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Medical Consequences of Obesity

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Obesity is an epidemic disease that threatens to inundate health care resources by increasing the incidence of diabetes, heart disease, hypertension, and cancer. These effects of obesity result from two factors: the increased mass of adipose tissue and the increased secretion of pathogenetic products from enlarged fat cells. This concept of the pathogenesis of obesity as a disease allows an easy division of disadvantages of obesity into those produced by the mass of fat and those produced by the metabolic effects of fat cells. In the former category are the social disabilities resulting from the stigma associated with obesity, sleep apnea that results in part from increased parapharyngeal fat deposits, and osteoarthritis resulting from the wear and tear on joints from carrying an increased mass of fat. The second category includes the metabolic factors associated with distant effects of products released from enlarged fat cells. The insulin-resistant state that is so common in obesity probably reflects the effects of increased release of fatty acids from fat cells that are then stored in the liver or muscle. When the secretory capacity of the pancreas is overwhelmed by battling insulin resistance, diabetes develops. The strong association of increased fat, especially visceral fat, with diabetes makes this consequence particularly ominous for health care costs. The release of cytokines, particularly IL-6, from the fat cell may stimulate the proinflammatory state that characterizes obesity. The increased secretion of prothrombin activator inhibitor-1 from fat cells may play a role in the procoagulant state of obesity and, along with changes in endothelial function, may be responsible for the increased risk of cardiovascular disease and hypertension. For cancer, the production of estrogens by the enlarged stromal mass plays a role in the risk for breast cancer. Increased cytokine release may play a role in other forms of proliferative growth. The combined effect of these pathogenetic consequences of increased fat stores is an increased risk of shortened life expectancy. (*J Clin Endocrinol Metab* 89: 2583–2589, 2004)

THE EFFECTS OF excess weight on morbidity and mortality have been known for more than 2000 yr. Hippocrates recognized that "sudden death is more common in those who are naturally fat than in the lean," and Malcolm Flemyng in 1760 observed that "corpulency, when in an extraordinary degree, may be reckoned a disease, as it in some measure obstructs the free exercise of the animal functions; and hath a tendency to shorten life, by paving the way to dangerous distempers."

Obesity is a chronic disease in the same sense as hypertension and atherosclerosis. The etiology or cause of obesity is an imbalance between the energy ingested in food and the energy expended. The excess energy is stored in fat cells that enlarge and/or increase in number. It is this hyperplasia and hypertrophy of fat cells that is the pathological lesion of obesity. Enlarged fat cells produce the clinical problems associated with obesity either because of either the weight or mass of the extra fat or because of the increased secretion of free fatty acids and numerous peptides from enlarged fat cells. The consequence of these two mechanisms is other diseases, such as diabetes mellitus, gallbladder disease, osteoarthritis, heart disease, and some forms of cancer. The spectrum of medical, social, and psychological disabilities includes a range of medical and behavioral problems.

Abbreviations: apo, Apolipoprotein; BMI, body mass index; CHD, coronary heart disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; VLDL, very LDL.

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Pathology of excess fat

Each disease whose risk is increased by overweight can be classified into one of two pathophysiological categories. The first category of disabilities arises from the increased mass of fat itself. These include the stigma of obesity and the behavioral responses it produces, osteoarthritis, and sleep apnea. The second category is risks that result from the metabolic changes associated with excess fat. These include diabetes mellitus, gallbladder disease, hypertension, cardiovascular disease, and some forms of cancer associated with overweight (Fig. 1).

The fat cell can be viewed as a type of endocrine cell, and adipose tissue as an endocrine organ. It is the hypertrophy and/or hyperplasia of this organ that is the pathologic lesion in obesity. After the identification of adipsin or complement D in the fat cell, a number of other secretory peptides were found. Leptin clearly is the most important and secures the role of the adipocyte as an endocrine cell and fat as an endocrine organ. From the pathophysiological perspective, however, the release of free fatty acids may be the most important.

Fat distribution is important in the response to the endocrine products of the fat cell. The accumulation of fat in visceral fat cells is modulated by a number of factors. Androgens and estrogen produced by the gonads and adrenals as well as peripheral conversion of Δ^4-androstenedione to estrone in fat cells are pivotal in body fat distribution. Male, or android, fat distribution and female, or gynoid, fat distribution develop during adolescence. The increasing accumulation of visceral fat in adult life is related to gender, but the effects of cortisol, decreasing GH, and changing testosterone levels are important in age-related fat accumulation.

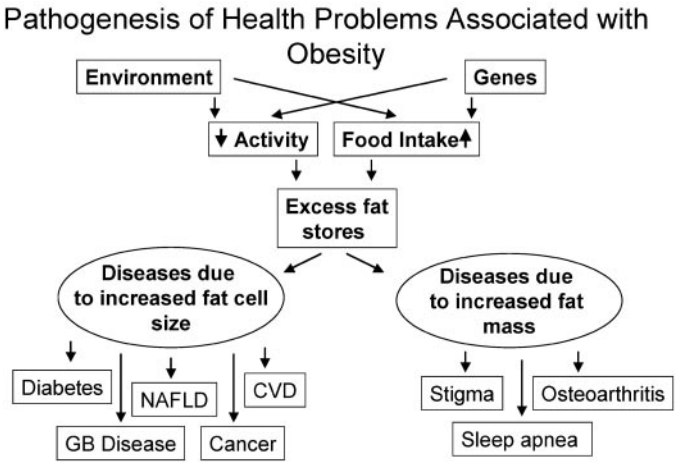

FIG. 1. The pathology of obesity produces the myriad of health related problems. These health-related problems can be attributed to either the increased mass of fat or the increased release of peptides from enlarged fat cells. CVD, Cardiovacular disease; GB, gallbladder.

Increased visceral fat enhances the degree of insulin resistance associated with obesity and hyperinsulinemia. Together, hyperinsulinemia and insulin resistance enhance the risk of the comorbidities described below.

Diseases associated with increased fat mass

Psychosocial function. Overweight is stigmatized (1); that is, overweight individuals are exposed to the consequences of public disapproval of their fatness. This stigma occurs in education, employment, health care, and elsewhere. One study that used the Medical Outcomes Study Short-Form Health Survey (SF-36) demonstrated that obese people presenting for treatment at a weight management center had profound abnormalities in health-related quality of life (2). Higher body mass index (BMI) values were associated with greater adverse effects. Obese women appear to be at greater risk of psychological dysfunction than obese men; this is potentially due to increased societal pressures on women to be thin (3). Intentional weight loss improves the quality of life (4). Severely obese patients who lost an average of 43 kg through gastric bypass demonstrated improvements in all domains of the SF-36 to such an extent that their postweight loss scores were equal to or better than population norms (5).

Sleep apnea. Alterations in pulmonary function have been described in overweight subjects, but subjects were free of other potential chronic pulmonary diseases in only a few studies. When underlying pulmonary disease was absent, only major degrees of increased body weight significantly affected pulmonary function. The chief effect is a decrease in residual lung volume associated with increased abdominal pressure on the diaphragm (6). Fat distribution, independent of total fat, also influences ventilatory capacity in men, possibly through the effects of visceral fat level.

In contrast to the relatively benign effects of excess weight on respiratory function, the overweight associated with sleep apnea can be severe (6). Overweight subjects with obstructive sleep apnea show a number of significant differences from overweight subjects without sleep apnea. Sleep apnea was considerably more common in men than women, and as a group, subjects were significantly taller than individuals without sleep apnea. People with sleep apnea have an increased snoring index and increased maximal nocturnal sound intensity. Nocturnal oxygen saturation also is significantly reduced. One interesting hypothesis is that the increased neck circumference and fat deposits in the pharyngeal area may lead to the obstructive sleep apnea of obesity.

Diseases of the bones, joints, muscles, connective tissue, and skin. Osteoarthritis is significantly increased in overweight individuals. The osteoarthritis that develops in the knees and ankles may be directly related to the trauma associated with the degree of excess body weight (7). However, the increased osteoarthritis in other nonweight-bearing joints suggests that some components of the overweight syndrome alter cartilage and bone metabolism independently of weight bearing. Increased osteoarthritis accounts for a significant component of the cost of overweight.

Several skin changes are associated with excess weight. Stretch marks, or striae, are common and reflect the pressures on the skin from expanding lobular deposits of fat. Acanthosis nigricans with deepening pigmentation in the folds of the neck, knuckles, and extensor surfaces occurs in many overweight individuals, but is not associated with increased risk of malignancy. Hirsutism in women may reflect the altered reproductive status in these individuals (8).

Diseases associated with hypersecretion from enlarged fat cells

Diabetes mellitus, insulin resistance, and the metabolic syndrome. Type 2 diabetes mellitus is strongly associated with overweight in both genders in all ethnic groups (9, 10). The risk of type 2 diabetes mellitus increases with the degree and duration of overweight and with a more central distribution of body fat. The relationship between increasing BMI and the risk of diabetes in the Nurses Health Study is shown in Fig. 2. The risk of diabetes was lowest in individuals with a BMI less than 22 kg/m^2. As BMI increased, the relative risk increased, such that at a BMI of 35 kg/m^2, the relative risk increased 40-fold, or 4000%. A similar strong curvilinear relationship was observed in men in the Health Professionals Follow-Up Study. The lowest risk in men was associated with a BMI less than 24 kg/m^2, slightly higher than that for the women in the Nurses Health Study. At a BMI above 35 kg/m^2, the age-adjusted relative risk for diabetes in nurses increased to 60.9, or more than 6000%.

Weight gain also increases the risk of diabetes. Up to 65% of cases of type 2 diabetes mellitus can be attributed to overweight. Of the 11.7 million cases of diabetes, overweight may account for two thirds of diabetic deaths. Using the BMI at age 18 yr, a 20-kg weight gain increased the risk for diabetes 15-fold, whereas a weight reduction of 20 kg reduced the risk to almost zero. In the Health Professionals Follow-Up Study, weight gain was also associated with an increasing risk of noninsulin-dependent diabetes mellitus, whereas a 3-kg weight loss was associated with a reduction in relative risk.

Weight gain appears to precede the onset of diabetes.

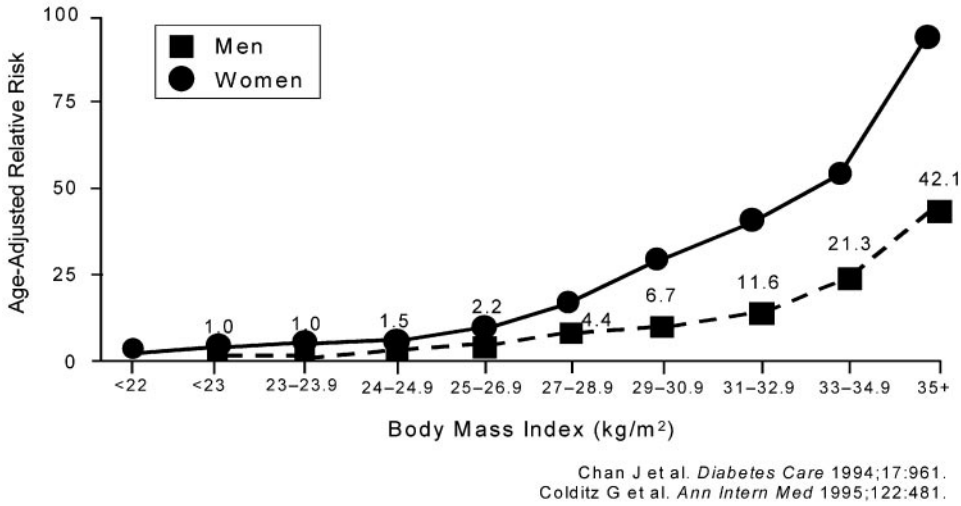

FIG. 2. Risk of developing diabetes mellitus in men and women based on data from the Nurses Health Study (9) and the Health Professionals Follow-Up Study (10).

Among the Pima Indians, body weight steadily and slowly increased by 30 kg (from 60 to 90 kg) in the years preceding the diagnosis of diabetes (11). After the diagnosis of diabetes, body weight slightly decreased. In the Health Professionals Follow-Up Study, relative risk of developing diabetes increased with weight gain as well as with increased BMI. In long-term follow-up studies, the duration of overweight and the change in plasma glucose during an oral glucose tolerance test also were strongly related. When overweight was present for less than 10 yr, plasma glucose was not increased. With longer durations, of up to 45 yr, a nearly linear increase in plasma glucose occurred after an oral glucose tolerance test. The risk of diabetes is increased in hypertensive individuals treated with diuretics or β-blocking drugs, and this risk is increased in overweight subjects.

In the Swedish Obese Subjects Study, Sjostrom *et al.* (12) observed that diabetes was present in 13–16% of obese subjects at baseline. Of those who underwent gastric bypass and subsequently lost weight, 69% who initially had diabetes went into remission, and only 0.5% of those who did not have diabetes at baseline developed it during the 2 yr of follow-up. In contrast, in the obese control group that lost no weight, the cure rate was low (16%), and the incidence of new cases of diabetes was 7.8%.

Weight loss or moderating weight gain over years reduces the risk of developing diabetes. This is most clearly shown in the Health Professionals Follow-Up Study, in which relative risk declined by nearly 50% with a weight loss of 5–11 kg. Type II diabetes was almost nonexistent with a weight loss of more than 20 kg or a BMI below 20 kg/m^2 (10).

Both increased insulin secretion and insulin resistance result from obesity. The relationship of insulin secretion to BMI has already been noted. A greater BMI correlates with greater insulin secretion. Obesity develops in more than 50% of nonhuman primates as they age. Nearly half of these obese animals subsequently develop diabetes. The time course for the development of obesity in nonhuman primates, like that in Pima Indians, is spread over a number of years. After the animals gain weight, the next demonstrable effects are impaired glucose removal and increased insulin resistance, as measured by impaired glucose clearance with a euglycemic hyperinsulinemic clamp. The hyperinsulinemia, in turn, increases hepatic very low density lipoprotein (VLDL) triglyceride synthesis and secretion, increases plasminogen activator inhibitor-1 synthesis, increases sympathetic nervous system activity, and increases renal sodium reabsorption.

TABLE 1. Criteria for the metabolic syndrome[a]

Risk factor	Defining level
Abdominal obesity (Waist circumference)	
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
HDL cholesterol	
Men	<40 mg/dl
Women	<50 mg/dl
Triglycerides	≥150 mg/dl
Fasting glucose	≥110 mg/dl
Blood pressure (systolic/diastolic)	≥130/≥85 mm Hg

[a] The syndrome is present if an individual has any three of the following five criteria.

Insulin resistance is the hallmark of the metabolic (or dysmetabolic) syndrome. The National Cholesterol Education Program Adult Treatment Panel III has recently provided defining values for this syndrome (Table 1). When three of the five criteria listed in table are abnormal, the patient has the metabolic syndrome. A central feature of this syndrome is increased visceral fat. This increased release of free fatty acids impairs insulin clearance by the liver and altered peripheral metabolism. The reduced production of adiponectin by the fat cell is another potential player in the development of insulin resistance.

Nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis. NAFLD is the term that describes a constellation of liver abnormalities associated with obesity, including hepatomegaly, elevated liver enzymes, and abnormal liver histology, such as steatosis, steatohepatitis, fibrosis, and cirrhosis (13). A retrospective analysis of liver biopsy specimens obtained from overweight and obese patients with abnormal liver biochemistries, but without evidence of acquired, autoimmune, or genetic liver disease, demonstrated a 30% prevalence of septal fibrosis and a 10% prevalence of cirrhosis (14). Another study using a cross-sectional analysis of

liver biopsies, suggests that in obese patients, the prevalences of steatosis, steatohepatitis, and cirrhosis are approximately 75%, 20%, and 2%, respectively (15).

Gallbladder disease. Cholelithiasis is the primary hepatobiliary pathology associated with overweight (16). The old clinical adage "fat, female, fertile, and forty" describes the epidemiological factors often associated with the development of gallbladder disease. This is admirably demonstrated in the Nurses' Health Study (17). When the BMI was less than 24 kg/m^2, the incidence of clinically symptomatic gallstones was approximately 250/100,000 person-years of follow-up. Incidence gradually increased with increased BMI (to 30 kg/m^2) and increased very steeply when the BMI exceeded 30 kg/m^2. This confirms published work by many other researchers.

Part of the explanation for the increased risk of gallstones is the increased cholesterol turnover related to total body fat (18). Cholesterol production is linearly related to body fat; approximately 20 mg of additional cholesterol are synthesized for each kilogram of extra body fat. Thus, a 10-kg increase in body fat leads to the daily synthesis of as much cholesterol as is contained in the yolk of one egg. The increased cholesterol is, in turn, excreted in the bile. High cholesterol concentrations relative to bile acids and phospholipids in bile increase the likelihood of precipitation of cholesterol gallstones in the gallbladder. Other factors, such as nidation conditions, also determine whether gallstones form (18).

During weight loss, the likelihood of gallstones increases because the flux of cholesterol is increased through the biliary system. Diets with moderate levels of fat that trigger gallbladder contraction and thus empty its cholesterol content may reduce this risk. Similarly, the use of bile acids, such as ursodeoxycholic acid, may be advisable if the risk of gallstone formation is thought to be increased.

The second gastrointestinal feature altered in obesity is the quantity of fat in the liver (18). Increased steatosis is characteristic of the livers of overweight individuals and may reflect increased VLDL production associated with hyperinsulinemia. The accumulation of lipid in the liver suggests that the secretion of VLDL in response to hyperinsulinemia is inadequate to keep up with the high rate of triglyceride turnover.

Hypertension. Blood pressure often is increased in overweight individuals (19). In the Swedish Obesity Study, hypertension was present at baseline in 44–51% of the subjects. One estimate suggests that control of overweight would eliminate 48% of the hypertension in whites and 28% in blacks. For each decline of 1 mm Hg in diastolic blood pressure, the risk of myocardial infarction decreases an estimated 2–3%.

Overweight and hypertension interact with cardiac function. Hypertension in normal weight people produces concentric hypertrophy of the heart, with thickening of the ventricular walls. In overweight individuals, eccentric dilatation occurs. Increased preload and stroke work are associated with hypertension. The combination of overweight and hypertension leads to thickening of the ventricular wall and larger heart volume, and thus to a greater likelihood of cardiac failure.

The hypertension of overweight people appears strongly related to altered sympathetic activity. During insulin infusion, overweight subjects have a much greater increase in the muscle sympathetic nerve firing rate than do normal weight subjects, but the altered activity is associated with a lesser change in the vascular resistance of calf muscles.

Hypertension is strongly associated with type II diabetes, impaired glucose tolerance, hypertriglyceridemia, and hypercholesterolemia, as noted above in the discussion of the metabolic syndrome. Hyperinsulinemia in overweight and hypertensive patients suggests insulin resistance and the metabolic syndrome. An analysis of the factors that predict blood pressure and changes in peripheral vascular resistance in response to body weight gain showed that a key determinant of the weight-induced increases in blood pressure was a disproportionate increase in cardiac output that could not be fully accounted for by the hemodynamic contribution of new tissue. This hemodynamic change may be attributable to a disproportionate increase in cardiac output related to an increase in sympathetic activity.

Obesity may also affect the kidney. Glomerulopathy was significantly increased in pathological specimens compared with other forms of end-stage renal disease (20).

Heart disease. Data from the Nurses' Health Study indicate that the risk for U.S. women developing coronary artery disease is increased 3.3-fold with a BMI greater than 29 kg/m^2 compared with that in women with a BMI less than 21 kg/m^2 (21). A BMI of 27 to less than 29 kg/m^2 increases the relative risk to 1.8. Weight gain also strongly affects this risk at any initial BMI (22). That is, at all levels of initial BMI, weight gain was associated with a graded increase in risk of heart disease. This was particularly evident in the highest quintile, in which weight gain was more than 20 kg.

Dyslipidemia may be important in the relationship of BMI to increased risk of heart disease (23). A positive correlation between BMI and triglycerides has been repeatedly demonstrated. However, the inverse relationship between high density lipoprotein (HDL) cholesterol and BMI may be even more important, because a low HDL cholesterol carries a greater relative risk than do elevated triglycerides. Central fat distribution is also important in lipid abnormalities. Waist circumference alone accounted for as much as or more of the variance in triglycerides and HDL cholesterol as either waist/hip ratio or sagittal diameter, two other measures of central fat. A positive correlation for central fat and triglyceride and the inverse relationship for HDL cholesterol are evident for all measures.

Increased body weight is associated with a number of cardiovascular abnormalities. Cardiac weight increases with increasing body weight, suggesting increased cardiac work. Heart weight as a percentage of body weight, however, is lower than that in a normal weight control group. The increased cardiac work associated with overweight may produce cardiomyopathy and heart failure in the absence of diabetes, hypertension, or atherosclerosis. Weight loss decreases heart weight; this decrease was linearly related to the degree of weight loss in both men and women. An echocardiographic study of left ventricular midwall function showed that obese individuals compensated by using car-

diac reserve, especially in the presence of hypertension. Interestingly, heart rate was well within normal limits.

Central fat distribution is associated with small, dense low density lipoproteins (LDL) as opposed to large, fluffy LDL particles (23). For a similar level of cholesterol, the risk of coronary heart disease (CHD) is significantly higher in individuals with small dense LDL than in those with large fluffy LDL. Because each LDL particle has a single molecule of apolipoprotein B (apo B) protein, the concentration of apo B can be used to estimate the number of LDL particles. Despres *et al.* (23) demonstrated that the level of apo B is a strong predictor of the risk for CHD. Based on a study of French Canadians, these researchers proposed that estimating apo B, the levels of fasting insulin, the concentration of triglyceride, the concentration of HDL cholesterol, and waist circumference could help identify individuals at high risk for the metabolic syndrome and coronary heart disease.

Cancer. Certain forms of cancer are significantly increased in overweight individuals (21, 24). Males face increased risk for neoplasms of the colon, rectum, and prostate. In women, cancers of the reproductive system and gallbladder are more common. One explanation for the increased risk of endometrial cancer in overweight women is the increased production of estrogens by adipose tissue stromal cells. This increased production is related to the degree of excess body fat that accounts for a major source of estrogen production in postmenopausal women. Breast cancer is not only related to total body fat, but also may have a more important relationship to central body fat (25). The increased visceral fat measured by computed tomography shows an important relationship to the risk of breast cancer.

Endocrine changes. A variety of endocrine changes are associated with overweight (Table 2). The changes in the reproductive system are among the most important. Irregular menses and frequent anovular cycles are common, and the rate of fertility may be reduced (26). Some reports describe increased risks of toxemia. Hypertension and cesarean section may also be more frequent. Irregular menses, amenorrhea, and infertility are associated with obesity (27). Women with a BMI greater than 30 kg/m^2 have abnormalities in secretion of hypothalamic GnRH, pituitary LH, and FSH, which results in anovulation (28).

Obesity shortens life

The net effect of the increased fat mass and the enlarged fat cells is a decrease in life expectancy that is detailed below.

TABLE 2. Endocrine changes associated with obesity

Increased	Decreased
Leptin in plasma	GH
TSH (upper normal range)	Ghrelin
Insulin	Adiponectin
IGF-I	
Androgens	
Progesterone	
Cytokines (IL-6)	
ACTH/cortisol	
Sympathetic nervous system activity	

Adapted from Ref. 42.

Years of life lost. Using data from the Framingham Study, Peeters *et al.* (29) estimated that nonsmoking women who were overweight (BMI, >25 kg/m^2) at age 40 yr lost 3.3 yr, and male nonsmoking men lost 3.1 yr compared with normal weight men and women. If obese with a BMI >30 kg/m^2, nonsmoking women lost 7.1 yr, and male nonsmokers lost 5.8 yr. Fontaine *et al.* (30) using data from the Third Health and Nutrition Examination Survey found that the optimal BMI for longevity in whites was 23–25, and that in blacks was 23–30 kg/m^2. The years of life lost with a BMI greater than 45 kg/m^2 was 13 yr for white men and 8 yr for white women. The effect on years of life lost in black women was considerably less, suggesting important ethnic differences in the health manifestations of obesity.

Excess body weight. The mortality associated with excess weight increases as the degree of obesity and overweight increases. One study estimated that between 280,000 and 325,000 deaths could be attributed to obesity annually in the United States (31). More than 80% of these deaths occur among people with a BMI greater than 30 kg/m^2. When the impact of a sedentary lifestyle is coupled with poor diet, the Centers for Disease Control and Prevention estimate that an extra 400,000 lives may be lost per year, putting these lifestyle issues just behind smoking as a leading cause of death in the United States (32). Several studies have contributed significantly to our understanding of the problem and these are summarized below.

Nurses' Health Study: In the Nurses' Health Study, the risk of death rose progressively in women with a BMI above 29 kg/m^2 (21). Mortality was lowest among women who weighed at least 15% less than the United States average for women of similar age and among those whose weight had been stable since early adulthood.

American Cancer Society's Cancer Prevention Study I: Among 62,116 white men and 262,019 white women (both groups were healthy nonsmokers) who were followed for 14 yr, a greater body mass index was associated with increased rate of death from all causes and from cardiovascular disease in both groups up to age 75 yr. The impact of the excess body weight was higher among younger subjects than older ones (33).

American Cancer Society's Cancer Prevention Study II: In an even larger study (457,785 men and 588,369 women) with a 14-yr follow-up, the association of BMI and mortality was affected by smoking status and history of other disease. Among the nonsmokers, the lowest mortality for men was in the group with a BMI from 23.5–24.9 kg/m^2; for women it was in the group with a BMI from 22.0–23.4 kg/m^2. Among subjects with a BMI more than 40 kg/m^2, the relative risk of death was 2.6 times higher for men and 2.0 times higher for women compared with those having a BMI between 23.5 and 24.9 kg/m^2. Black men and women had lower risks than corresponding categories of whites. Among those with a BMI more than 40 kg/m^2, the relative risk of death was 1.4 for the black men and 1.2 for black women. There was no effect of age, and the risk of death or cardiovascular disease did not significantly increase over the BMI range 22.0–26.4 kg/m^2 for men and 20.5–24.9 kg/m^2 for women (34).

Aerobics Center Longitudinal Study: In this study 25,714 men were followed from 1–10 yr. The all cause mortality and cardiovascular mortality were higher in men with a BMI greater than 30 kg/m^2 and lowest in those with a BMI between 18.5 and 24.9 kg/m^2, with men with a BMI of 25–29.9 kg/m^2 falling in between (35). In this same population the deaths from cardiovascular disease increased from just over five deaths per 10,000 man-years with a body fat of less than 16.7% to nearly eight deaths per 10,000 man-years in men with a body fat of 16.7 to less than 25.0% to nearly 12 deaths per 10,000 man-years in men with a body fat above 25.0% (35).

Finnish Heart Study: The association between obesity and the risk of death from CHD was confirmed by a study of 8373 Finnish women (aged 30–59 yr) followed for 15 yr (36). This study found that for each increase in body weight of approximately 1 kg, the risk of coronary mortality increased by 1–1.5%. A substantial part of this risk was mediated through the link between body weight and blood pressure.

Regional fat distribution. Regional fat distribution is also important in the risk of death (23, 37). The life insurance industry first noted this at the beginning of the 20th century. This theme was picked up again after World War II, when researchers noted that obese individuals with an android, or male, distribution of body fat were at higher risk for diabetes and heart disease than were those with a gynoid, or female, type of obesity. However, clinical and epidemiological work in the 1980s convinced the world of the relationship between body fat distribution and risk of excess mortality. The Framingham Study has examined the relationship between fat distribution and metabolic risk factors. Three clusters could be detected with some overlap. The metabolic complex of insulin, glucose, triglycerides, and BMI was one constellation. A second cluster included cholesterol, LDL cholesterol, and HDL cholesterol. The final cluster was BMI, systolic blood pressure, and diastolic blood pressure (22).

Benefits of weight loss

If overweight increases the risk of mortality, then we would anticipate that intentional weight loss would reduce it. A definitive demonstration of this prediction is not available, but several studies suggest that intentional weight loss does reduce risk. Weight loss maintained for 2 yr reduces blood pressure, improves abnormal lipid levels, and reduces the risk of diabetes (12). A follow-up of women aged 40–64 yr in the American Cancer Society study who intentionally lost weight found a significant reduction in all cause mortality of 20–25% (38). Using the National Health Interview Survey with a 9-yr follow-up, intentional weight loss lowers mortality rate (Hazard Rate Ratio) by 24% (0.76; 95% confidence interval, 0.60–0.97). In contrast, those with unintentional weight loss had a 31% higher mortality rate (1.31; 95% confidence interval, 1.01–1.70) (39).

Weight loss affects a number of risk factors. The data from participants in the Swedish Obesity Study show the degree of weight loss for individual risk factors. Changes in blood pressure and triglycerides are very responsive to weight loss, decreasing after a 5–10% weight loss. HDL cholesterol increases with a similar weight-related change. Total cholesterol, on the other hand, does not show a sustained effect until weight loss exceeds 20%. For most comorbidities, however, a 10% weight loss is sufficient to see significant improvement in risk factors (12). However, blood pressure returns to baseline by 4–6 yr even when weight loss is maintained (12).

Recent studies buttress the idea that losing about 5% of body weight can significantly reduce the risk of developing type 2 diabetes in high risk individuals. In studies from Finland (40) and the United States (41), conversion rates from impaired glucose tolerance to diabetes were reduced by 58%.

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