Medical consequences of obesity

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Abstract

Obesity is now one of the most important global public health issues and preventable causes of disease and mortality. In 2004, increased BMI alone was estimated to account for 2.8 million deaths; when combined with physical inactivity the total was 6.0 million, surpassing the excess mortality associated with tobacco, and approaching that of high blood pressure, the top risk factor for death. Type 2 diabetes mellitus is strongly linked with obesity — a 25% increase in risk for every 1 kg/m^2 increase in BMI above 22. Obesity has a particular impact on the cardiovascular system including an increased prevalence of heart failure, hypertension and coronary heart disease. Obstructive sleep apnoea, symptoms of breathlessness and asthma are all more common in the obese. Non-alcoholic fatty liver disease, and its transition to non-alcoholic steatohepatitis, threatens to become the leading cause of cirrhosis and hepatocellular carcinoma. Many cancers are more common in the obese and the outcome of treatment is often less successful. Psychosocial and psychiatric consequences of obesity are also increasingly recognized. It is estimated that in Europe 2—8% of health care budgets are spent on obesity-related disease, equating to 0.6% of gross domestic product.

Keywords Cancer; cardiovascular disease; diabetes; dyslipidaemia; heart failure; hyperinsulinaemia; hypertension; non-alcoholic steatohepatitis; sleep apnoea syndrome

Obesity is a chronic disease with important health and psychosocial consequences and a major risk factor for non-communicable diseases. The medical complications affect almost every body system (Figure 1). Evidence for these risks comes from both cross-sectional surveys and large, prospective studies following cohorts of men and women over decades. The now widely accepted concept of obesity as an inflammatory disease (due to inflammatory cytokine secretion from adipocytes) helps better to explain the pathophysiology of obesity than just the mechanical, load-bearing consequences.

Mortality

Many studies have reported a 'U-shaped' or 'J-shaped' curve relating BMI to mortality. The greater mortality at low BMI is partly explained by the association of smoking and pre-existing illness with low body weight. Several factors account for a weakened link between BMI and mortality with increasing age, partly because of the increasing prevalence of diseases that increase mortality and also cause weight loss, partly because harmful visceral fat deposition is greater at lower BMI, and

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possibly due to increasing sarcopenic obesity (increased fat with low lean body mass). A large collaborative analysis of baseline BMI versus mortality in 57 prospective studies including nearly 900,000 participants, mostly in western Europe and North America, showed that for each 5 kg/m^2 higher BMI, overall mortality increased by 30% (a hazard ratio of 1.29), explained by increases of 40% for vascular diseases, 60—120% for diabetic, renal, and hepatic diseases, 20% for respiratory disease and 10% for cancers. At BMI 30—35 kg/m^2, median survival was reduced by 2—4 years; at 40—45 kg/m^2 it was reduced by 8—10 years (comparable with the effects of smoking) (Figure 2).[1]

Type 2 diabetes mellitus

The link between type 2 diabetes mellitus (T2DM) and obesity is strong within and between ethnic and population groups; about 75% of patients with diabetes are overweight or obese. In Europe and North America, the risk of T2DM begins to increase from BMI 22 kg/m^2 in women and 24 kg/m^2 in men; in Asian populations, the risk begins to increase at BMIs of 1—2 kg/m^2 lower. Weight gain also carries a risk. In men aged 40—75 years followed for 5 years, the risk of diabetes was 6.4-fold greater in those who had a BMI of 27 kg/m^2 at age 21 years and, independently, 3.5-fold greater in those who gained 9 kg from that age.[2,3] The relative risk of developing diabetes increases by 25% for every 1 kg/m^2 increase in BMI above 22 kg/m^2. The projected increase in obesity prevalence in the UK over the next 20 years (73%—26 million people) is predicted to raise the number of people with diabetes by 1 million. With the onset of obesity earlier in life, the average age of onset of type 2 diabetes is also falling: from 52 to 46 years between 1994 and 2000 in the USA.

Central or upper body fat distribution, as measured by waist circumference, is an independent risk factor for the development of T2DM (Figure 3).[2] Visceral obesity is associated with insulin resistance, which is present at the level of the peripheral tissues (muscle and adipose tissue) and the liver. The clinical hallmark of insulin resistance is acanthosis nigricans, a darkening and ridging of the skin seen on the neck (where it is often associated with skin tags), knuckles, knees and elbows (Figure 4).

Cardiovascular system

The most common and most deleterious effects of obesity are on the cardiovascular system, and include hypertension, heart failure, coronary heart disease (CHD) and stroke associated with disorders of lipids and haemostasis. Roughly, one half of the excess mortality of obesity can be attributed to increased cardiovascular mortality.[4] However, the relationship between obesity and mortality is complex. The phenomenon commonly referred to as 'reverse causality' or 'reverse epidemiology' describes the observation that in some populations, such as in patients with heart failure, leaner individuals are at increased rather than decreased risk. However, this may be a reflection of the poor performance of BMI in defining excess adiposity and the much higher risk associated with sarcopenia in such cohorts. While the increased inflammatory state of obesity drives cardiovascular damage through altered endothelial dysfunction, the role of increased central sympathetic nervous system outflow driving endothelial, arterial and cardiac dysfunction is increasingly recognized (Figure 5). Early vascular ageing can be

Clinical disease linked to obesity

Pulmonary
- Hypoventilation
- Obstructive sleep apnoea
- Asthma

Dermatological
- Hirsutism
- Sweating
- Psoriasis

Gastrointestinal
- Gall stones
- Non alcoholic fatty liver
- Colon cancer
- Gastro oesophageal reflux
- Oesophageal cancer
- Periodontal disease

Gynaecological/Obstetric
- Oligomenorrhea
- Infertility
- Cancer of uterus, breast, cervix
- Pregnancy morbidity

CNS
- Intracranial hypertension
- Migraine/headache
- Stroke
- Psychological/psychiatric
- Dementia

Cardiovascular
- Hypertension
- Ischaemic heart disease
- Heart failure
- Thromboembolism

Andrology
- Hypogonadism
- Prostate cancer

Musculo-skeletal
- Osteoarthritis
- Gout

Metabolic
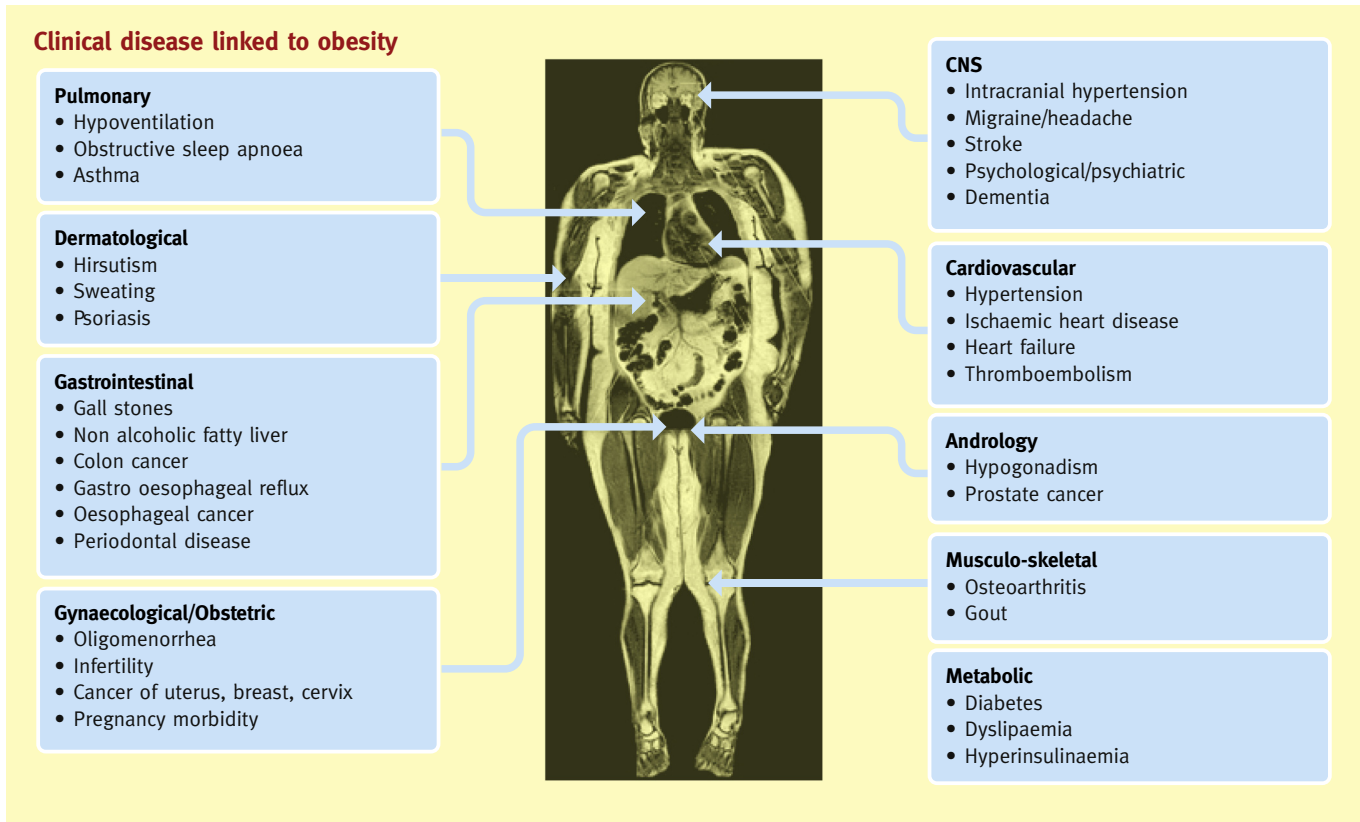- Diabetes
- Dyslipaemia
- Hyperinsulinaemia

Figure 1

assessed by measuring so called 'tissue biomarkers', including arterial stiffness, central blood pressure, carotid intima-media thickness and flow-mediated vasodilatation. These measurements reflect different components of vascular dysfunction and have been extensively investigated in overweight and obese individuals; they have been shown to be abnormal in overweight children and adolescents.

Left ventricular (LV) mass − there is a direct relationship between BMI and LV mass, representing an adaptation to the increased cardiac output required to meet the high metabolic demands of greater body mass.[5] The total circulating volume expands, causing an increase in pre-load and LV end-diastolic volume. increased LV mass seen in obesity also results from fatty infiltration of epicardial fat into the myocardium (and may have a role in the arrhythmias associated with obesity).

Hypertension and heart failure − more than one-third of obese adults have hypertension (blood pressure $\geq$140/90 mmHg) − twice the prevalence in those with BMI less than 25 kg/m^2. It has been estimated that, for every 10% increase in weight, there is a blood pressure increase of 6 mmHg systolic and 4 mmHg diastolic. Hypertension in the obese develops secondary to increased sodium retention and vascular resistance related to changes in the renin−angiotensin system, insulin resistance and increased peripheral sympathetic nervous system activity (Table 1). Increased sympathetic activity correlates with 24-hour urinary excretion of noradrenaline, which in turn correlates directly with BMI, waist:hip ratio, and glucose and fasting insulin concentrations. The combination of eccentric LV hypertrophy and hypertension leads eventually to heart failure.

Several studies have identified congestive heart failure as a common complication of obesity and an important cause of death.[6] After adjustment for established risk factors, there was an increase in the risk of heart failure during a 14-year follow-up of 5% for men and 7% for women for each increment of 1 in body-mass index.[7] As compared with subjects with a normal body-mass index, obese subjects had a doubling of the risk of heart failure. Even in the absence of hypertension, obesity-related cardiac structural changes can lead to 'obesity
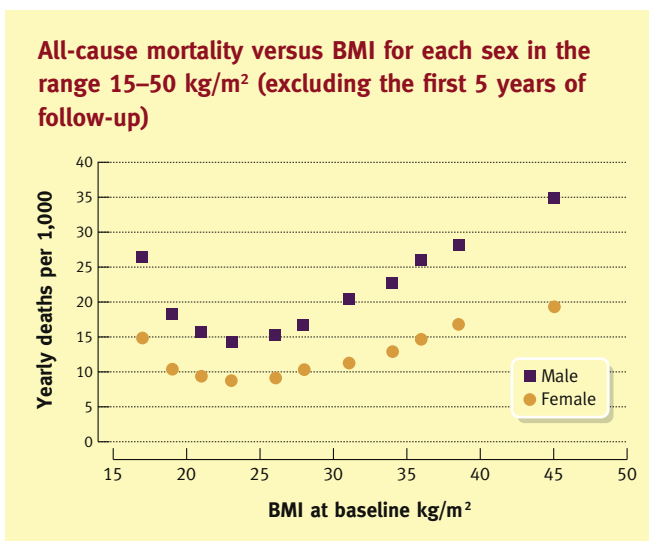
All-cause mortality versus BMI for each sex in the range 15–50 kg/m² (excluding the first 5 years of follow-up)
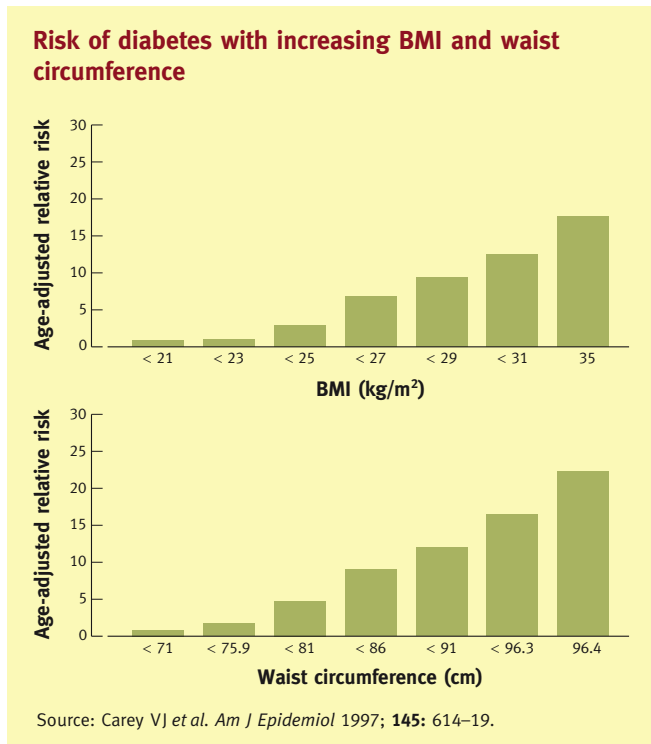
Figure 2

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Figure 3

cardiomyopathy'. The most important mechanisms in the development of obesity cardiomyopathy are metabolic disturbances (insulin resistance, increased free fatty acid levels, and also increased levels of adipokines), activation of the renin-angiotensin-aldosterone and sympathetic nervous systems, myocardial remodelling, and small-vessel disease (both micro-angiopathy and endothelial dysfunction).[8]

CHD is also associated with weight gain and obesity. The Nurses' Health Study showed a clear relationship between CHD and elevated BMI, even when controlling for age, smoking,

Figure 4 Acanthosis nigricans: a sign of insulin resistance.

menopausal status and family history. Compared with BMI less than 21 kg/m^2, the risk of CHD began to increase at BMI 22–23 kg/m^2, was doubled at 25–28.9 kg/m^2 and was more than three times higher above 29 kg/m^2.[9] In UK men, the risk of CHD increases by 10% with every 1 kg/m^2 increase in BMI above 22 kg/m^2. Again, excess visceral fat as clinically determined by an elevated waist circumference may be a better predictor of susceptibility to CHD.

Other problems – obese individuals are more prone to thrombosis, stroke and myocardial infarction. Altered rheology is also seen, and levels of clotting factors VII and X are elevated.

Respiratory dysfunction

Dyspnoea and breathlessness at rest and particularly on exertion are common complaints of the obese. These symptoms arise partly because of the mechanical effects of excess weight on respiratory compliance (stiffness of the thoracic cage). Greater weight imposes higher ventilatory demands, to meet the greater consumption of oxygen on exercise; these demands are usually met by an increased ventilatory rate sufficient to maintain arterial oxygen and carbon dioxide levels. End-expiratory lung volume is reduced at rest in obesity because of the mechanical load on the chest wall, but does not decrease normally in response to exercise, impairing the normal increase in mechanical advantage of the diaphragm and the balance between inspiratory and expiratory muscles. This impaired exercise response seems to account for the symptoms of breathlessness, even in patients who maintain normal gas exchange.

In the early stages of obesity, compensatory mechanisms operate to maintain a eucapnic state through increased central respiratory drive, which may increase three- to fourfold. However, these mechanisms fail to meet the demand as weight increases, leading to the development of pulmonary hypoventilation, which can result in more severe cardio-respiratory compromise.

Obstructive sleep apnoea (OSA) and obesity –hypoventilation syndrome (OHS) – OSA is a common feature of morbid obesity. It is characterized by disturbed sleep at night and somnolence during the day (with a tendency to fall asleep while resting or driving). The patient's partner may report snoring and episodes of apnoea at night. The causes are partly mechanical (reduced upper airway dimensions and shape changes through fat deposition, large tongue, reduction of lung volume from abdominal obesity). However, it seems clear that impaired muscle tone of the upper airway muscles and a possible afferent sensory defect (from chronic airway vibration and occlusion) are also important determinants. In practice, some degree of OSA occurs in all men with a neck circumference of more than 42 cm.[10]

Asthma – recent research has suggested a link between obesity and asthma. In the US National Health and Nutrition Study (which lasted more than 6 years and involved more than 7000 children aged 4–17 years), the fattest children were 77% more likely to suffer symptoms of asthma. It was suggested that increased weight might lead to inflammation in the respiratory tract, which could be the key factor in inducing asthma, but it is impossible to determine whether these children were obese as a result of asthma (possibly because they took less exercise) or vice versa.
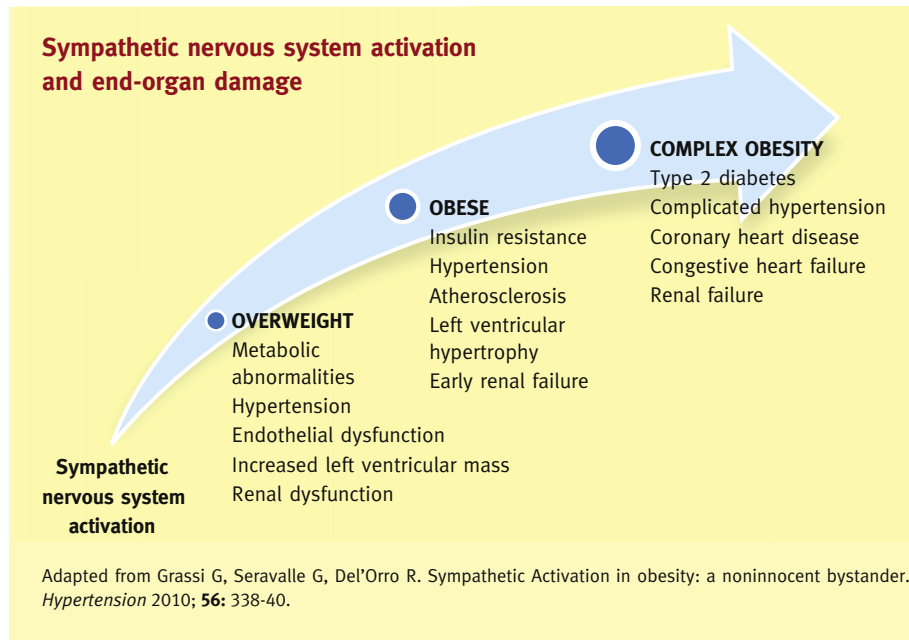
Sympathetic nervous system activation and end-organ damage

COMPLEX OBESITY
Type 2 diabetes
Complicated hypertension
Coronary heart disease
Congestive heart failure
Renal failure

OBESE
Insulin resistance
Hypertension
Atherosclerosis
Left ventricular hypertrophy
Early renal failure

OVERWEIGHT
Metabolic abnormalities
Hypertension
Endothelial dysfunction
Increased left ventricular mass
Renal dysfunction

Sympathetic nervous system activation

Adapted from Grassi G, Seravalle G, Del'Orro R. Sympathetic Activation in obesity: a noninnocent bystander. *Hypertension* 2010; **56:** 338-40.

Figure 5

In a multivariate analysis, the relative risk of adult-onset asthma was strongly associated ($p = 0.001$) with BMI.[11] Using the strictest case definition of asthma (subjects who reported physician-diagnosed asthma within 1 month of symptom onset, plus use of a prescribed long-term, preventive asthma medication in the last year), nurses who had gained more than 25 kg in weight since the age of 18 years had the highest relative risk (4.7) for the development of asthma.

Non-alcoholic fatty liver disease (NAFLD) and steatohepatitis (NASH) and gall stones

Non-alcoholic fatty liver disease (NAFLD) is a chronic liver disease that may affect up to one-third of the adult population in industrialized countries. It includes two histologically distinct entities: steatosis or fatty liver characterized by increased liver fat (often seen on ultrasound as a 'bright' signal) and steatohepatitis (NASH) characterized by lobular inflammation with or without fibrosis. The prevalence of NAFLD is estimated to 20−30% of US, European and Japanese populations and threatens to become the most common cause of end-stage liver failure in developed countries. Between 4% and 10% of children have evidence of NAFLD. NAFLD and T2DM are closely associated: NALFD was present in 50−70% of patients with T2DM, depending on the methods of diagnosis.[12] The progression of steatosis to NASH is not inevitable but a number of single-nucleotide polymorphisms have been identified from genome-wide association studies that increase the odds of developing NAFLD by 1.5- to 4-fold possibly by promoting lipotoxicity. A 'second hit', possibly a genetic risk factor, appears to transform 25% of patients with simple and benign fatty infiltration (hepatic steatosis) into a sequence of inflammation, cirrhosis, portal hypertension, and hepatocellular carcinoma.

The incidence of gallstones is greater in obese women, but the relationship is not strong in men. The risk is increased twofold in those with a BMI of 30 kg/m^2 and sevenfold at BMI more than 45 kg/m^2. Mechanisms include increased cholesterol synthesis, reduced bile acids, changes in cholesterol:bile acid ratio and impaired motility in the gallbladder, probably as a consequence of impaired responsiveness of the gallbladder to cholecystokinin.

Cancers

Obesity is associated with an increased relative risk (RR) of developing many cancers including hormone-dependent cancers such as breast (post-menopausal 1.25 RR), endometrial (2−3 RR) and prostate (1.2 RR), as well as colorectal (1.3 RR), oesophagus (1.2−2.0 RR), gall bladder (1.5−1.8 RR) renal (1.7 RR), liver (1.4−4.0 RR) and pancreatic (1.35 RR)[13] (Table 2). Current levels of overweight and obesity in the UK are estimated to account for 19,000 cases of cancer each year. There is also evidence that patients with obesity have a worse prognosis, with a great risk of recurrence of some cancers (e.g. prostate) and poorer responses to treatment than lean individuals.

Proposed mechanisms by which hyperinsulinaemia contributes to hypertension

- Vasodilatation
- Increased sympathetic nervous system activity, directly and from vasodilatation
- Increased renal tubular 'salt sensitivity', sodium retention
- Increased renal sodium/hydrogen exchange
- Lower free fatty acids stimulating aldosterone secretion
- Vascular smooth muscle cell proliferation
- Atherosclerosis increasing vascular rigidity

Table 1

Table 2

Psychosocial

Obese individuals face discrimination in education, work, health care and social relationships. In a US study of 16—24 year-olds followed for 7 years, women who were overweight at the start of the study completed fewer years at school, were less likely to be married, had lower household incomes and experienced higher rates of household poverty. In contrast, overweight men in the study were only less likely to be married. The obese often receive a lower standard of education than their thinner counterparts and perform less well in educational environments. Obese students tend to complete fewer years at school and, in the USA, obese women are about 65% less likely to be accepted by their first-choice college than are thinner students, even when they have the same grades.

Several studies have shown a general reluctance to employ obese individuals. In a recent study of job recruitment decisions, obese applicants and applicants with diabetes were both less likely to be hired than 'healthy' applicants, but for different reasons — the obese applicants were considered to have poor work habits and were thought more likely to have emotional and interpersonal problems.

It is clear that obesity is considered a social stigma, though ethnicity is an important confounding factor. Obese women tend to suffer greater prejudice than obese men; studies have shown that obese women have more difficulty being upwardly mobile and relating to others.

While psychological and emotional distress appears to be more common in the obese, there is also evidence for a link to psychiatric disease, particularly relating to affective disorders.[14] Obese individuals have about 55% increased odds of developing depression; the diminished quality of life and functioning from a depressed mood presents additional threats to obese individuals by negatively influencing adherence to treatment and lifestyle changes. Factors that are thought to drive this association include specific dietary factors, such as a high intake of saturated fat or a relative deficiency of polyunsaturated fats, and endocrine mediators such as hypercortisolaemia, mediated perhaps by increased leptin concentrations. ◆

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