Chapter 2
The Health Burden of Obesity

Eugenia A. Lin, Gillian M. Barlow and Ruchi Mathur

"Corpulence is not only a disease itself but a harbinger of others." Hippocrates

Obesity: Definitions

The obesity epidemic affects people of all ages, socioeconomic levels, geographic regions, and ethnicities, and causes significant medical consequences. Obesity has been defined as a medical condition in which excess body fat accumulates to an extent that may have short- and long-term consequences on morbidity and mortality [1, 2]. Globally, in an analysis of 199 countries, 1.46 billion adults worldwide are estimated as being overweight, and 502 million are estimated as being obese [3]. In the USA, the prevalence of obesity (2009–2010) has been reported as 35.7% [4]. "Overweight" technically refers to an excess of body weight, whereas "obesity" refers to an excess of fat. However, the methods used to directly measure body fat are not available in daily practice. For this reason, obesity is often assessed by means

R. Mathur (✉)
Division of Endocrine Diabetes and Metabolism, Department of Medicine,
Cedars-Sinai Medical Center, Los Angeles, CA, USA
e-mail: ruchi.mathur@cshs.org

E. A. Lin
Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, CA, USA
e-mail: eames.lin@gmail.com

G. M. Barlow
Departments of Medicine and Ob/Gyn, Cedars-Sinai Medical Center,
Los Angeles, CA, USA
e-mail: Gillian.Barlow@cshs.org

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of indirect estimates of body fat (i.e., anthropometrics). In the clinical setting, adult obesity is most often defined by the use of body mass index (BMI), which is a calculation based on the weight of a person in kilograms over their height in meters squared (kg/m^2). Though widely used, there are fundamental concerns with this method of classification. While easy to calculate, and routinely used as a population measurement of overweight and obesity, BMI does not take into account body composition. We are well aware that a person with a percent body fat of 8% who is a body builder may have the same weight as someone with a body fat of 35% who is inactive. Herein lies the flaw of simply measuring BMI. While there are more accurate means of measuring body composition, such as skin-fold thickness, waist circumference, and techniques such as ultrasound, computed tomography, and magnetic resonance imaging (MRI), many of these are not possible in the routine office setting. More recently, a newer model of measurement, the body adiposity index (BAI), has been proposed. The BAI mathematical model takes into account hip circumference and appears to better measure percent adiposity [5]. However, as BMI is still the most commonly used model for calculating obesity, we focus our discussion on this criterion.

The BMI criteria for adult obesity in Western societies are accepted as noted in Table 2.1 [6], whereas in Asian populations, the criteria are more stringent. This difference is based on the observations of investigators [7–9], along with health policy-making organizations [10, 11], which have shown that cardiovascular risk and diabetes in some Asian countries increase significantly in those with weight parameters that are only modestly elevated by American standards. Thus, the current proposal is that definitions and thresholds of overweight and obesity should be lower in Asian countries. It should be noted that there is considerable debate on this point, and over whether BMI criteria should be country-specific, or ethnicity-based [12]. At present, the Japanese define obesity as a BMI greater than 25kg/m^2 [13], while the Chinese use a cut off of 28 kg/m^2 [14].

Table 2.1 Weight categories for adults and youth

Category	Adults (20+ years)	Youth (2–19 years) CDC, AAP, IOM, ES, IOTF
Underweight	BMI < 18.5	BMI < 5th percentile for age
Normal weight	BMI 18.5–24.9	BMI ≥ 5th to < 85th percentile
Overweight	BMI 25–29.9	BMI ≥ 85th to < 95th percentile
Obesity	BMI ≥ 30	BMI ≥ 95th percentile
Class III obesity (super obesity)	BMI ≥ 40	Not used[a]

AAP American Academy of Pediatrics, *IOM* Institute of Medicine, *ES* Endocrine Society, *CDC* Centers for Disease Control, *IOTF* International obesity task force, *BMI* body mass index

[a] In children, proposed definitions of severe obesity are BMI > 120% of the 95th percentile, or BMI > 99th percentile

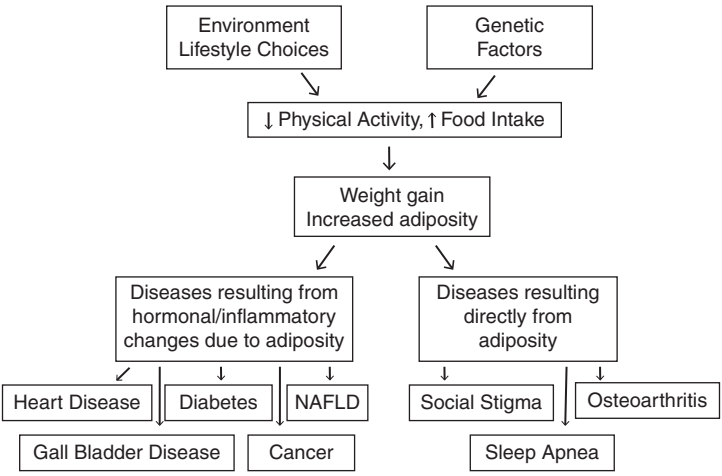

Fig. 2.1 Heath problems related to the development of obesity. (Adapted from [26])

In children, defining criteria for obesity is more complex, as the age, sex, expected growth curves, and body composition must all be factored in. A child's weight status is determined using an age- and sex-specific percentile for BMI rather than the BMI categories. The Centers for Disease Control growth charts are used to determine the corresponding BMI-for-age and sex percentile. For children and adolescents (aged 2–19 years), overweight is defined as a BMI at or above the 85th percentile and lower than the 95th percentile for children of the same age and sex, while obesity is defined as a BMI at or above the 95th percentile for children of the same age and sex [15]. Figure 2.1 shows the classification of obesity for children based on the American Academy of Pediatrics, the Institute of Medicine, the Centers for Disease Control, and the International Obesity Task Force.

The Economic Burden of Obesity

Globally, in an analysis of 199 countries, 1.46 billion adults worldwide were estimated as overweight, with 502 million estimated as obese [3]. The global economic burden of obesity accounts for an average of 0.7–2.8% of a country's total health-care costs [16]. These costs represent the monetary value of health-care resources devoted to managing obesity-related disorders. This includes such costs as those incurred through the use of outpatient clinics and visits, hospitalizations, pharmaceutical therapy, laboratory testing, and chronic care. Obese individuals have, on average worldwide, medical costs 30% higher than those with normal weight [16]. Interestingly, in the USA specifically, the medical economic burden of obesity is higher: an estimated US$ 75 billion in 2003 [17], accounting for 4–7% of total health-care expenditure. The increase in costs seen in obese individuals tends to be

largely driven by the increased incidence of type 2 diabetes, the increased cardiovascular burden, and obesity-related cancers [18].

Overweight/obesity in middle age appears to have long-term adverse consequences for health-care costs as one ages. A review of US Medicare data collected from 1984 to 2002 showed that after multivariate analysis, Medicare health charges were significantly higher by baseline BMI in both men and women [19]. This held true for overall costs, and costs specifically related to diabetes and cardiovascular disease. After adjusting for variables such as baseline age, race, education, and smoking, the total average annual medical-related charges for overweight, obese, and severely obese men were US$ 8390, $ 10,128, and $ 13,674, respectively. This is a significant trend over normal-weight men who, as a group, averaged an annual health-care cost of $ 7205. Other US data show that compared to normal-weight individuals, obese patients incur 27% more outpatient visits, and 80% more prescription costs [20]. In addition, in the inpatient setting, obese patients have an increased cost of 46% over nonobese patients. Similar trends have been reported in the UK, France, and the Netherlands.

The Health Burden of Obesity

The World Health Organization describes obesity as one of the most neglected public health problems we face today [21]. The health implications of obesity are not geographically limited. Sequelae of obesity include commonly thought of conditions, such as hypertension, heart disease, fatty liver, and diabetes, [22] to more esoteric associations such as infertility [22], idiopathic intracranial hypertension [23], and gout [24]. The incidences of certain cancers also increase with obesity, including cancers of the breast, ovaries, esophagus, colon, liver, pancreas, endometrium, and prostate [25].

The health conditions associated with obesity are thought to arise as either a direct consequence of adiposity—such as with social stigmatization, sleep apnea, and osteoarthritis; or via the various changes associated with the increase in adipose cell hypertrophy and/or hyperplasia (Fig. 2.1) [26]. It is important to remember that adipose tissue is a functional endocrine organ, with secretory products such as cytokines (interleukin (IL)-1 and 6) and tumor necrosis factor alpha (TNF-α). These cytokines have further effects, including suppression of adiponectin—which worsens insulin resistance. Diabetes, cancer, cardiovascular disease, and non-alcoholic liver disease are a few examples of disease states attributed in part to these hormonal and metabolic alterations. Having abdominal obesity seems to worsen these associated conditions, in part because of the high influx of free fatty acids, adipokines, and cytokines into the portal circulation by virtue of approximation. Subsequent hepatic production of very-low-density lipoprotein (VLDL) and dysregulation of insulin release set off a cascade of metabolic derangements [22].

Social Stigmatization

Many societies tend to chastise those who are overweight, and many consider those with weight issues as being unable or unwilling to control impulsive/compulsive behaviors. There is often public disapproval expressed openly by colleagues, neighbors, family members, and acquaintances. Such reproach often results in measurable changes in the quality of life parameters reported by obese subjects [26, 27]. These changes are more profound in women, and tend to reverse with intentional weight loss [28, 29]. Children and adolescents also tend to suffer the psychosocial consequences of obesity, including alienation [30], distorted peer relationships, poor self-esteem [31, 32], anxiety [33], and depression [34, 35]. The risk of psychosocial morbidity increases with increasing age during childhood, and is greater among girls than boys [36–38].

The distorted and negative self-images that develop in adolescence often persist into adulthood, especially in women. Data from the National Longitudinal Survey of Youth indicate that women who were obese in late adolescence and early adulthood completed fewer years of advanced education, and had lower rates of marriage and higher rates of poverty compared to their *non-obese* peers [39]. Interestingly, these long-term social repercussions were not nearly as profound in obese men.

Sleep Apnea

In the absence of underlying pulmonary disease, obese patients are noted as having pulmonary-related issues only in the presence of significant obesity. The main obesity-related change in pulmonary function testing is an increase in residual lung volume associated with an increase in intra-abdominal pressure [40, 41]. While these pulmonary function changes may be mild, the other effects of obesity on the respiratory system can be quite significant. Obstructive sleep apnea (OSA) is a syndrome characterized by episodic hypopnea or apnea due to recurrent partial or complete upper airway obstruction during sleep. Obesity is the most documented risk factor for OSA. Significant sleep apnea is present in approximately 40% of obese individuals, and the prevalence of OSA progressively increases as the BMI increases [42].

OSA frequently coexists with, and may be one of the causes of obesity hypoventilation syndrome (OHS). OHS is defined as obesity and chronic alveolar hypoventilation (arterial carbon dioxide tension [$PaCO_2$] >45 mmHg) during wakefulness, which occur in the absence of other conditions that cause hypoventilation [43].

Osteoarthritis

Diseases of the bone including osteoarthritis and other joint issues are directly related to the weight placed on the joints by obesity [44]. For example, the incidence of knee osteoarthritis was found to be increased in men in heaviest quintile of weight compared with those in the lightest three quintiles (age-adjusted relative risk, 1.51; 95% confidence interval (CI), 1.14–1.98), and was further increased in women in the heaviest quintile versus those in the lightest three quintiles (relative risk 2.07; 95% CI, 1.67–2.55) [44]. There is some suggestion that non-weight-bearing joints also suffer changes in the obese; however, the mechanism underlying these changes is not known.

Nonalcoholic Fatty Liver Disease (NAFLD)

NAFLD is a term describing a collection of liver abnormalities including hepatomegaly, elevated liver enzymes, and changes in histology which include (in progressive order) steatosis, non-alcoholic steatohepatitis, fibrosis, and cirrhosis [45]. Once NAFLD has progressed to cirrhosis, liver failure may ensue. Obesity is associated with this clinical spectrum of liver damage and disease [45, 46]. The pathogenesis of NAFLD in overweight and obese individuals is not fully understood, but insulin resistance appears to be an important component [47]. A retrospective analysis of liver biopsies in individuals who were overweight and obese without any other underlying contributors to liver disease showed the presence of fibrosis in 30% of samples, and cirrhosis in a further 10% [48]. Other authors have performed cross-sectional analysis of liver biopsies and suggest that the prevalence of steatosis is 75% in the obese population [49]. In another study, metabolic syndrome (of which obesity and insulin resistance are components) was associated with an odds ratio (OR) of 3.5 for the development of severe liver fibrosis [50].

Hypertension

Obesity is associated with hypertension. The relation between obesity and hypertension is clinically important because weight loss may lead to a significant fall in systemic blood pressure (BP) [51, 52]. The impact of obesity on the presence of hypertension may have ethnic differences. It is estimated that weight control would eliminate hypertension in 28% of the Black population. This is almost doubled to an estimated 48% in the White population [53].

The mechanism by which obesity raises the BP is not well understood. One postulate is that hyperinsulinemia is the cornerstone of this relationship [54], and many mechanisms have been proposed to explain the resultant increase in BP including increased sympathetic activity [55], volume expansion due to increased renal so-

dium reabsorption [56], endothelial dysfunction [57], upregulation of angiotensin II receptors [57], and decreased cardiac natriuretic peptide [58]. The risk of hypertension appears to be greatest in people who have predominantly upper body and abdominal obesity. The mechanism by which upper body obesity raises BP remains unclear. Insulin resistance is thought to be a central component, leading to impaired glucose tolerance and hyperinsulinemia. Hyperinsulinemia may then raise the BP by the mechanisms noted above. Despite these observations, insulin resistance or hyperinsulinemia as a cause of hypertension remains controversial. There is also mounting evidence that leptin may have a role in obesity-related hypertension, via increased sympathetic activity [54].

The sleep apnea syndrome associated with obesity is an additional contributing factor to the development of hypertension [59]. It is thought that activation of the sympathetic nervous system, elevated aldosterone levels, and increased levels of endothelin by repeated episodes of hypoxia are responsible for the associated hypertension [60].

The presence of sustained weight loss has a beneficial effect on hypertension. The long-term effect of weight loss was evaluated over an 8-year period among overweight 30- to 49-year-olds and overweight 50- to 65-year-olds [61]. A sustained reduction in weight of 6.8 kg or more was associated with a 22 % reduction in relative risk for developing hypertension (defined by 140/90 mmHg) in the younger age group and 26 % reduction in relative risk in the older overweight population. A simple relationship to remember is that for each 1 kg of weight loss, systolic and diastolic pressures fall by approximately 1 mmHg [62].

Cardiovascular Disease and Stroke

Overweight and obesity are associated with multiple cardiovascular abnormalities. In addition to an association with coronary artery disease, there is an increase in cardiac volume, cardiac work increases, and this may produce cardiomyopathy and heart failure.

Heart Failure

It is often forgotten that obesity can be an independent etiology of heart failure that is just as significant as hypertension, coronary disease, and diabetes. Evidence from the Framingham Heart Study showed that obesity doubled the risk of heart failure. In the 6000 subjects studied, multivariate analysis showed a 5–7 % increase in risk for every 1 kg/m^2 increase in BMI [63]. The physiologic processes responsible for this increase are likely multifactorial, and include an increase in cardiac work, an association with insulin resistance, subclinical right ventricular dysfunction, and association with diabetes, sleep apnea, and hypertension.

Cardiac Rhythm Abnormalities

Patients with a BMI of greater than 30 kg/m^2 are significantly more likely to develop atrial fibrillation than individuals of normal weight. [64]. This increased risk has also been shown in many studies, and appears to be particularly associated with sustained atrial fibrillation as compared to transient or intermittent atrial fibrillation [65]. There does not appear to be an increased risk in ventricular dysrhythmias associated directly with increasing BMI or weight gain.

Coronary Heart Disease (CHD)

The Nurses' Health Study has shown a 3.3-fold higher risk of developing coronary artery disease in women with a BMI greater than 29 when compared to lean women [66]. When followed longitudinally, there is also an associated increase in heart disease with weight gain in women over time. This finding was highest in women who gained over 20 kg, and was independent of starting BMI. The association between obesity and CHD has also been observed in many other large-scale population-based studies [67–69]. The distribution of body fat again appears to play a role, with those subjects having predominantly abdominal or central fat being the group at greatest risk. Using the waist-to-hip ratio as a measurement for abdominal obesity in a female cohort, researchers have shown that a value of >0.88 provides a three-fold higher risk of CHD when compared to women with a ratio of <0.72 [70]. Others have shown that the risk appears to increase sharply once the ratio is >0.8 [71].

It is well known that dyslipidemia is an important risk factor for the development of atherosclerosis. The classic dyslipidemic pattern of obesity consists of an elevated triglyceride (TG) level and a decreased level of high-density lipoprotein (HDL). While the decrease in HDL may be an important contributor to the development of heart disease in obesity, perhaps more suspect is the changes associated with the character and quality of low-density lipoprotein (LDL) seen in obesity. Central fat distribution is associated with an increase in small, dense LDL. This form of LDL is more atherogenic than the alternate large fluffy LDL [72]. It has also been postulated that obesity poses an increased CHD risk because of associated low concentrations of adiponectin, which has antiathrogenic properties and lowers insulin resistance [73].

Stroke

The data linking obesity to stroke risk are not as clear as the data linking obesity to CHD. The Emerging Risk Factors Collaboration reviewed data on over 85,000 subjects and found that the risk of ischemic stroke increased by 20% for every 1 standard deviation increase in BMI [74]. However, this risk was dramatically attenuated once adjusted for age, smoking, hypertension, diabetes, and cholesterol status. Some studies have shown an increased risk of both ischemic and hemorrhag-

ic stroke in obese patients [75]. Most other studies have not seen this association with hemorrhagic stroke [76]. The Nurses' Health Study indicates that both a BMI of greater than 27 kg/m^2 and accelerated weight gain after age 18 are associated with increased ischemic stroke risk. The relative risk reported was 2.4 for a BMI of 32 kg/m^2 or greater when compared to a BMI of 21 kg/m^2 or less [77]. The Women's Health Study also reported similar findings [78].

Insulin Resistance and Diabetes

Insulin Resistance

Insulin resistance and type 2 diabetes are significant health risks well known to be associated with obesity, such that even mild detriment to insulin release has been shown to have profound effects on metabolic processes, and thus regulation of weight and obesity [79]. Insulin resistance is stimulated by fat deposited within cells and cytokines (IL1, IL6, TNF-α) secreted by adipocytes that actively suppresses insulin sensitizers. Insulin resistance is only one part of the pathophysiology of type 2 diabetes, with B cell dysfunction in the pancreas also playing a role. Notably, the connection between insulin resistance and inflammatory pathways provides an explanation for the comorbid association between type 2 diabetes and obesity, examined further in clinical studies associating weight loss with an increase in insulin sensitivity in adults ($P < 0.002$) [80, 81]. Environmental, genetic, and societal factors contribute to the development and repercussions of obesity and insulin resistance, as well as differences in ethnicity and gender. Men and African Americans exhibit a greater prevalence for insulin resistance, with African Americans constituting the highest rate of diagnosed diabetes among all the races at 11.2% [82].

Diabetes

Data from the Behavioral Risk Factor Surveillance System (BRFSS) from 2001 of 195,005 adults in the USA showed that obese adults (BMI ≥40) have greater than a sevenfold OR for a diagnosis of diabetes than the average adult [82]. This figure may be a staggering underestimation of the true presence of diabetes in the population due to various survey constraints within the survey population and the criterion that only doctor-diagnosed diabetes was tabulated, though an estimated 27% of those affected by diabetes remain undiagnosed [83]. The link is irrefutable when the converse association is considered: 64% of men and 77% of women with type 2 diabetes are overweight or obese. There is also sufficient evidence linking obesity to the development of gestational diabetes mellitus. Using a regression analysis between prepregnancy BMI and presence of gestational diabetes, researchers calculated the percentage of gestational diabetes attributed to obesity and found a statistically significant higher risk of gestational diabetes correlated to higher BMI

and 46.2% of gestational diabetes occurrences ascribed to being overweight, obese, or extremely obese (95% CI =26.1, 56.3) [84]. With an estimated $ 174 billion spent annually on the treatment of diabetes and a projected number of one in three Americans with diabetes by 2050, the health burden of obesity and its connection to insulin resistance and type 2 diabetes poses as an immense public health problem for worldwide populations [85].

Cancers

In 2008, there were an estimated 12.7 million cancer cases and 7.6 million cancer deaths worldwide [86, 87]. Together, modifiable risks such as tobacco use, excess weight, poor diet, and inactivity are thought to account for almost 70% of all cancers in the USA [88]. Obesity as a sole risk factor is estimated to cause 20% of all cancers [89]. Excess weight and obesity are associated with an increased risk of developing multiple cancers including colorectal, postmenopausal breast, endometrial, renal, and esophageal cancer. The attributable risk of excess weight ranges from 9% (postmenopausal breast cancer) to 39% (endometrial cancer) [90]. Newer data suggest that excess body weight and increased body fat also have a direct association with additional cancers including pancreas, thyroid, non-Hodgkin lymphoma, leukemia, and myeloma [91].

Weight gain itself is also associated with cancer risk. For example in a Canadian report, men who gained ≥21 kg after age 20 had a 60% higher risk of colorectal cancer than men who gained only 1–5 kg [92]. In another study, women who lost≥10 kg after menopause and kept it off saw a 50% reduction in breast cancer risk [93].

The exact mechanism behind the association of weight with cancer development is not clear—and is likely multiple. One contributing factor is thought to be related to the increased aromatization that occurs in fat tissue, resulting in higher levels of estrogen. This may be a factor in endometrial cancer and breast cancer risk. Other proposed mechanisms include the influence of obesity and weight gain on insulin resistance and subsequent effects on inflammation. The latter may be particularly important in colon cancer [89].

A recent report suggests that bariatric surgery is associated with a 60% reduction in overall cancer mortality (5.5 vs. 13.3 per 10,000 person-years). The follow-up for this study was 7 years, however, more data of this sort are needed to confirm this observation [94]. In addition, this benefit seen with bariatric surgery may not be the case with every cancer (see *colon cancer*).

While the above refers directly to excess body weight as a contributor to cancer risk, it is important to remember that physical inactivity and poor dietary intake are also contributors to cancer risk. While often intertwined with obesity, these two factors are independent and carry with them their own cancer risks that are beyond the scope of this chapter's discussion.

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