such as angina or arthritis might be needed as well as the management of low self-esteem and depression.

Dietary management

Management of the diet is much neglected by doctors and even misinterpreted by dietitians if energy intake is based on dietary history. The weight conscious and the obese systematically underestimate intake. Intake is better predicted by estimation of the patient's energy expenditure from their sex, age, weight, and crude classification of exercise patterns.[104] This approach together with an individualised diet with an energy deficit of 500–600 kcal (2·09–2·51 MJ) is almost universally used in longer-term trials and has been identified in Cochrane analyses as one of the best options. A lower energy intake triggers the drive to eat, and a standard diet of 1000 kcal or 1200 kcal (4·18 MJ or 5·02 MJ) puts heavier patients under greater physiological stress.

Dietary quality is important;[41] about 20% protein restricts the recognised inevitable loss of about 25% lean tissue that accompanies fat loss and helps satiety. Dietary benefits are amplified by daily intake of 400–600 g vegetables and fruits, with less than 20% fat, adequate n-3 fatty acids but the lowest possible amount of saturated fatty acids, less than 5% sugar, and fibre-rich carbohydrates; such diets also have lower energy density and greater bulk, which further improves satiety. Explicit guidance on transferring to a low-energy-density diet can double the quantity of food eaten and still achieve the energy deficit needed.

Patients are helped by avoidance of eating or drinking on their feet or while watching TV, thereby improving cognitive control of intake. Calorie counting is tedious and not very effective[39] because few patients, let alone their doctors, know their true energy requirements. Monitoring with a simple diary the portion sizes, cooking habits, and the bulk of family purchases of vegetable oils, sugar, soft drinks, fast foods, and alcohol provides important insights for both the patient and the management team.

Lately, very strict diets such as the low-carbohydrate Atkins diet have become popular. They have been shown to have good effects on blood lipid concentrations, blood pressure, and glucose control. These effects are, however, generally short lived and not superior to standard approaches over the longer term.[39,105–107] The degree of weight loss strongly depends on the ability of patients to adhere to their diets,[108] and the more restrictive the regimen the greater the demand for intense discipline in the face of an intense physiological desire to eat. Meal-replacement therapy, in which two meals are replaced by a standard low-energy drink or meal during weight loss and one during weight maintenance, can succeed for some patients,[109] but the recognised longer-term benefits of a low-energy-dense diet rich in the appropriate foods and nutrients are compromised. As with all dietary trials for weight loss and maintenance, the outcomes in terms of the main causes of death are still awaited, although the benefits of appropriate dietary interventions for delaying the onset of type 2 diabetes and improving the main contributors to cardiovascular ill-health are clear.

Pharmacotherapy and surgery

Objections to pharmacotherapy linger, stimulated by memories of cocktails of diuretics, thyroid extract, and amphetamines combined with barbiturates. These

concerns were fuelled by the withdrawal of fenfluramine and mixtures of ephedrine and caffeine,[110,111] which has led to a rigorous demand for evidence of efficacy when obesity drugs are evaluated. The only agents currently accepted by most regulatory agencies on the basis of extensive data are orlistat and sibutramine; rimonabant is undergoing evaluation.[112] These drugs in general increase by three to four times the proportion of patients achieving at least 5% weight loss at 1 year. They have other beneficial effects on blood lipid concentrations, blood pressure, and insulin resistance, which may exceed that expected for the degree of weight loss achieved. However, these additional effects vary depending on each drug's particular mode of action. The effects of orlistat and sibutramine have been dealt with extensively elsewhere.[39,109,113–115]

The criteria of the US National Institutes of Health or the European Union for the use of pharmacotherapy include a BMI of at least 27·0 kg/m^2 with a persistent comorbidity or a BMI of at least 30·0 kg/m^2. Asian medical groups propose lower BMI criteria reflecting their concern about higher rates of comorbidities at lower BMI in Asian populations. Phentermine, an analogue of dexamfetamine, on the market for decades, is permitted in the USA and elsewhere but was allowed back on the market in the European Union only after a legal challenge to the ban by the European Agency for the Evaluation of Medicinal Products (EMAE). The proposed restriction was based on the absence of long-term data on the efficacy and safety of phentermine, the latter being mainly based on post-marketing data. None of these drugs is a magic bullet to induce involuntary and substantial weight loss; they are most effective when used as ancillary therapy in a well-organised weight-management programme.

Surgical treatment is increasingly used,[116] particularly in the USA, on patients with BMI of more than 40·0 kg/m^2 and those with severe comorbidity at BMI more than 35·0 kg/m^2. Laparoscopic adjustable banding of the stomach along with Roux-en-Y and other forms of gastric bypass are now favoured. In experienced surgical centres, the operative mortality is well below 1%, with average weight losses of 25–30% and rapid normalisation of glucose handling and blood pressure in patients with diabetes and hypertension.[117] Long-term monitoring is needed, and patients can eat a nutritionally poor diet without fruit and vegetables. As yet there is only slight evidence of reduced mortality in long-term analyses of surgical treatment,[118,119] but most patients feel transformed by the degree of weight loss. Schizophrenia, personality disorders, and uncontrolled depression are absolute contraindications for surgery and great care is needed in assessing the use of surgery in patients with eating disorders.

How are health-care systems going to cope with the obesity epidemic?

No health-service system has yet developed a useful strategy for managing the huge numbers of overweight and obese people in the community. Nursing, dietetic, and physical-activity expertise and collaboration with public and private community slimming groups are needed. The challenge of prevention as well as managing the millions already affected is overwhelming.[120,121] The challenge to think in novel ways was also emphasised by the new WHO global agreement[122] to develop strategies to deal with the burden of cardiovascular disease, cancer, and diabetes now being fuelled by the obesity epidemic.

The medical profession is only now waking up to the political and industrial challenges as well as the medical challenge. The industrial interests, with powers exceeding even those of the tobacco industry, are on the alert and often acting to slow the drive for change, by intense political lobbying at the highest level and by engaging in tactics well rehearsed by the tobacco companies. Our new scientific understanding of obesity is helping to validate a new approach to tackling the problem but the response of the medical profession to both its management and prevention is still at an early stage.

Conflict of interest statement

The National Obesity Forum receives or has received support for its activities from GlaxoSmithKline, Sanofi-Aventis, and Roche. DWH has received honoraria and expenses from conference organisers for individual lectures and advisory groups on obesity from the above organisations; he is an investigator for the SCOUT trial. The International Association for the Study of Obesity receives or has received support for its activities from Abbott, GlaxoSmithKline, Roche, and Sanofi-Aventis. WPTJ has received personal consultancies or honoraria and travel support from conference organisers for individual lectures and for chairing sessions on obesity from Abbott, GlaxoSmithKline, Johnson & Johnson, Pharmacia, Roche, and Sanofi-Aventis. Since August, 2002, he has chaired the Executive Steering Committee for the SCOUT trial on the effects of weight management on morbidity and mortality in patients with diabetes at high risk of cardiovascular disease.

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