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Epidemiology, Trends, and Morbidities of Obesity and the Metabolic Syndrome

George A. Bray and Tracy Bellanger

Pennington Biomedical Research Center, Baton Rouge, LA

Obesity has been described as an epidemic because of the rapid increase in the number of overweight and obese individuals over the past 20 yr. This increasing prevalence of obesity is a worldwide phenomenon affecting both children and adults. The metabolic syndrome is a constellation of central adiposity, impaired fasting glucose, elevated blood pressure, and dyslipidemia (high triglyceride and low HDL cholesterol). When three of these five criteria are present, the risk of cardiovascular disease and diabetes is increased 1.5- to 2-fold. As body weight, expressed as the BMI, rises, there are a number of other diseases that are associated with it. First, life span is shortened and the risk of sudden death increases. Second, the risk of diabetes, gall bladder disease, hypertension, heart disease, osteoarthritis, sleep apnea, and certain forms of cancer also increase.

Key Words: Central adiposity; body mass index; prevalence; morbidity; mortality; diabetes; cardiovascular disease.

Introduction

We start with the premise that we all want to have a healthy weight, and that no one wants to be obese. Interest in obesity has taken a sharp up-turn in recent years and the prevalence of this problem by any standards has increased rapidly. An unhealthy weight can be viewed as a chronic, stigmatized, neurochemical disease *(1)*. In this context, the goal is to return weight to a healthy level and to remove the stigma associated with the use of the word obesity. To consider it in the context of a neurochemical derangement has the advantage of focusing on the underlying mechanisms that produce the distortion in energy balance that produces the unhealthy weight *(2)*.

At birth, the human infant contains about 12% body fat. During the first years of life, body fat rises rapidly to reach a peak of about 25% by 6 mo of age and the declines to 18% over the next 10 yr. At puberty, there is a significant increase in the percentage of body fat in females and a fall in males. By age 18, males have approx 15–18% body fat, and females 25–28%. Between ages 20 and 50, the fat content of males approximately doubles and that of females goes up by about 50%. Total body weight, however, rises by only 10–15% indicating that fat is accounting for a larger part by the rise in body weight and is accompanied by a reduction in lean body mass.

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Author to whom all correspondence and reprint requests should be addressed: George A. Bray, MD, 6400 Perkins Road, Baton Rouge, LA 70808. E-mail: brayga@pbrc.edu

Definition of Obesity and the Metabolic Syndrome

Body Mass Index

Throughout the past 50 yr there has been a steady rightward shift in the distribution curve for body weight *(3)*. This trend can most effectively be traced using the BMI, defined as the weight in kilograms divided by the height in meters squared [$W/(H)^2$], which provides a useful operating definition of overweight. A normal BMI is between 18.5 and <25 kg/m^2, a BMI between 25 and 29.9 kg/m^2 is operationally defined as overweight, and individuals with BMI > 30 kg/m^2 are obese, after taking into consideration muscle builders, and other resistance-trained athletes. BMI also provides one way to estimate the risk associated with obesity *(4,5)*. However, to interpret BMI properly several other pieces of information are needed. These include information about the ethnicity of the individual. For Asians, a BMI above 23 kg/m^2 is considered overweight, and the cut-point for obesity is a BMI of greater than 25 kg/m^2, well below that of the 30 kg/m^2 used as the cut-point for obesity in the white population. Age is also an important consideration. A high BMI at a young age implies longer years of excess weight and a higher risk *(6)*. Whether the BMI is rising, falling, or stable is important. A rising BMI carries more risk than a stable one. Whether an individual is physically active is also important. Higher levels of physical activity reduce the detrimental effects of any given BMI and all Americans should be encouraged to have a regular program of physical activity. The final piece of information needed to interpret the BMI is whether it is associated with an increase in central adiposity.

Central Adiposity

Centrally distributed body fat carries more risk for health than fat located primarily on the hips and thighs. The waist circumference is a practical measure of central adiposity and is a surrogate for more precise measures such as a CT

Table 1
Criteria for the Metabolic Syndrome

Criterion	ATP III Panel*	IDF Panel†
Central Adiposity		
M	> 102 cm (40 in.)	> 94 cm (37 in.)
F	> 88 cm (35 in.)	> 80 cm (37.5 in.)
HDL		
M	< 40 mg/dL	< 40 mg/dL
F	< 50 mg/dL	< 50 mg/dL
Triglycerides	< 150 mg/dL	> 150 mg/dL
Fasting Glucose	100–126 mg/dL	100–126 mg/dL
BP	> 130/>85 mmHg	>130/>85 mmHg

*Three of five required.
†Central adiposity required; two of subsequent four required.

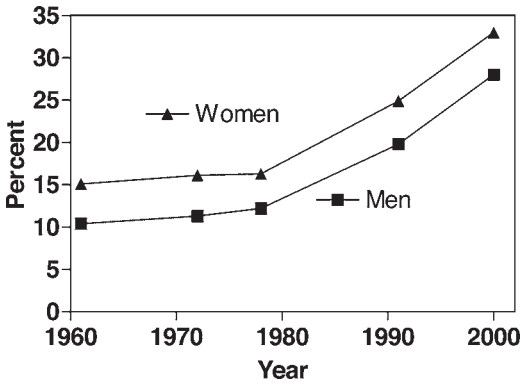

Fig. 1. Prevalence of obesity.

or MRI scan of the abdomen at the L-4-5 position. When BMI and waist circumference were used to predict the risk of hypertension, dyslipidemia, and the metabolic syndrome, the waist circumference was shown to be a better predictor than the BMI *(7,8)*.

Metabolic Syndrome

Central adiposity is a key diagnostic feature of the metabolic syndrome. In addition to central adiposity, most definitions include impaired fasting glucose, elevated blood pressure, dyslipidemia reflected in low HDL-cholesterol and high triglycerides. Additional features that may be part of the syndrome are microalbuminuria, a pro-coagulant state, a proinflammatory state, and hyperuricemia. The definitions proposed by the Adult Treatment Panel III of the National Cholesterol Education Program *(9)* and the International Diabetes Federation are presented in Table 1. The IDF definition requires an increased waist size defined as a waist circumference of > 94 cm for men and > 85 cm for women. In addition they require two of the other four, whereas the ATP III requires that any three of the five be present.

Prevalence of Obesity and the Metabolic Syndrome

Obesity

Using the BMI it is clear that there is an epidemic of obesity that began in the 1980s and that continues unabated *(10)*. It affects children *(11)* as well as adults. We are now seeing a rise in the prevalence of type 2 diabetes in adolescents that is directly related to obesity. Obesity and overweight now affect more than 60% of adult Americans *(12)*. Diabetes mellitus, hypertension, heart disease, gall bladder disease, and some forms of cancer result from obesity *(8)*. Whether these diseases are yet present or not, the obese patient should be encouraged to maintain a stable weight or better yet, to lose weight by appropriate methods to reduce the future likelihood that they will develop obesity-related conditions. More females than males are overweight at any age. The frequency of overweight increases with age to reach a peak at 45–54 yr in men and at age 55–64 in women. The National Health and Nutrition Examination Surveys (NHANES) conducted by the US government found a BMI of 25 or more in 65.7% of men and women age 20 yr or older. The prevalence of obesity (BMI 30 or more) was 27.6% in men and 33.2% in women *(10)*. The incidence of obesity continues to increase dramatically. A number of factors including age, sex, and physical inactivity influence the amount of body fat. When examining data on the prevalence of obesity, be alert to the difference between a BMI that is based on direct measurements of height and weight *(12)* and those that use telephone surveys to obtain height and weight *(13)*.

Using the BMI calculated from self-report in the Behavioral Risk Factor Surveillance Survey telephone interview gave an estimated prevalence for obesity of 19.5%, compared with 30.6% when height and weight were directly measured—a 50% difference *(10)*.

Obesity has a higher prevalence in Latino and African-American populations *(3,11,12)*. The rising prevalence is shown in Fig. 1.

Recent data from the National Center for Disease Control show that both height and weight have increased in adults aged 20–74 between 1960 and 2002. Men increased from 68 to 69.5 in. (173 to 176 cm) and women from 63 to 64 in. (160 to 162 cm) during this period. For men weight rose from 166.3 to 191 lb (75.6 to 86.8 kg) and for women from 140.2 to 164.3 lb (63.7 to 74.2 kg), for an average increase of BMI from 25.2 to 28 kg/m^2 for men and from 24.8 to 28.2 kg/m^2 for women during this 42 yr period. The increase in weight was greater in older than younger men, but the reverse was true for women with older women gaining less than younger women. Similar effects are seen in children with the weight of 10-yr-old boys rising from 74.2 lb (33.7 kg) in 1963 to 85 lb (38.6 kg) in 2002 and for 10-yr-old girls rising from 77.4 lb (35.2 kg) to 88 lb (40 kg) in this same interval. These increases in weight were associated with increases in BMI for both boys and girls. For 7-yr-old boys the BMI increased from 15.8 to 17.0 kg/m^2 between 1963 and 2002 and for 7-yr-old girls it rose from

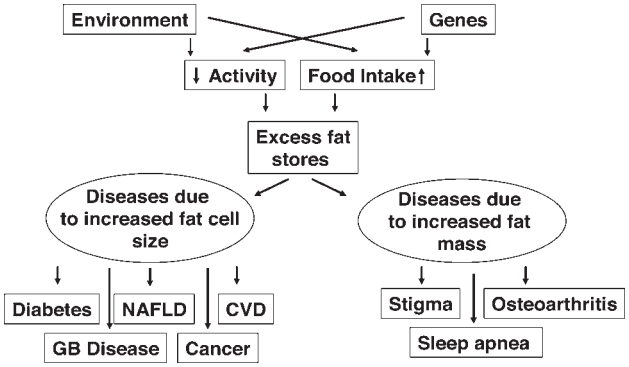

Fig. 2. Pathogenesis of health problems associated with obesity.

15.8 to 16.6 kg/m^2. For 16-yr-old boys it went from 21.3 to 24.1 kg/m^2 in this interval and for girls from 21.9 to 24.0 kg/m^2 *(14)*.

Metabolic Syndrome

The prevalence of the metabolic syndrome depends on the criteria that are used. Using the NCHS data and the Adult Treatment Panel III criterion, Ford et al. *(15)* found that the prevalence of the metabolic syndrome was 24% for adults Americans between age 20 and 74. There were no gender differences, but there were some modest ethnic differences. The study of Atherosclerosis Risk in Communities (ARIC) *(16)* found a prevalence of 23%. The recent proposal to lower the glucose level in the diagnostic criterion for metabolic syndrome from 110 mg/dL (mmol/L) to 100 mg/dL (5.5 mmol/L) has a major impact on the prevalence of the metabolic syndrome. From the 25% found with the NCHS using the 110 mg/dL lower limit, the prevalence of the metabolic syndrome increased to 40% *(17)*.

The Pathophysiology of Central and Total Fat

Each disease whose risk is increased by overweight can be classified into one of two pathophysiologic categories *(8)* (Fig. 2). The first category includes the risks that result from the metabolic changes associated with the products secreted from the excess fat. These include diabetes mellitus, gall bladder disease, hypertension, cardiovascular disease, and some forms of cancer associated with overweight (Fig. 2). The second category of disabilities arises from the increased mass of fat itself. These include osteoarthritis, sleep apnea, the stigma of obesity, and the behavioral responses it produces.

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 these fat cells 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 most important, and cements the role of the adipocyte as an endocrine cell and fat as an endocrine organ. From the pathophysiologic 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 growth hormone, and changing testosterone levels are important in age-related fat accumulation. 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.

Risks Related to Obesity

Obesity and Excess Mortality

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

Years of Life Lost

Using data from the Framingham Study *(18)*, Peeters et al. estimated that non-smoking women who were overweight (BMI > 25 kg/m^2) at age 40 lost 3.3 yr and non-smoking men lost 3.1 yr compared to normal weight men and women. If obese with a BMI > 30 kg/m^2, non-smoking women lost 7.1 yr and non-smoking men lost 5.8 yr. Fontaine et al. *(6)* using data from the Third Health and Nutrition Examination Survey found that the optimal BMI for longevity in whites was a BMI of 23–25 and in blacks was a BMI of 23–30 kg/m^2. The years of life lost with a BMI > 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

As the BMI increases, there is a curvilinear rise in excess mortality *(19)*. This excess mortality rises more rapidly when the BMI is above 30 kg/m^2. A BMI greater than 40 kg/m^2 is associated with a further increase in overall risk and for the risk of sudden death. The principal causes of the excess mortality associated with overweight include hypertension, stroke and other cardiovascular diseases, diabetes mellitus, certain cancers, reproductive disorders, gall bladder disease, and sudden death. One study estimated that between 280,000 and 325,000 deaths could be attributed to obesity annually in the United States *(20)*. More than 80% of these deaths occur among people with a BMI >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 365,000 lives may be lost per year, putting these

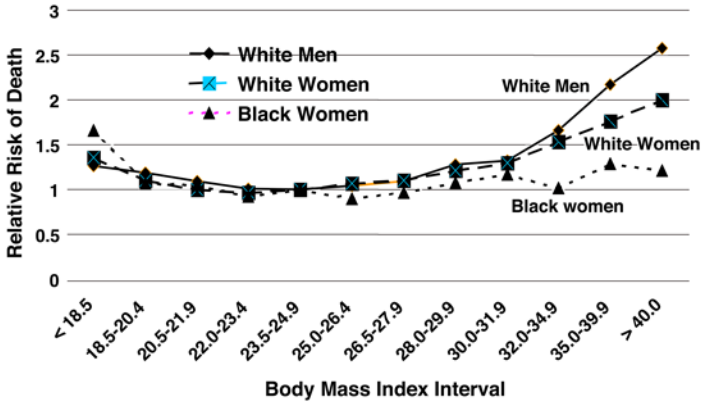

Fig. 3. BMI and mortality. (Adapted from ref. *23*.)

lifestyle issues just behind smoking as a leading cause of death in the United States *(21)*. A more recent estimate decreased the number of excess deaths to 112,000 *(12)*. Because all of these studies used the same data sources (NHANES I, II, III), but with different assumptions, there remains uncertainty about the actual size of the excess death rate.

There are two important reasons for the difference in estimates of excess mortality associated with obesity. The first is the way in which the comparison group is selected, and the second is the duration of follow-up. The relation of mortality and BMI is curvilinear as shown in Fig. 3. In the large population studies *(22–24)*, the lowest mortality is associated with a BMI of 22–23 kg/m^2. As BMI rises on either side of this lowest mortality, there is an increase in mortality. When desirable body weights were obtained from life insurance tables, the normal body weight range was from a BMI of about 20 to about 25 kg/m^2. When the BMI was adopted by the NHLBI and WHO in 1998, they selected a lower limit of 18.5 for BMI with the normal range of 18.5–25 kg/m^2. As seen in Fig. 3 including this lower limit increases the number of people in the "normal" range. It also raises the overall mortality with the "normal range" because the risk is rising from a minimal death rate at a BMI of 22–23 kg/m^2. When the relative risk of mortality for those with a BMI of 25–30 kg/m^2 is compared to the reference, it depends on the reference. With the 18.5 kg/m^2 to 25 kg/m^2 range there are more deaths providing a small or negligible change for the range from 25–30 kg/m^2. If the comparison range were 20–25 kg/m^2, the death rate in the 25–30 kg/m^2 category would be somewhat increased. If the comparison were from 22 kg/m^2, the minimal death rate the relative risk for a BMI of 25–30 kg/m^2 would be even higher. Thus, the comparison BMI becomes an important consideration in the conclusion that is reached. Because few Americans or Europeans have BMI values below 20, including the range from 18.5 to 20 makes the slightly overweight group appear to have a lower relative risk.

A second consideration in evaluating studies dealing with obesity and mortality is the duration of follow-up. Short-term follow-up tends to bias the results. As Sjostrom noted in his review of BMI and mortality *(25)*, the BMI predicted increased mortality with large population groups followed for a short time or with smaller groups followed for a much longer time. The NCHS data samples range from 9000 to 14,000 people and are thus in epidemiological terms relatively small, compared to the Nurses Health study with more than 100,000, the American Cancer Society Follow-up study with nearly 1 million, and the Life Insurance Follow-up with nearly 5 million. It may thus be unreasonable to draw conclusions from the more recent NHANES studies since they have only been followed for a short time period.

Diseases Associated With Molecules Secreted from Enlarged Fat Cells

Diabetes Mellitus, Insulin Resistance, and the Metabolic Syndrome

Type 2 diabetes mellitus is strongly associated with overweight in both genders and in all ethnic groups *(26,27)*. 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. 4 *(26,27)*. The risk of diabetes was lowest in women with a BMI below 22 kg/m^2. As BMI increased, the relative risk of type 2 diabetes increased such that at a BMI of 35 kg/m^2, the relative risk for women increased to 93.2, or more than 9000%. A similar strong curvilinear relationship was observed in men in the Health Professionals Follow-up Study *(26)*. The lowest risk in men was associated with a BMI below 24 kg/m^2, slightly higher than the 22 kg/m^2 for the women in the Nurses Health Study. At a BMI above 35 kg/m^2, the age-adjusted relative risk for diabetes for men increased to 42.1, or more than 4000%.

Weight gain also increases the risk of diabetes. Up to 65% of the cases of type 2 diabetes mellitus are associated with overweight. Using the BMI at age 18, 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

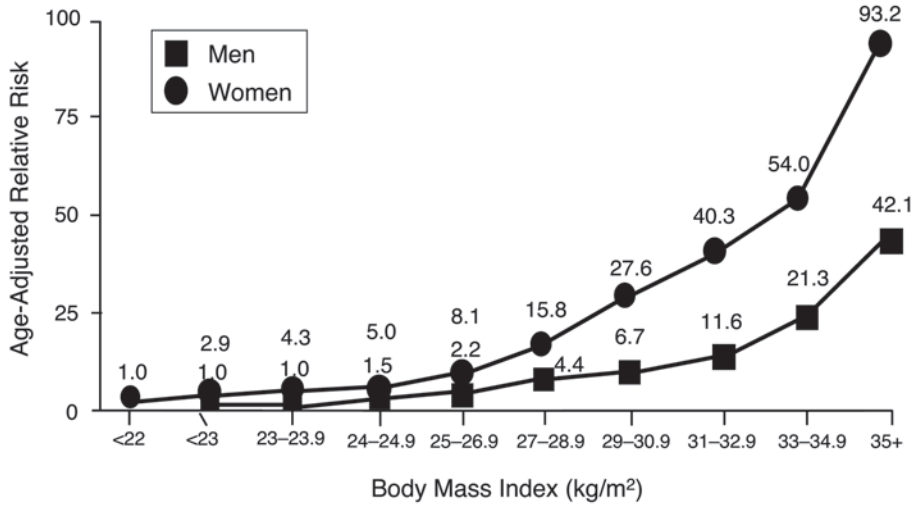

Fig. 4. Relationship between BMI and risk of type 2 diabetes mellitus. (Adapted from refs. *26* and *27*.)

Health Professionals Follow-up Study, weight gain was also associated with an increasing risk of NIDDM, whereas a 3-kg weight loss was associated with a reduction in relative risk *(26,27)*.

Weight gain appears to precede the onset of diabetes. 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 *(28)*. 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. Risk of diabetes is increased in hypertensive individuals treated with diuretics or β-blocking drugs, and this risk was increased in the overweight.

In the Swedish Obese Subjects Study, Sjostrom et al. observed that diabetes was present in 13–16% of obese subjects at baseline *(29)*. 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 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 2 diabetes was almost nonexistent with a weight loss of more than 20 kg or a BMI below 20 kg/m^2 *(27)*.

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 *(30)*. Nearly half of these obese animals subsequently develop diabetes. The time course for the development of obesity in nonhuman primates, like in the 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 an euglycemic hyperinsulinemic clamp. The hyperinsulinemia in turn increases hepatic VLDL triglyceride synthesis and secretion, increases plasminogen activator inhibitor-1 (PAI-1) synthesis, increases sympathetic nervous system activity, and increases renal sodium reabsorption.

Insulin resistance is the hallmark of the Metabolic (or Dysmetabolic) Syndrome. Visceral fat is also a central feature of this syndrome. The increased release of free fatty acids from visceral fat impairs insulin clearance by the liver and alters 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 (NASH)

Nonalcoholic fatty liver disease (NAFLD) is the term given to describe a constellation of liver abnormalities associated with obesity, including hepatomegaly, elevated liver enzymes, and abnormal liver histology such as steatosis, steatohepatitis, fibrosis, and cirrhosis *(31)*. 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 *(31)*. Another study utilizing a cross-sectional analysis of liver biopsies suggests that in obese patients the prevalence of steatosis, steatohepatitis, and cirrhosis are approx 75%, 20%, and 2%, respectively *(32)*.

Gall Bladder Disease

Cholelithiasis is the primary hepatobiliary pathology associated with overweight *(33)*. The old clinical adage "fat, female, fertile, and forty" describes the epidemiologic factors often associated with the development of gall bladder disease. This is admirably demonstrated in the Nurses' Health Study *(34)*. When BMI was below 24 kg/m^2, the incidence of clinically symptomatic gallstones was approx 250 per 100,000 person-years of follow-up. Incidence gradually increased to a BMI of 30 kg/m^2, and increased very steeply when 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 *(35)*. Cholesterol production is linearly related to body fat; approx 20 mg of additional cholesterol is 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 gall bladder. Additional factors, such as nidation conditions, are also involved in whether gallstones form *(35)*.

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 gall bladder 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 GI feature altered in obesity is the quantity of fat in the liver *(35)*. Increased steatosis is characteristic of the livers of overweight people, 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 is often increased in overweight individuals *(36)*. In the Swedish Obese Subjects Study, hypertension was present at baseline in 44–51% of 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 mmHg 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 muscle sympathetic nerve firing rate than do normal-weight subjects, but the altered activity is associated with a smaller change in the vascular resistance of calf muscles.

Hypertension is strongly associated with type 2 diabetes, impaired glucose tolerance, hypertriglyceridemia, and hyper-cholesterolemia, as noted above in the discussion of the metabolic syndrome. Hyperinsulinemia in overweight and in 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 kidneys. A glomerulopathy that has significantly increased in pathological specimens compared to other forms of end-stage renal disease *(37)*. Kidney stones are also an increased risk of obesity *(38)*.

Heart Disease

Data from the Nurses' Health Study indicate that the risk for US women developing coronary artery disease is increased 3.3-fold with a BMI >29 kg/m^2, compared with women with a BMI <21 kg/m^2 *(22)*. A BMI of 27 to <29 kg/m^2 increases the relative risk to 1.8. Weight gain also strongly affects this risk at any initial BMI *(39)*. 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 *(40)*. A positive correlation between BMI and triglyceride has been repeatedly demonstrated. However, the inverse relationship between 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 WHR or sagittal diameter, two other measures of central fat. A positive correlation for central fat and triglyceride and the inverse relationship for HDL cholesterol is evident for all measures.

Table 2
Mortality from Cancer
in American Men and Women

Men	Women
Liver	Uterus
Pancreas	Kidney
Stomach/esophagus	Cervix
Colon/rectum	Pancreas
Gall bladder	Esophagus
Multiple myeloma	Gall bladder
Kidney	Breast
Non-Hodgkins	Non-Hodgkin's
Prostate	Liver
	Ovary
	Colon/Rectum

Table 3
Endocrine Changes Associated with Obesity

Increased	Decreased
Leptin in plasma	Growth hormone
Thyrotropin (upper normal range)	Ghrelin
Insulin	Adiponectin
Insulin-like growth factor-1	
Androgens	
Progesterone	
Cytokines (IL-6)	
ACTH/cortisol	
Sympathetic nervous system activity	

Adapted from Pinckney, J. H. and Kopelman, P. G. (2004). Endocrine determinants of obesity. In: *Handbook of obesity: etiology and pathophysiology,* 2nd ed. Dekker: New York, pp. 655–669.

Increased body weight is associated with a number of cardiovascular abnormalities *(41)*. Cardiac weight increases with increasing body weight, consistent with increased cardiac work. Heart weight as a percentage of body weight, however, is lower than 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 *(41)*. 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 cardiac reserve, especially in the presence of hypertension. Interestingly, heart rate was well within normal limits.

Central fat distribution is associated with small dense lipoproteins (LDL) as opposed to large fluffy LDL particles *(40)*. For a similar level of cholesterol, the risk of coronary heart disease (CHD) is significantly higher in individuals with small dense LDL than with large fluffy LDL. Because each LDL particle has a single molecule of apo B protein, the concentration of apo B can be used to estimate the number of LDL particles. Despres et al. *(40)* demonstrated that the level of apo B is a strong predictor of the risk for CHD *(22)*. 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 *(22,23)* (Table 2). Males face increased risk for neoplasms of the colon, rectum, and prostate. In women, cancers of the reproductive system and gall bladder 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 *(42)*. 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 3). 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 *(43)*. 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 *(44)*. Women with a BMI greater than 30 kg/m^2 have abnormalities in secretion of hypothalamic gonadotropin releasing hormone (GnRH), pituitary luteinizing hormone (LH), and follicle stimulating hormone (FSH), which results in anovulation *(45)*.

Diseases Associated With Increased Fat Mass

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 *(46)*. Fat distribution, independent of total fat, also influences ventilatory capacity in men, possibly through 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 *(46)*. 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 was 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. Continuous positive airway pressure at night or weight loss are effective therapies *(47)*.

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 *(48)*. However, the increased osteoarthritis in other non-weight-bearing joints suggests that some components of the overweight syndrome alter cartilage and bone metabolism, independent 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 *(19)*.

Psychosocial Dysfunction

Overweight is stigmatized *(49–51)*, 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 utilized 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 *(52)*. Higher BMI values were associated with greater adverse effects. Obese women appear to be at greater risk of psychological dysfunction, when compared to obese men; this is potentially due to increased societal pressures on women to be thin *(53)*. Intentional weight loss improves the quality of life *(54)*. Severely obese patients who lost an average of 43 kg through gastric bypass demonstrated improvements on all domains of the SF-36 to such an extent that their post-weight loss scores were equal to or better than population norms *(55)*.

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