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 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

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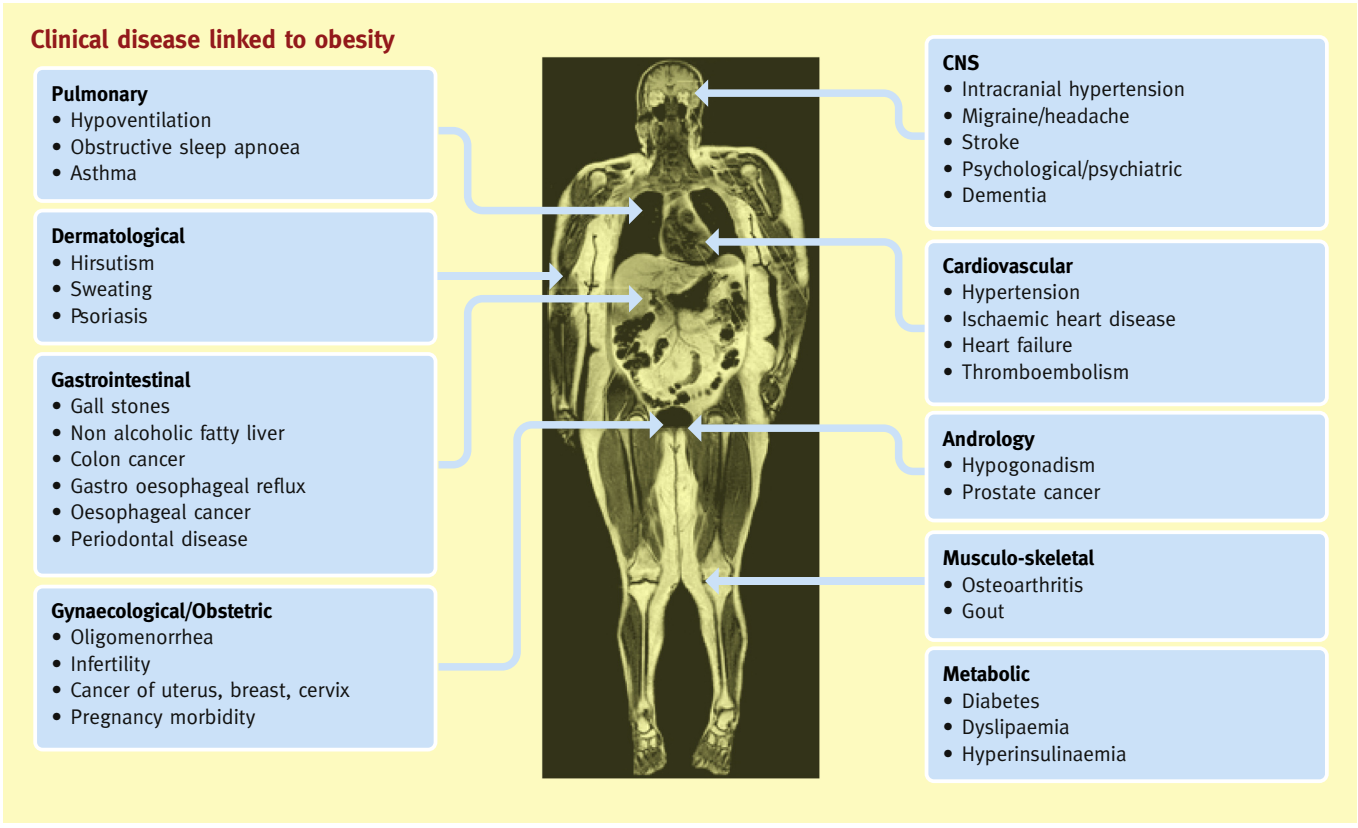

Figure 1

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).

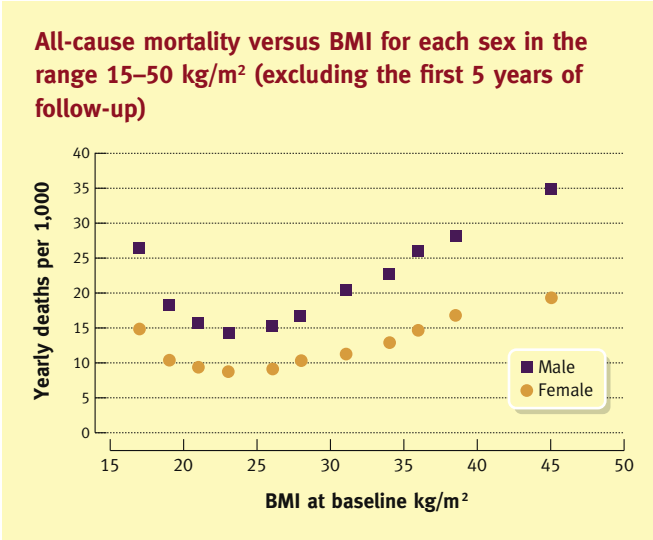

Figure 2

Hypertension and heart failure – more than one-third of obese adults have hypertension (blood pressure ≥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

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