Diseases and Disorders Associated with Excess Body Weight

Joseph A. Knight
Department of Pathology, University of Utah School of Medicine, Salt Lake City, Utah 84132

Abstract. Excess body weight is a very serious problem, especially in North America and Europe. It has been referred to as a “pandemic” since it has progressively increased over the past several decades. Moreover, excess body weight significantly increases the risk of numerous diseases and clinical disorders, including all-cause mortality, coronary and cerebrovascular diseases, various cancers, type 2 diabetes mellitus, hypertension, liver disease and asthma, as well as psychopathology, among others. Unfortunately, overweight and obesity are now common in both young children and adolescents. Although the causes of excess body weight are multi-factorial, the most important factors are excess caloric intake coupled with limited energy expenditure. Therefore, lifestyle modification can significantly reduce the risk of morbidity and mortality and thereby increase longevity and improve the quality of life.

Keywords: obesity and disease; body mass index; waist circumference

Introduction

Excess body weight is a very serious global epidemic. Due to the rapid increase in the number of overweight (body mass index, [BMI] 25.0-29.9) and obese (BMI > 30) individuals over the past several decades, it is often referred to as a “pandemic”. Indeed, 1.1 billion worldwide adults and 10% of children are overweight or obese [1]. However, since the current BMI cut-off for overweight Asians is 23.0 kg/m2, the number is significantly higher (1.7 billion adults) [2].

A recent study of 63 countries estimated that 40% of men and 30% of women were overweight and 24% of men and 27% of women were obese [3]. In 2000, an estimated 131 million Americans were overweight or obese [4]. However, since the obesity prevalence increased 24% from 2000 to 2005 [5], the current number is significantly greater. Indeed, in 2010, an estimated 72.5 million American adults were obese [6]. Moreover, the prevalence of morbid obesity (BMI > 40) increased by 50% and for a BMI > 50, it increased 75%. Flegal et al recently estimated that the age-adjusted prevalence of obesity was 33.8% overall; 32.2% of men and 35.5% of women [7]. When overweight and obesity were combined, the prevalence estimates were 68%, 72% and 64%, respectively. If the current trend continues, Wang et al estimated that 86.3% of American adults will be overweight or obese by 2030 and essentially all Americans will be overweight or obese by the year 2048 [8].

Excess body weight is not limited to adults. To examine changes in state-specific overweight and obesity, Singh and associates carried out a cross-sectional analysis of 46,707 and 44,101 children aged 10 to 17 years in 2003 and 2007, respectively [9]. In 2007, 16.4% of U.S. children were obese and 31.6% were overweight. Overweight prevalence varied from a low of 23.1% for children in Utah to 44.5% in Mississippi. During this time, obesity prevalence increased 10% for all U.S. children and 18% for female children. Moreover, adolescent obesity (< 20 years; BMI > 95th percentile of the sex-specific BMI-for-age growth chart or BMI > 30) is significantly associated with an increased risk of severe obesity (BMI > 40) in adulthood [10].
It is important to recognize that there exists a significant level of bias in self-reported height and weight and therefore BMI. For example, in agreement with several previous reports [11-14], a recent study concluded that “….BMI based on self-reported height and weight is underestimated for both men and women, increasingly so with older age and weight” [15]. Thus, overweight and obesity are somewhat greater, especially in older adults, than generally reported.

Excess body weight is a serious chronic disorder that has become a major health problem, especially in North American and European countries due to its high prevalence, causal relationship with numerous diseases and disorders, increased morbidity and mortality, accelerated aging, and decreased quality of life (Table 1). As noted by Sturm [16], “obesity has roughly the same association with chronic health conditions as does twenty years aging; this greatly exceeds the associations of smoking or problem drinking.” Similarly, Stewart et al concluded that “if past obesity trends continue unchecked, the negative effects on the health of the U.S. population will increasingly outweigh the positive effects gained from decreasing smoking rates” [17].

Table 1. Overweight/Obesity Associated Diseases and Disorders

<table>
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<td>All-cause mortality</td>
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<td>Asthma</td>
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<td>Coronary heart disease</td>
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<td>Cerebrovascular disease</td>
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<td>Cancer (several types)</td>
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<td>Dementia/Alzheimer's</td>
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<td>Gout</td>
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<td>Hypertension</td>
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<td>Inflammation</td>
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<td>Liver diseases (steatosis, steatohepatitis)</td>
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<td>Metabolic syndrome</td>
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<td>Osteoarthritis</td>
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<td>Oxidative stress, accelerated aging</td>
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<td>Psychopathology</td>
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<td>Sleep disorders</td>
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<td>Quality of life</td>
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In 1999, the estimated number of American deaths attributable to obesity was 280,184 [18]. When estimated for nonsmokers and never-smokers, the estimate was 324,940. Since about two thirds of American adults are currently overweight or obese, the annual number of deaths is significantly higher [6]. Indeed, excess body weight was predicted to overtake smoking in 2005 as the major preventable cause of illness and premature death [19].

Waist circumference (WC) and the waist:hip ratio (WHR) are also very useful body measurements. Lean and associates compared WC with BMI and WHR [20]. They found that a WC > 94 cm (> 37 in) for men and > 80 cm (> 31.5 in) for women identified those with an elevated BMI. A WC > 102 cm (> 40.2 in) for men and > 88 cm (> 34.6 in) for women identified those with a BMI of 30 kg/m2 or higher (obese). For WHRs, abdominal obesity exists when the values are > 1.0 for men and > 0.80 for women. Using the National Health and Nutrition Examination Surveys (NHANES) data, the age- adjusted mean WC increased from 96.0 cm (38.4 in) to 100.4 cm (40.2 in) in men and 89.0 cm (35.6 in) to 94.0 cm (37.6 in) in women between 1988-1994 and 2003-2004 [21]. Indeed, abdominal obesity may be a better predictor for disease risk factor and all-cause mortality than BMI. For example, Jacobs et al recently examined the association between WC and mortality among 48,500 men and 56,343 women, 50 years and older [22]. After adjustment for BMI and other risk factors, the relative mortality risk for men was 2.02 for WC > 120 cm (47.2 in) compared with < 90 cm (35.4 in). Among women, the relative mortality risk was 2.36 for WC > 110 cm (43.3 in) compared with < 75 cm (29.5 in).

The causes of overweight and obesity are multifactorial relating to a complex interplay of genetic, nutritional, physiological, psychological, environmental, and social factors. However, the most important factors underlying the excess body weight pandemic are the current excess caloric intake coupled with limited energy expenditure. Nevertheless, lifestyle-modification characterized by an increase in physical activity and a balanced diet can reduce obesity and the risk of obesity-associated co-morbid conditions despite minimal or no weight loss [23].
Overweight, Obesity and All-Cause Mortality

As the BMI increases above 25.0, the risk of various diseases and mortality also increases. Fontaine and associates estimated the number of years of life lost (YLL) due to excess body weight across a person’s lifespan [24]. Using a BMI of 24 as the reference point, there were significant race, sex, and age differences in YLL. Among whites, the YLL showed a J- or U-shaped curve for overweight and obesity. The optimal BMI for whites was 23-25 and 23-30 for blacks. For any degree of overweight, young adults had greater YLL compared with older adults. Thus, the maximum YLL for white males aged 20-30 years with severe obesity was 13 years and eight years for white females. For young blacks with severe obesity, the maximum YLL was 20 years for men and five for women.

In an early 14-year prospective study of more than one million American never smoker adults, the BMI nadir was 23.5-24.9 in men and 22.0-23.4 in women [25]. Among those with the highest BMI (men > 35; women > 40), the relative risks of premature death was 2.58 for men and 2.00 for women. As with other studies, black men and women with the highest BMI indexes had significantly lower risks of death (1.35 and 1.21, respectively). A more recent prospective study, which involved 527,265 U.S. men and women, aged 50 to 71 years at enrollment in the National Institutes of Health-AARP cohort, evaluated the risk of death with increasing body weight [26]. After ten years of follow-up, there was an increased risk of death for both the highest and lowest BMI categories for men, women, all racial/ethnic groups, and all ages. For 50 year-old non-smokers, the risk of death increased 20% to 40% among overweight (BMI 25.0-29.9) persons and 2- to 3-fold among obese persons (BMI > 30).

Since studies of the association of abdominal adiposity with all-cause, cardiovascular, and cancer mortality have been somewhat inconsistent, a recent Nurse’s Health Study prospectively followed 44,636 women for 16 years [27]. After adjustment for BMI and potential confounders, the relative risks across the lowest to the highest WC quintiles were 1.00, 1.11, 1.17, 1.31 and 1.79 for all-cause mortality; 1.00, 1.04, 1.04, 1.28 and 1.99 for cardiovascular mortality; and 1.00, 1.18, 1.20, 1.34 and 1.63 for cancer mortality. Thus, abdominal adiposity was “strongly and positively associated with all-cause, CVD, and cancer mortality independently of body mass index.” More recently, Jacobs et al examined the association between WC and mortality among 48,500 men and 56,343 women, 50 years and older, in the Cancer Prevention Study II Nutrition Cohort [28]. After adjustment for BMI and other risk factors, high levels of WC were associated with an approximately 2-fold higher mortality risk in both sexes [among men, relative risk 2.02 for WC > 120 cm (47.2 in) compared with < 90 cm (35.4 in); for women the relative risk was 2.36 for WC > 110 cm (43.3 in) compared with < 75 cm (29.5 in). The authors concluded that the results demonstrate “the importance of WC as a risk factor for mortality in older adults, regardless of BMI.”

Overweight/Obesity-Associated Diseases and Disorders

1. Coronary Heart Disease

Heart disease is the leading cause of death among both men and women in the U.S. and most other Western countries. In 2004, 652,486 Americans died of heart disease [29]. Although there has been a significant decrease in the cardiovascular death rate over the past several decades, the overall incidence of acute myocardial infarction has not declined. Rather, it has actually increased among women [30]. For example, a recent study found a significant increase in the coronary heart disease (CHD) death rate in women aged 35 to 44 years from 1997 to 2002 [31]. The authors suggested that the increased obesity rate is probably the major risk factor.

Obese adults, especially those who were overweight during childhood and those with abdominal obesity, are at a significantly increased risk for CHD. An early study involving 115,818 women (Nurses’ Health Study), aged 30 to 55
years in 1976, were followed for 14 years [32]. After controlling for various confounders, and using as a reference BMI of less than 21 kg/m², the relative risks for CHD were 1.19, 1.46, 2.06, and 3.56 for BMIs of 21.0-21.9, 23.0-24.9, 25.0-28.9, and over 29.0, respectively. In a separate study, these researchers reported that among never smoking women, the relative risk for death from CHD was 4.1 for those with a BMI of 32.0 or higher compared with a BMI less than 19.0 [33]. A subsequent 8-year Nurses’ Health Study showed that both WHR and WC were independently associated with increased CHD [34]. For women with a WHR of 0.88 or greater, the relative risk was 3.25 compared with a ratio less than 0.72. If the WC was 96.5 cm (38 in) or more, the relative risk was 3.06. Studies have also shown that obesity increases the risk of CHD in men. Indeed, a prospective 10-year study of English men aged 35 to 74 years indicated that overweight and obesity are more important risk factors for CHD than smoking, level of physical activity, education load, and income [35]. Here, 32% had an increased 10-year risk of CHD and of this group, 47% of the high risk was attributed to excess body weight (BMI > 25 and/or a WHR of 0.95 or more). Thus, “Overweight and obesity now dominate the standard risk factors of CHD in men…..” More specifically, in an early three-year prospective study of 29,122 men aged 40 to 75 years, the relative risks for CHD in men younger than 65 were 1.72, 2.61, and 3.44 for those with a BMI of 25.0-28.9, 29.0 to 32.9, and 33.0 or greater [36]. Interestingly, data from the Dallas Heart Study indicated that the WHR for both men and women was “independently associated with prevalent atherosclerosis, and provided better discrimination than either BMI or WC” [37].

2. Cerebrovascular Disease
In 2004, 150,074 Americans died from cerebrovascular disease (CVD), the third most common cause of death in the U.S. [29]. Stroke deaths are higher in Southeastern U.S. than in other regions [38]. Moreover, blacks, American Indians/Alaska Natives, Asian/Pacific Islanders, and Hispanics die from stroke at younger ages than whites [39]. Overweight and obesity significantly increase the risk of stroke in both men and women. In an early Nurses’ Health Study, 116,759 women aged 30 to 50 years at baseline, and free of CHD, cancer, and stroke were followed for 16 years [40]. After adjustment for age, smoking, hormone use, and menopausal status, women with a BMI of 27.0 or more had a significantly higher risk for ischemic stroke. The relative risks for BMIs 27.0-28.9, 29.0-31.9, and 32 or more were 1.75, 1.90, and 2.37, respectively. More recently, Kurth and associates prospectively studied 39,053 healthy women for an average of 10 years [41]. Compared with a BMI less than 25.0, the hazard ratios for obese women were 1.50 for total stroke, 0.82 for hemorrhagic stroke, and 1.72 for ischemic stroke. Similarly, 28,643 U.S. male health professionals, aged 40 to 75 years at baseline, were followed for five years [42]. After this time, the relative risk was 1.29 for men in the highest BMI quintile compared with those in the lowest quintile. However, the age-adjusted relative risk between the lowest and highest quintiles of WHR was 2.33. For WC, the relative risk was 1.52 for those in the highest quintile (> 40.2 in) compared with men in the lowest quintile (< 34.5 in). In a more recent Physicians’ Health Study, there were 631 ischemic, 104 hemorrhagic, and 12 undefined strokes during 12.5 years of follow-up [43]. Compared with men with a BMI less than 23.0, those with a BMI of 30.0 or greater had a relative risk of 2.00 for total stroke, 1.95 for ischemic stroke, and 2.25 for hemorrhagic stroke.

3. Cancer
Cancer is the second leading cause of death across all ages in the U.S. However, it is reportedly the leading cause of death in those younger than 85 years [29]. The various cancer types associated with increased body weight are listed in Table 2.
Excess body weight, morbidity, and mortality

Two early American Cancer Society prospective studies involving 750,000 men and women compared the death rates for those who were overweight compared with those of average weight [44,45]. After 12 years of follow-up, the mortality ratio for men and women who were 40% or more overweight were 1.33 and 1.55, respectively. Overweight men had significantly higher mortality risks for colorectal and prostate cancer; overweight women had significantly higher risks for breast, ovary, endometrium, cervix, and gall bladder cancers.

More recently (2002), an international research group concluded that taken together, excess body weight and physical inactivity accounted for about 25% to 33% of cancers of the breast, colon, endometrium, kidney and esophagus [46]. Importantly, between 1992 and 2004, the overall cancer incidence rate declined by about 0.6% per year [47].

Similarly, in a large prospective population study of men (404,576) and women (495,477) who were free of cancer in 1982, Calle et al examined the association between BMI and the risk of death from all cancers, as well as those at specific sites [48]. Both men and women who were morbidly obese (BMI > 40) had combined death rates that were 52% higher for men and 62% higher for women than those of normal weight (BMI < 25). The relative risks were 1.52 and 1.62 for men and women, respectively. For both men and women, BMI was also significantly associated with higher death rates from carcinoma of the colon, rectum, esophagus, liver, gall bladder, pancreas, and kidney, as well as from multiple myeloma and non-Hodgkin's lymphoma. Significant death trends were also observed for cancers of the stomach and prostate in men and breast, uterus, cervix and ovary in women. The researchers estimated that overweight and obesity accounted for about 14% of all cancer deaths in men and 20% in women.

More recently, Renehan and associates analyzed 141 studies involving 282,131 incident cancer cases [49]. Using strict inclusion criteria, their results showed that a higher BMI was associated with an increased risk of thyroid, renal, esophageal, and colon cancers, multiple myeloma, leukemia, and non-Hodgkins lymphoma in both sexes; rectal carcinoma and malignant melanoma in men and gallbladder, pancreas, endometrial, and postmenopausal breast cancers in women. Moreover, the associations were generally similar to studies from Europe, North America, Australia, and the Asia-Pacific region.

4. Type 2 Diabetes Mellitus

Type 2 diabetes, which comprises about 95% of all diabetes cases, is the sixth leading cause of death in the United States [50]. In reality, it is significantly higher since it is a major risk factor for coronary heart disease, the leading cause of death in Western and other societies [51,52].

Since type 2 diabetes and obesity are so closely associated, Sims and associates coined the term “diabesity” in the early 1970s [53]. Indeed, a world-wide diabetes pandemic has emerged over the past several decades. For example, Hu et al followed 84,941 women at baseline (Nurses’ Health Study) from 1980 to 1996 [54]. After evaluating five variables (BMI, diet, physical activity, smoking, alcohol intake), they concluded that 91% of cases were lifestyle-related; the single most important determinant was excess body weight.

The burden of diabetes on society’s health and welfare continues to rise. The number of diagnosed cases in the U.S. increased from 1.5 million in 1958 to 17.9 million in 2007; as of 2009, 23.6 million Americans had type 2 diabetes [55]. Among minorities, the prevalence among Hispanic and African

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<th>Table 2. Increased Body Weight and Malignancy</th>
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<td>Breast</td>
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<td>Colorectal</td>
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<td>Esophagus/gastric cardia</td>
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<td>Gall bladder</td>
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<td>Kidney</td>
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<td>Leukemia</td>
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Americans was 10.4% and 14.7%, respectively. Unfortunately, an estimated 25% of Americans with diabetes are unaware that they have the disease.

The age-adjusted prevalence of diagnosed diabetes increased 43% from 1997 to 2005 [56]. In addition, about one-fourth of U.S. adults have pre-diabetes, a disorder defined as having impaired fasting glucose levels (plasma glucose >100 mg/dL to < 126 mg/dL), impaired glucose tolerance (plasma glucose level >140 mg/dL to < 200 mg/dL after a 2-hour glucose tolerance test), or both [57,58]. Therefore, there is a significant delay in diagnosing diabetes. In the Atherosclerosis Risk in Communities Study, the median delay from onset to diagnosis was 2.4 years and more than 7% of incident cases were undiagnosed for at least 7.5 years [59]. Using data from the Framingham Heart Study, Franco et al reported that diabetic men and women live 7.5 and 8.2 years less than their non-diabetic counterparts [60]. The differences in life expectancy from cardiovascular disease were 7.8 and 8.4 years for men and women, respectively.

Diabetes is also a major risk factor for chronic renal disease and hypertension. Indeed, the prevalence of chronic renal disease increased significantly from 1988 to 1994 [61]. The authors concluded that “This increase is partly explained by the increasing prevalence of diabetes and hypertension.....” Indeed, diabetic nephropathy occurs in about one third of individuals with diabetes.

Type 2 diabetes is also emerging as a significant health problem in children and adolescents [62,63]. Recent studies from the SEARCH for Diabetes in Youth Studies have shown that the prevalence of type 2 diabetes, as with obesity, is progressively increasing in non-Hispanic white youth [64], African-American youth [65], Hispanic-American youth [66], and Asian and Pacific Islander-American youth [67]. Indeed, as with adults, altered glucose metabolism in children and adolescents is strongly associated with the increased prevalence of childhood obesity. Interestingly, data from a recent study “support an association of obesity and higher body weight” with adenovirus 36 infection in children and adolescents [68].

Is diabetes a pathway for the aging phenomenon? Protein glycosylation is a major theory of aging [69]. Since diabetics have increased glucose levels, protein glycosylation is increased. Increased glucose levels also potentiate injury to mitochondrial DNA [70]. Moreover, oxidative stress, a major aging theory, is significantly increased in diabetics, a fact that appears to underlie the development of diabetic complications [71].

5. Hypertension

Obesity is a well-established risk factor for hypertension. An early study noted that the risk of hypertension is about five times higher among obese individuals compared with those of normal weight [72]. In this longitudinal Framingham study, blood pressure increased 6.5 mm Hg for every 10% increase in body weight.

Several subsequent studies also showed a linear association between hypertension and BMI [73-76]. For example, in the Nationwide Community Hypertension Evaluation Study of more than one million adults, the prevalence of hypertension in the overweight was 50% to 300% higher than in those of normal weight [75]. Recent NHANES III data showed that the age-adjusted prevalence of hypertension was more than two-fold higher in obese men and women compared with lean adults [77]. Unfortunately, weight-related hypertension is now recognized as an increasing problem in children and adolescents [78,79].

6. Metabolic Syndrome

The metabolic syndrome is also referred to as the insulin-resistance syndrome, syndrome X, Reaven's syndrome, diabesity syndrome, and morbesity syndrome. The syndrome is characterized by three or more of the following: (1) waist circumference > 102 cm in men and > 88 cm in women; (2) serum triglyceride level >
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150 mg/dL; (3) serum high-density lipoprotein cholesterol (HDL) level < 40 mg/dL in men and < 50 mg/dL in women; (4) blood pressure > 130/85 mm Hg; and (5) fasting serum glucose > 110 mg/dL [80,81]. When three or more of these criteria are present, the risk of coronary heart disease and type 2 diabetes is increased 1.5- to 2.0-fold [82].

Since the prevalence of the metabolic syndrome was unknown, Ford et al analyzed data from 8,814 men and women aged 20 years and older [83]. Their findings showed the following: (1) unadjusted and age-adjusted prevalence was 21.8% and 23.7%, respectively; (2) prevalence was 6.7%, 43.5%, and 42.0% in those aged 20 to 29 years, 60 to 69 years, and 70 or more years, respectively; (3) Mexican-Americans had the highest age-adjusted rate (31.9%); (4) among African-Americans, the prevalence rate was 57% higher in women than in men; Mexican-American women had a 26% higher prevalence than men; and (5) as of 2000, the metabolic syndrome was present in about 47 million Americans.

7. Lung Disorders

Obesity is associated with various pulmonary function abnormalities including asthma, obstructive sleep apnea, and hypoventilation. Moreover, abdominal obesity may decrease respiratory compliance, restrict ventilation, increase the work of breathing, and produce atelectasis.

a. Asthma

The prevalence of obesity and asthma have significantly increased in many countries over the past several decades. However, the association between obesity and asthma in men, compared with women, has been somewhat inconsistent. For example, a recent study of asthmatic individuals aged 18 to 34 years indicated that the association was significantly stronger in women than men [84]. Across increasing categories of BMI, there was an increased dose-response association in women (odds ratios 1.0 to 3.2), but only a non-significant risk in severely obese men. However, in a subgroup analysis, the obesity-asthma association was present in some minority groups, including black and Hispanic men. Other studies also found an increased risk in obese women compared with obese men [85,86].

Nevertheless, in a recent meta-analysis of seven studies (333,102 subjects), overweight (BMI 25.0-29.9) and obesity (BMI > 30) were associated with a dose-dependent risk of incident asthma in both men and women (odds ratios, 1.46 and 1.68, respectively) [87]. It was also noted in a literature review that “In adults cross-sectional, case-control, prospective, and weight-loss studies are in aggregate consistent with a role for obesity in the pathogenesis of asthma” [88]. Three of four prospective studies also showed a significant association between excess body weight and asthma in children.

b. Obstructive Sleep Apnea

Obstructive sleep apnea (OSA), a form of sleep disordered breathing, is characterized by excessive episodes of apnea and hypopnea due to partial or complete upper airway obstruction. Although OSA is associated with coronary heart disease, heart failure, hypertension, and cerebrovascular accidents, it remains underdiagnosed and undertreated [89]. As a result, the risk of death in these individuals from heart disease and stroke is significantly increased [90,91]. OSA is also an independent risk factor for all-cause mortality [92,93].

The majority of individuals with OSA are obese [94-96], have increased abdominal fat [97,98], and a large neck circumference [99,100]. Indeed, a neck circumference of 43.0 cm or more in men and 40.5 cm in women “is associated with episodes of disrupted breathing, recurring up to 30 times a night” [3]. Waist circumference in midlife, as well as an increase in waist circumference in adults with over 30 years of adult life, are also independent risk factors for sleep apnea in male subjects aged 71 to 91 years [96].

8. Musculoskeletal Diseases

a. Osteoarthritis

The risk of osteoarthritis in weight-bearing joints, particularly the knees, is significantly...
increased in overweight and obese individuals. Prior knee injury and occupational factors have also been associated with knee osteoarthritis [101]. Although increased body weight increases the risk of osteoarthritis in both men and women, the relationship is significantly stronger in women [102-104]. Indeed, the risk of osteoarthritis at the tibiofemoral and patellofemoral joints of the knee and carpometacarpal joints of the hands reportedly increases 9% to 13% per kg increase in body weight in women [105].

Data from the Baltimore Longitudinal Study of Aging showed that women in the middle and highest tertile of percent body fat had a significantly increased risk of bilateral knee osteoarthritis; men in the highest tertile of waist-to-hip ratio also had a significantly increased risk of bilateral knee osteoarthritis [106]. Importantly, Fontaine et al recently reported that obese persons with osteoarthritis receiving professional advice to lose weight were significantly more likely to lose weight than those who did not receive this advice [107]. Unfortunately, only 45.7% of the obese were ever advised to lose weight by their physician or health professional.

**b. Gout**

Early longitudinal and cross-sectional studies showed that obesity is a significant risk factor for gout in both men and women [108,109]. This latter study involved 1,337 primarily white male medical students, mean age 22 years at cohort entry. At age 35 years, BMI, excessive weight gain ( > 1.88 kg/m²), and development of hypertension were all significant risk factors. Similarly, Choi and associates studied the risk of gout in 47,150 males over a 12-year period [110]. Comceived with a BMI of 21.0-22.9, the relative risks were 1.95, 2.23, and 2.95 for BMIs of 25-29, 30-34.9, and greater than 35, respectively. Moreover, compared with men who maintained their weight since age 21 years, the relative risk for those who gained 30 or more pounds was 1.99. Conversely, for those who lost 10 or more pounds since the study baseline, the relative risk was 0.61.

Serum uric acid levels are not only associated with an increased BMI, but also with other risk factors [111,112]. Indeed, hyperuricemia is significantly related to increased waist-to-hip ratio, waist-to-thigh girth, serum triglyceride and LDL cholesterol levels, and systolic and diastolic blood pressures (i.e., insulin resistance syndrome factors).

**9. Gallbladder Disease**

Obesity is a significant risk factor for gallbladder disease, particularly in women. In an early study, the mean gallstone prevalence in moderately obese Caucasian American women was 31% compared with 10% in the normal weight control group [113]. According to the NHANES III study, more than 20 million Americans (6.3 million men; 14.2 million women) had gallstones or had undergone gallbladder surgery [114,115]. The prevalence was similar in non-Hispanic whites (8.6%) and Mexican-American men (9.9%); both were higher than black men (5.3%). Among women, the prevalence was highest among Mexican-Americans (26.7%) followed by non-Hispanic whites (16.6%) and non-Hispanic blacks (13.9%).

In an early Nurses’ Health Study of women aged 34 to 59 years at baseline, there was a linear association between relative weight and the risk of gallstones [116]. In a follow-up nurses’ study [117], obese women (BMI > 30) had a two-fold increased risk of symptomatic gallstones compared with those of normal weight; severely obese women (BMI > 45) had a seven-fold increased risk.

A study of Japanese men indicated a low rate of gallstones (2%) and prior cholecystectomy (3%) but “a strong relationship between obesity and gallstones was confirmed” [118]. In a follow-up report, increased BMI and waist-to-hip ratio were both associated with an increased risk of gallstones and prior cholecystectomy [119]. More recently, Tsai et al prospectively examined the association of abdominal adiposity and waist-to-hip ratio with the risk of gallbladder disease in 29,847 men (Health Professionals’ Follow-up Study) [120]. After adjustment for BMI and other risk factors for gallstones, men
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with a height-adjusted waist circumference of 102.2 cm or more (> 40.4 in) had a relative risk of 2.29 compared with men with a waist circumference less than 86.4 cm (34 in). For men with a waist-to-hip ratio of 0.99 or more, the relative risk was 1.78 compared with those with a ratio less than 0.89. Of further concern is a study of the prevalence of gallstones in obese children and adolescents in which gallstones were present in 2% of those aged 8 to 19 years (80% were females) [121].

10. Pancreatitis

As with cholelithiasis, both retrospective and prospective studies have shown that excess body weight increases the risk of pancreatitis. In a recent Swedish study, the prevalence of cholelithiasis, cholecystitis, cholecystectomies and pancreatitis was significantly higher in obese subjects [122]. In women, BMI and waist-to-hip ratio were independently associated with these diseases, whereas only BMI was significant in men.

Increased body weight also has a significant impact on the complications and outcome of acute pancreatitis. For example, compared with normal weight individuals, all categories of overweight and obesity were associated with an increased risk of developing “severe” acute pancreatitis (odds ratio, 3.55) [123]. Thus, the odds ratio for patients with class I obesity (BMI 30.0-34.9) was 3.5 for developing organ failure and local complications. Patients in class II and III obesity (BMI 35.0-49.9) had, in addition to organ failure and local complications, more metabolic problems (odds ratio, 7.3).

The degree of obesity is also an important prognostic factor in acute pancreatitis. As noted by Funnell et al, severe pancreatitis may be associated with increased fat deposits in the retroperitoneal and peri-pancreatic spaces, thereby increasing the risk of fat necrosis, abscess formation, and death [124]. Indeed, in a recent meta-analysis involving 739 patients with pancreatitis, the authors concluded that “Obesity is not only a risk factor for the development of local and systemic complications in acute pancreatitis, it also increases the mortality of this disease” [125].

11. Dementia

Prospective population studies have emerged showing that both overweight and obesity in midlife are associated with a significantly increased risk of ischemic dementia and Alzheimer’s disease (AD), independent of diabetes and cardiovascular disease [126]. In an 18-year follow-up of non-demented Swedish women, those who developed dementia, especially AD between ages 79 and 88 years, were significantly overweight at ages 70, 75, and 79 years compared with non-demented women [127].

Others evaluated the association between obesity in middle age and the risk of dementia later in life [128]. This multiethnic cohort of 10,276 men and women was initially evaluated from 1964 to 1973 when they were aged 40 to 45 years. From 1994 to 2003, dementia was present in 713 (6.9%) participants. Compared with the normal weight participants, those who were overweight had a 35% greater risk of dementia; the risk was 74% greater in those who were obese.

Kivipelto et al evaluated the association between midlife BMI and the development of dementia and AD [129]. After 21 years of follow-up, and adjustments for social demographic variables, the odds ratio for developing dementia and AD later in life was 2.4 for those with a BMI of 30 or more. Others also compared midlife BMI and the risk of vascular dementia and AD [130]. Compared with persons of normal weight, those whose BMI was 30 or more at midlife had twice the risk of AD and vascular dementia (odds ratio 2.01 and 1.95, respectively). Abdominal obesity is also an independent risk factor for AD [131]. Here, the odds ratio for developing AD in abdominally obese persons (waist-to-hip ratio > 0.90 for men; > 0.80 for women) was 2.5.

12. Psychological Problems and Quality of Life

In a study of 9,125 U.S. residents, obesity was associated with a 25% increased risk of mood and anxiety disorders [132]. This association held regardless of age, sex, or whether the
individual was a smoker. More recently, data from 41,654 respondents in the National Epidemiologic Survey on Alcohol and Related Conditions indicated that an increased BMI was significantly associated with an increased incidence of mood, anxiety, and personality disorders [133]. Moreover, in a recent study of 12,992 New Zealand residents 16 years and older, obesity was significantly associated with mood disorders [odds ratio (OR), 1.23], major depressive disorder (OR, 1.27), any anxiety disorder (OR, 1.46), and post-traumatic stress disorder (OR, 2.64) [134].

Obese women may be at a greater risk of psychological disorders than obese men, presumably due to greater social pressures on them to be of normal weight [135]. In this study, increased BMI among women was associated with both major depression and suicidal ideation. Cross-sectional and prospective data have also indicated that individuals with body dysmorphic disorder (BDD), a preconception with an imagined body “ugliness”, have high rates of suicidal ideation and attempts. For example, in a 4-year prospective study of suicidality in 185 subjects, a mean of 57.8% per year considered suicide and 2.6% attempted suicide [136]. Similarly, a study of 200 subjects with BDD had high rates of lifetime suicidality (78.0%) and attempted suicide (27.5%) [137]. BDD was the major reason for suicidal ideation (70.5%) and a past suicide attempt (about 50%).

13. Miscellaneous Obesity-Associated Disorders
   a. Inflammation
   Several studies have shown that obesity is associated with an increased prevalence and severity of nosocomial infections [138-140]. Since the mechanism whereby obesity increases the prevalence of infections was unknown, Fontana et al studied the effects of adiposity and weight loss on blood macrophage chemoattractant protein-1 (MCP-1) and interferon-gamma (INF-gamma), both of which are important components of the immune response to infectious agents [141]. At baseline, stimulated MCP-1 and INF-gamma productions were 93.6% and 88.8% lower, respectively, in obese compared with normal weight subjects. However, weight loss normalized the ability of stimulated blood mononuclear cells to produce MCP-1 and INF-gamma.

Others recently reported that there was a graded association between the blood leukocyte count and the incidence of four types of cancer (breast, colorectal, endometrial, lung), as well as an increased risk of cancer mortality in post-menopausal women [142]. Moreover, overweight and obese adults also have increased plasma C-reactive protein levels, indicating a state of low-grade inflammation [143].

   b. Non-Alcoholic Fatty Liver Disease
   The term “non-alcoholic steatohepatitis (NASH)” was coined in 1980 to describe “all the pathological and clinical features of non-alcohol liver disease associated with the pathological features commonly seen in alcoholic liver disease itself” [144]. Non-alcoholic fatty liver disease (NAFLD), the current recommended term, has markedly increased since 1980. The epidemic of NAFLD in the U.S. and other Western countries is highly significant. Indeed, NAFLD, probably the most prevalent pathological hepatic disorder, has been referred to as “another disease of affluence” [145]. As a result, NAFLD is commonly diagnosed in obese patients referred for evaluation of abnormal liver function tests (e.g., increased alanine amiotransferase, gamma-glutamyltransferase, etc.). Unfortunately, the increasing prevalence of obesity in children and adolescents is also associated with NAFLD [146-148].

Since NAFLD is very common in obese individuals, it may become a common cause of end-stage liver failure since it progresses from benign fatty liver changes (steatosis) to fatty changes with inflammation (steatohepatitis), cirrhosis, portal hypertension, and hepatocellular carcinoma [149]. Although this disorder is generally asymptomatic early in its’ course, some obese people complain of tiredness and abdominal discomfort, probably due to hepatomegaly, which occurs in about 75% of cases.
c. Other Diseases and Disorders

Other diseases/disorders associated with excess body weight include both dyslipidemia and physical disability (e.g., difficulty walking one-fourth mile, walking up 10 steps, lifting 10 pounds, stooping, dressing) [150]. Polycystic ovary syndrome [151], anovulatory infertility [152,153], and erectile dysfunction [154] have also been associated with obesity.

Summary

Because of the rapid increase in excess body weight in adults, as well as in adolescents and children in many world countries, it has been regarded as a pandemic. As a result, there has been a marked increase in the prevalence of numerous diseases/disorders, including coronary and cerebrovascular diseases, various cancers, type 2 diabetes, hypertension, osteoarthritis, gout, asthma and dementia, among others. Although there were an estimated 112,000 obesity-attributable deaths in the U.S. in 2000, the number is significantly greater today [155]. Moreover, the overall life expectancy is significantly shortened and the quality of life decreased in those who are excessively overweight. Indeed, unless this pandemic is reversed, morbidity and mortality will continue to increase and the steady rise in life expectancy since 1900 may soon end.

References


Excess body weight, morbidity, and mortality


