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Impact of Overweight on Morbidity and Mortality

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Background of this Report

Our report examines the available evidence in the scientific literature on the health risks of being overweight, with a specific focus on the relationship between BMI and type 2 diabetes, cardiovascular disease, cancer, and morbidity. Janine Pillitteri, Ph.D., conducted a review of the literature for relevant articles and wrote the initial draft of the report. We reviewed and extensively discussed the draft report on May 24, 2006, at a meeting of our panel in Washington, DC. Our panel was chaired by George Blackburn, M.D., Ph.D., and the members included Madeline Fernstrom, Ph.D., John Foreyt, Ph.D., Arthur Frank, M.D., and Anne Wolf, M.S., R.D. Following this meeting, we thoroughly reviewed modifications to the report and provided additional information. We then approved the final version of the report. This final report represents our panel's consensus on the state of the literature which demonstrates that overweight is an independent risk factor for obesity, type 2 diabetes, cardiovascular disease, and cancer.

Introduction

The most widely used measure of body fat is the body mass index (BMI, also called the Quetelet Index), defined as weight in kilograms divided by height in meters squared. The standard BMI categories that are recommended by the World Health Organization (World Health Organization, 1995; 1998) and supported by other advisory committees and expert panels to federal agencies (National Institutes of Health, 1998; 2000; US Department of Health and Human Services, 2005) are as follows[1]:

- Normal weight = 18.5-24.9 kg/m^2
- Overweight = 25-29.9 kg/m^2
- Obesity = 30 kg/m^2 or greater
    - Class I obesity = 30-34.9 kg/m^2
    - Class II obesity = 35-39.9 kg/m^2
    - Class III obesity = 40 or greater kg/m^2

This review examines the available evidence addressing the health risks of being overweight. Specifically, a literature review was conducted to identify studies that included an assessment of the relationship between BMI and type 2 diabetes, cardiovascular disease, cancer, and morbidity. Many older studies could not be included in the review because the BMI cutoffs used were not consistent with the standard categories identified above. For example, studies may have classified overweight as 25 or greater, thus incorporating the 'obesity' category (i.e., 30 or greater) into the 'overweight' category, making it impossible to do an assessment of the overweight category alone.

1 Question: Does overweight (BMI = 25-29.9) contribute to morbidity (i.e., obesity, type 2 diabetes, cancer, and cardiovascular disease)?

A number of large, population-based cohort studies and systematic reviews have been published that examine the association between overweight and morbidity. Most of the studies do not focus on defining the BMI at which risk of morbidity increases. Rather, they identify the amount of risk associated with the categories that correspond to normal weight, overweight, and obesity. Overall, the accumulated evidence is strong and indicates that overweight is associated with increased risk for several diseases including obesity, type 2 diabetes, several types of cancer, and cardiovascular disease (Field et al., 2001; McTigue et al., 2002; Must et al., 1999; National Task Force on the Prevention and Treatment of Obesity, 2000; NIH, 1998; 2000; Willett et al., 1999). In addition, in some cases this risk has been shown to increase in BMIs below 25 (i.e., in the normal weight range). Most of the studies that provide evidence of the health risks of overweight were published within the last 5 years.

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[1] Unless otherwise indicated, use of the terms 'normal weight', 'overweight', and 'obesity' refer to these specific BMI categories.

1.1 Obesity

The proportion of Americans who are obese has increased at an alarming rate in recent years. Between 1980 and 2002, obesity prevalence doubled in US adults (Flegal et al., 2002; Hedley et al., 2004) and is currently estimated at 32% (Ogden et al., 2006). The direct and indirect costs associated with overweight and obesity are estimated to exceed $75 billion per year (Finkelstein et al., 2004). Though the percentage of US medical expenditures associated with excess body weight are higher per capita for obese individuals, actual medical expenditures are in fact highest for overweight individuals, who constitute a much larger percentage of the population (Arterburn et al., 2005).

All individuals who are obese were at one time overweight, and research suggests that the progression from overweight to obesity is quite common; therefore, overweight is an independent risk factor for obesity. In a prospective, cohort study examining weight trends in over 9,000 young adults followed for 20 years, being mildly or moderately overweight at ages 20-22 was linked with a substantial incidence of obesity by ages 35-37 (McTigue et al., 2002). For example, 41% of white, 47% of Hispanic, and 66% of black women who had a BMI of 24-25 at ages 20-22 became obese by ages 35-37. Among women who had a BMI of 26-27.9 at 20-22 years of age, approximately 80% became obese by ages 35-37, regardless of racial or ethnic group. Therefore, overweight individuals are at increased risk of subsequent obesity as they age.

1.2 Type 2 Diabetes

In the United States, approximately 20.8 million people have diabetes, with over 6.2 million of these people unaware that they have the disease. Diabetes costs about $92 billion per year in direct medical expenditures and $40.8 billion in indirect expenditures through lost productivity for a total of $132.8 billion per year (Centers for Disease Control and Prevention, 2004; Hogan et al., 2003). Almost 90% of people with type 2 diabetes are overweight or obese (American Diabetes Association; www.diabetes.org).

Risk of developing diabetes increases dramatically as BMI increases, and several studies note increasing risk of diabetes at BMIs in the normal and overweight range (See Table 1). Colditz et al. (1990) reported a strong relationship between BMI and the risk of diabetes among women in the Nurses' Health Study. Even women with BMIs within the normal weight range (23-24) had a risk of diabetes 3.6 times greater than women with lower BMIs. Subsequent follow-up data from the Nurses' Health Study reported similar results (Colditz et al., 1995) – the risk of diabetes increased monotonically with BMIs greater than 22. For those with a BMI in the overweight range (defined as 25-28.9 in this particular study), the risk of diabetes was up to 10 times greater relative to those with a BMI of 22 or less. Hu et al. (2001) examined 16 years of follow-up data from the Nurses' Health Study and found that even a BMI at the high end of the normal range (i.e., 23-24.9) was associated with an increased risk of diabetes (relative risk [RR] of 2.67; 95% confidence interval [CI] 2.13-3.34) compared to a BMI of 23 or less. For women with a BMI of 25-29.9 (i.e., overweight), the relative risk of diabetes was 7.59 (95% CI 6.27-9.19).

To assess the risk of developing diabetes associated with overweight in both women and men, Field et al. (2001) analyzed data from two prospective cohort studies (i.e., Nurses' Health Study with women and the Health Professionals Follow-up Study with men). In both cohorts, the risk of developing diabetes increased progressively with increasing level of BMI. Among both women and men, those who were overweight (25-29.9) were significantly more likely to develop diabetes (RR = 4.6, 95% CI 3.9-5.4 for women; RR = 3.5, 95% CI 2.9-4.1 for men) than their same-sex, normal weight peers.

The risk of diabetes was also reported to increase progressively with increasing level of BMI in the San Antonio Heart Study, a recent prospective, population-based study (Burke et al., 2003) of Mexican Americans and non-Hispanic whites. Among Mexican Americans, those who were overweight had a risk 2.7 times greater than those of normal weight; for overweight, non-Hispanic whites, the risk of diabetes was 4.0 times greater than for those of normal weight.

A recent study (St-Onge et al., 2004) using NHANES III data examined the association between BMI and risk of the metabolic syndrome (i.e., a constellation of diabetes, hypertension, and dyslipidemia [abnormal lipid concentrations in the blood] risk factors) among individuals in the normal weight and slightly overweight range. The likelihood of having the metabolic syndrome increased with increasing BMI. More importantly, adults with a BMI in the lower end of the overweight range (i.e., 25-26.9) as well as adults of normal weight (i.e., 21-24.9) had a significantly increased risk of having the metabolic syndrome relative to those with a BMI of 18.5-20.9. An increased risk of the metabolic syndrome among overweight individuals relative to their normal weight peers was also recently reported by Janssen et al. (2004) in an earlier analysis of NHANES III data (odds ratio [OR] = 2.51, 95% CI 1.70-3.70 for women; OR = 2.49, 95% CI 1.81-3.44 for men).

1.3 Cancer

Cancer, the second most common cause of death in the US, currently affects about 9.6 million people (approximately 3% of the population). Estimates of the economic impact of cancer are about $206.3 billion, with indirect productivity losses contributing approximately $95 billion of this figure (National Institutes of Health, 2005; Eyre et al., 2004).

Several case-control and prospective cohort studies have found that the risk of several types of cancers increases with increasing BMI (see Table 2), and individuals who are overweight are at increased risk of developing certain cancers (Bianchini et al., 2002). A recent review (Calle & Kaaks, 2004) summarized the evidence on overweight, obesity, and cancer risk using a comprehensive evaluation of the available literature on the issue (International Agency for Research on Cancer, 2002). The review concluded that based on the results from epidemiological studies, those who are overweight are at increased risk of developing several cancer types including colon cancer (RR = 1.5 for men and 1.2 for women); postmenopausal breast cancer in women (RR = 1.3); endometrial cancer (RR = 2.0); kidney cancer (RR = 1.5); esophageal adenocarcinoma (RR = 2.0); pancreatic cancer (RR = 1.3); gallbladder cancer (RR = 1.5); and gastric cardia adenocarcinoma (RR = 1.5) (95% confidence intervals not reported).

A more recent report released on October 31, 2007 (World Cancer Research Fund / American Institute for Cancer Research, 2007) reached the same conclusions as the earlier review (Calle & Kaaks, 2004). This comprehensive report on global cancer prevention concluded that being overweight increases the risk of esophageal adenocarcinoma, pancreatic cancer, colorectal cancer, postmenopausal breast cancer, endometrial cancer, and kidney cancer. In addition, the evidence indicated a very probable association between overweight and gallbladder cancer.

The association between BMI and risk of mortality from cancer was examined using data from a prospective study of a large cohort of U.S. adults (Cancer Prevention Study II) (Calle et al., 2003). The authors reported that, compared to women of normal weight (18.5-24.9), overweight women (i.e., BMI of 25-29.9) had a significantly elevated risk of death from all cancers (RR = 1.08, 95% CI 1.05-1.11), as well as colorectal cancer (RR = 1.10, 95% CI 1.01-1.19); breast cancer (RR = 1.34, 95% CI 1.23-1.46); uterine cancer (RR = 1.50, 95% CI 1.26-1.78); ovarian cancer (RR = 1.15, 95% CI 1.02-1.29); kidney cancer (RR = 1.33, 95% CI 1.08-1.63) and non-Hodgkin's lymphoma (RR = 1.22, 95% CI 1.06-1.40). In comparison to men of normal weight,

men with a BMI between 25-29.9 had significantly elevated risks of colorectal cancer (RR = 1.20, 95% CI 1.12-1.30); pancreatic cancer (RR = 1.13, 95% CI 1.03-1.25); prostate cancer (RR = 1.08, 95% CI 1.01-1.15); kidney cancer (RR = 1.18, 95% CI 1.02-1.37); multiple myeloma (RR = 1.18, 95% CI 1.01-1.39); and leukemia (RR = 1.14, 95% CI 1.02-1.28). Calle et al. (2003) estimated that more than 90,000 annual cancer-related deaths could be prevented if all adults had a BMI less than 25 throughout their lives.

1.4 Cardiovascular Disease

Approximately 21% of the US population has one or more types of cardiovascular disease which includes heart disease, stroke, atherosclerosis, coronary heart disease, coronary artery disease, hypertension, congestive heart failure, and congenital cardiovascular defects. The estimated direct and indirect costs of cardiovascular disease is $403 billion (Eyre et al., 2004; National Institutes of Health, 2005).

Published reports strongly suggest that being overweight is an important risk factor for cardiovascular disease (Anderson & Konz, 2001; Eckel & Krauss, 1998; Krauss et al., 1998), and those with BMIs in the overweight range carry elevated risk relative to those of normal weight (see Table 3). Using data from the Nurses' Health Study, Willett et al. (1995) examined the association between BMI and coronary heart disease risk in women. Risk of coronary heart disease increased monotonically with increasing BMI, and even women with BMIs in the normal weight range (23-24.9) were at excess risk (RR = 1.46, 95% CI 1.20-1.77) compared to those with a BMI of less than 21. Women with BMIs within the overweight range (25-28.9) had twice the risk of coronary heart disease (RR = 2.06, 95% CI 1.72-2.48). Similarly, using the Health Professionals Follow-up Study data, it was reported that men within the overweight category (25-28.9) had a relative risk of coronary heart disease of 1.49 (95% CI 1.11-2.00) compared to men with a BMI of less than 23 (Rimm et al., 1995).

Field et al. (2001) examined the risk of hypertension, hypercholesterolemia, and heart disease in the 10-year follow-up of women and men, respectively, in the Nurses' Health Study and the Health Professionals Follow-up Study. In both cohorts, those who were overweight were significantly more likely than their normal weight peers to develop hypertension, hypercholesterolemia, and heart disease (for women: RR = 1.7, 95% CI 1.6-1.8; RR = 1.1, 95% CI = 1.1-1.2; RR = 1.4, 95% CI = 1.2-1.5, respectively; for men: RR = 1.7, 95% CI 1.6-1.8; RR = 1.3, 95% CI 1.2-1.3; RR = 1.5, 95% CI 1.4-1.7, respectively). Janssen et al. (2004) found a similar association between BMI and cardiovascular disease risk factors using NHANES III data. BMI was related to hypertension and hypercholesterolemia in a graded fashion – as BMI increased, the odds of these conditions also increased. The odds of hypertension and hypercholesterolemia, respectively, were significantly greater for overweight men and women than for their normal weight counterparts (for women: OR = 1.92, 95% CI 1.56-2.35; OR = 2.26, 95% CI 1.80-2.82; for men: OR = 1.75, 95% CI 1.44-2.11; OR = 1.57, 95% CI 1.25-1.97).

Cardiovascular risk factors were also shown to be significantly influenced by BMI in a large, population-based study of Dutch men and women (Monitoring Cardiovascular Health in the Netherlands) (Lean et al., 1999). Compared to those of normal weight, overweight individuals were at greater risk of hypertension and hypercholesterolemia – the odds ratios for hypertension were 1.95 (95% CI 1.57-2.43) for women and 2.89 (95% CI = 2.27-3.68) for men, and the odds ratios for hypercholesterolemia were 1.52 (95% CI = 1.29-1.79) for women and 1.58 (95% CI 1.33-1.88) for men.

Using data from the Framingham Heart Study cohort, Wilson et al. (2002) demonstrated an increased risk of hypertension, hypercholesterolemia, and cardiovascular disease (which

included angina pectoris, myocardial infarction, coronary heart disease, or stroke) among overweight men and women. In comparison to those of normal weight, the risk of hypertension and hypercholesterolemia, respectively, was increased for overweight BMIs (for women: RR = 1.75, 95% CI 1.54-2.00; RR = 1.35, 95% CI 1.20-1.52; for men: RR = 1.46, 95% CI 1.24-1.75; RR = 1.19, 95% CI 1.04-1.37). The same relationship was found for overweight BMIs and risk of cardiovascular disease in women (RR = 1.20, 95% CI 1.03-1.41) and in men (RR = 1.21, 95 CI 1.05-1.40).

2 Question: Is overweight (BMI = 25-29.9) associated with all-cause mortality?

An extensive body of literature exists on the relationship between body weight and mortality. It is well accepted that *obesity* is associated with increased mortality, particularly at the higher levels of obesity (e.g., BMI of 35 or greater) (Allison et al., 1999; NIH, 1998; Stevens et al., 1998). However, the relationship between body weight and mortality across the entire weight spectrum has been the subject of intense debate and controversy for over 20 years (Flegal et al., 2005; Manson et al., 1987; Willet et al., 1999). Although it is clear that marked obesity is associated with mortality, the impact of being mildly to moderately overweight is less certain. Recent evidence suggests a stronger relationship between overweight and mortality than had previously existed.

A diversity of findings exist regarding the nature of the relationship between weight and mortality. Most recently it has been suggested that the relationship is J-shaped or U-shaped, with increased death rates among both the leanest and the heaviest people. This controversy exists in part because most studies include one or more methodological limitations which preclude a valid assessment of the relationship between body weight and mortality (Manson et al., 1987; Willett et al., 1999). A major methodological limitation and potential source of bias is the failure to account for cigarette smoking. Since smoking tends to be more prevalent among those with lower BMIs and is an independent risk factor for mortality, failure to control for its effects will make leaner persons appear to be at elevated risk of mortality. A second limitation concerns inappropriate statistical control for the physiological effects of excess body fat such as hypertension, dyslipidemia, and diabetes, thus artificially removing some of the effects of being overweight. Conditions such as these, rather than being confounding variables, are effects of obesity and links in the causal pathway by which obesity exerts its influence on mortality risk. A third major problem with studies of body weight and mortality is the failure to consider bias from illness-related weight loss that leads to mortality. This is the issue of reverse causation (i.e., weight loss as a result of illness that ultimately leads to mortality creates the appearance of higher mortality among those with lower weights). Although this is most apparent among the very lean, the weight loss associated with illness will lead to an underestimate of the weight-mortality slope throughout the weight range.

Very few studies to date have attempted simultaneously to consider these methodological limitations when investigating the association between body weight and mortality. As a result, one or more of these limitations is present in most studies, and the controversy continues regarding the relationship between BMI and mortality.

A recent study estimated mortality associated with underweight, overweight, and obesity using all available mortality data from the National Health and Nutrition Examination Surveys (NHANES; including NHANES I, II, and III) (Flegal et al., 2005). However, even this study is not without its critics (Ding, 2005; Greenberg, 2005; Strickler et al., 2005; Willett et al., 2005). The NHANES surveys used in this study each included a different nationally representative cross-

sectional sample of the US population. Using the combined survey data, the results indicated that overweight is not associated with an increased risk of mortality relative to the normal weight category (RR = 0.83, 95% CI 0.65-1.06 for ages 25-59; RR = 0.95, 95% CI 0.80-1.13 for ages 60-69; RR = 0.91, 95% CI 0.83-1.01 for ages 70 and older). Overweight was actually associated with a reduction in mortality – 86,094 fewer deaths (95% CI -161,223 to -10,966) – relative to normal weight. Underweight and obesity, however, were associated with increased mortality, with 33,746 excess deaths (95% CI 15,726-51,766) due to underweight and 111,909 excess deaths (95% CI 53,754-170,064) due to obesity.

The authors reported adjustments for confounding factors in their analyses, and they also conducted extensive supplemental analyses to determine whether the estimates of excess deaths were affected by factors such as smoking status, weight loss caused by illness, or weight stability. Even after they excluded smokers from the analysis, excluded the first 5 years of follow-up during which sick subjects are expected to die, and restricted the analysis to subjects who maintained their weight for 10 years, the broad pattern of results did not change.

A more recent prospective study, however, did find an increased risk of mortality due to overweight (Adams et al., 2006). Data from the National Institutes of Health -- American Association of Retired Persons (AARP) Diet and Health Study was used to examine BMI and risk of death from any cause in 527,265 U.S. adults who were 50 to 71 years of age at enrollment in 1995-1996. The authors reported adjustments for potential bias due to pre-existing disease and confounding due to smoking status by using midlife BMI values and restricting analyses to never smokers -- after such adjustments, the data showed an increased risk of mortality even at moderate elevations in BMI, including overweight. For example, when analyses were restricted to healthy individuals who had never smoked, overweight was associated with increased mortality. Similarly, the risk of death among those who were overweight at age 50 and had never smoked was 20-40% higher than that of those who had a BMI of 23.5 to 24.9 at the same age. Therefore, although the authors indicate that they "cannot conclude with complete certainty that the relation between adiposity and the risk of death is causal" (p. 777), their findings suggest that overweight is associated with an increased risk of death.

The recent study by Adams and colleagues suggests a somewhat stronger association between overweight and mortality than had previously been believed to be the case. However, overweight is very strongly associated with morbidity, including type 2 diabetes, cardiovascular disease, and cancer.

3 References

Adams KF, Schatzkin A, Harris TB, Kipnis V, Mouw T, Ballard-Barbash R, Hollenback A, Leitzmann MF. Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. NEJM 2006;355:763-778.

Allison DB, Fontaine KR, Manson JE, Stevens J, Van Itallie TB. Annual deaths attributable to obesity. JAMA 1999;282:1530-1538.

Anderson JW, Konz EC. Obesity and disease management: effects of weight loss on comorbid conditions. Obes Res 2001;9(Suppl 4):326S-334S.

Arterburn DE, Maciejewski ML, Tsevat J. Impact of morbid obesity on medical expenditures in adults. Internat J Obes 2005;29:334-339.

Bianchini F, Kaaks R, Vainio H. Overweight, obesity, and cancer risk. Lancet Oncol 2002;3:565-574.

Burke JP, Williams K, Venkat Narayan KM, Leibson C, Haffner SM, Stern MP. A population perspective on diabetes prevention: Whom should we target for preventing weight gain? Diabetes Care 2003;26:1999-2004.

Calle EE, Kaaks R. Overweight, obesity and cancer: Epidemiological evidence and proposed mechanisms. Nature 2004;4:579-591.

Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 2003;348:1625-1638.

Centers for Disease Control and Prevention. The burden of chronic diseases and their risk factors: National and state perspectives. 2004. http://www.cdc.gov/nccdphp/burdenbook2004/pdf/burden_book2004.pdf.

Colditz GA, Willett WC, Stampfer MJ, et al. Weight as a risk factor for clinical diabetes in women. Am J Epidemiol 1990;132:501-513.

Colditz GA, Willett WC, Rotnitzky A, Manson JE. Weight gain as a risk factor for clinical diabetes mellitus in women. Ann Intern Med 1995;122:481-486.

Ding EL. Underweight, overweight, obesity, and excess deaths. Letter to the editor. JAMA 2005;294:552.

Eckel RH, Krauss RM. American Heart Association call to action: obesity as a major risk factor for coronary heart disease. Circulation 1998;97:2099-2100.

Eyre H, Kahn R, Roberson RM, et al. Preventing cancer, cardiovascular disease, and diabetes: A common agenda for the American Cancer Society, the American Diabetes Association, and the American Heart Association. Stroke 2004;35:1999-2010.

Field AE, Coakley EH, Must A, et al. Impact of overweight on the risk of developing common chronic diseases during a 10-year period. Arch Intern Med 2001;161:1581-1586.

Finkelstein EA, Fiebelkorn IC, Wang G. State-level estimates of annual medical expenditures attributable to obesity. Obes Res 2004:12:18-24.

Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999-2000. JAMA 2002;288:1723-1727.

Flegal KM, Graubard BI, Williamson DF, Gail MH. Excess deaths associated with underweight, overweight, and obesity. JAMA 2005;293:1861-1867.

Greenberg J. Underweight, overweight, obesity, and excess deaths. Letter to the editor. JAMA 2005;294:552.

Hedley AA, Ogden CL, Johnson CL, Carroll MD, Curtin LR, Flegal KM. Prevalence of overweight and obesity among US children, adolescents, and adults, 1999-2002. JAMA 2004;291:2847-2850.

Hogan P, Dall T, Nikolov P. American Diabetes Association. Economic costs of diabetes in the U.S. in 2002. Diabetes Care 2003;26:917-932.

Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG, Willett WC. Diet, lifestyle, and the risk of type 2 diabetes in women. NEJM 2001;345;790-797.

James WPT, Jackson-Leach R, Mhurchu CN, Kalamara E, Shayeghi M, Rigby NJ, Nishida C, Rodgers A. Overweight and obesity (high body mass index). In: M Ezzati, AD Lopez, A Rodgers, CJL Murray (eds.) Comparative Quantification of Health Risks – Global and Regional Burden of Disease Attributable to Selected Major Risk Factors. Volume 1 (pp.497-596). Geneva: World Health Organization, 2004.

Janssen I, Katzmarzyk PT, Ross R. Waist circumference and not body mass index explains obesity-related health risk. Am J Clin Nutr 2004;79:379-384.

International Agency for Research on Cancer. IARC Handbooks of Cancer Prevention. Weight Control and Physical Activity. International Agency for Research on Cancer, Lyon, 2002.

Krauss RM, Winston M, Fletcher BJ, Grundy SM. Obesity: Impact on cardiovascular disease. Circulation 1998;98:1472-1476.

Lean ME, Han TS, Seidell JC. Impairment of health and quality of life using new US federal guidelines for the identification of obesity. Arch Intern Med 1999;159:837-843.

Manson JE, Stampfer MJ, Hennekens CH, Willett WC. Body weight and longevity: A reassessment. JAMA 1987;257:353-358.

McTigue KM, Garrett JM, Popkin BM. The natural history of the development of obesity in a cohort of young U.S. adults between 1981 and 1998. Ann Intern Med 2002;136;857-864.

Must A, Spadano J, Coakley EH, Field AE, Colditz G, Dietz WH. The disease burden associated with overweight and obesity. JAMA 1999;282:1523-1529.

National Institutes of Health. NHLBI Fact Book Fiscal Year 2005. Bethesda, MD: National Institutes of Health; 2005. http://www.nhlbi.nih.gov/about/05factbk.pdf

National Institutes of Health. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report. NIH Publication No. 98-4083. September 1998. http://www.nhlbi.nih.gov/guidelines/obesity/ob_gdlns.pdf

National Institutes of Health. The Practical Guide. Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. NIH Publication No. 00-4084. October 2000. http://www.nhlbi.nih.gov/guidelines/obesity/prctgd_b.pdf

National Task Force on the Prevention and Treatment of Obesity. Overweight, obesity, and health risk. Arch Intern Med 2000;160:898-904.

Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999-2004. JAMA 2006;295:1549-1555.

Rimm EB, Stampfer JM, Giovannucci E, Ascherio A, Spiegelman D, Colditz GA, Willett WC. Body size and fat distribution as predictors of coronary heart disease among middle-aged and older U.S. men. Am J Epidemiol 1995;141:1117-1127.

Stevens J, Cai J, Pamuk ER, Williamson DF, Thun MJ, Wood JL. The effect of age on the association between body-mass index and mortality. NEJM 1998;338:1-7.

St-Onge MP, Janssen I, Heymsfield SB. Metabolic syndrome in normal-weight Americans: New definition of the metabolically obese, normal-weight individual. Diabetes Care 2004;27:2222-2228.

Strickler HD, Hall C, Wylie-Rosett J, Rohan T. Underweight, overweight, obesity, and excess deaths. Letter to the editor. JAMA 2005;294:551-552.

US Department of Health and Human Services and US Department of Agriculture. Dietary Guidelines for Americans, 2005. 6th Edition, Washington, DC: US Government Printing Office, January 2005. http://www.health.gov/dietaryguidelines/dga2005/document/pdf/DGA2005.pdf

Willett WC, Dietz WH, Colditz GA. Guidelines for healthy weight. NEJM 1999;341:427-434.

Willett WC, Hu FB, Colditz GA, Manson JE. Underweight, overweight, obesity, and excess deaths. Letter to the editor. JAMA 2005;294:551.

Willett WC, Manson JE, Stampfer MJ, Colditz GA, Rosner B, Speizer FE, Hennekens CH. Weight, weight change, and coronary heart disease in women. JAMA 1995;273:461-465.

Wilson PWF, D'Agostino RB, Sullivan L, Parise H, Kannel WB. Overweight and obesity as determinants of cardiovascular risk. The Framingham experience. Arch Intern Med 2002;162:1867-1872.

World Cancer Research Fund / American Institute for Cancer Research. Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective. Washington, DC: AICR, 2007.

World Health Organization. Obesity: Preventing and managing the global epidemic. Report of a WHO Consultation on Obesity, Geneva, 3-5 June, 1997. World Health Organization. Geneva: 1998.

World Health Organization. Physical Status: The Use and Interpretation of Anthropometry. Geneva, World Health Organization, 1995. WHO Technical Report Series 854.

Table 1. Relative risk (and 95% confidence intervals) of Type 2 diabetes

Colditz et al. (1990)* Nurses' Health Study		**Colditz et al. (1995)** Nurses' Health Study		**Hu et al. (2001)** Nurses' Health Study		**Field et al. (2001)** Nurses' Health Study Health Professionals Follow-up Study	
WOMEN		**WOMEN**		**WOMEN**		**WOMEN**	
BMI	RR	BMI	RR (95%CI)	BMI	RR (95%CI)	BMI	RR (95%CI)
<22	1.0	<22	1.0	<23	1.0	<25	1.0
22-22.9	2.2	22-22.9	2.9 (2.0-4.1)	23-24.9	2.67 (2.13-3.34)	25-29.9	4.6 (3.9-5.4)
23-23.9	3.6	23-23.9	4.3 (3.1-5.8)	25-29.9	7.59 (6.27-9.19)	30-34.9	10.0 (8.4-11.8)
24-24.9	3.1	24-24.9	5.0 (3.6-6.6)	30-34.9	20.1 (16.6-24.4)	≥35	17.0 (14.2-20.5)
25-26.9	5.5	25-26.9	8.1 (6.2-10.5)	≥35	38.8 (31.9-47.2)		
27-28.9	10.1	27-28.9	15.8 (12.7-19.8)				
29-30.9	20.0	29-30.9	27.6 (22.7-33.5)				
31-32.9	29.6	31-32.9	40.3 (33.7-48.3)				
33-34.9	40.2	33-34.9	54.0 (45.6-64.0)				
≥35	60.9	≥35	93.2 (81.4-106.6)				
						MEN	
						BMI	RR (95%CI)
						<25	1.0
						25-29.9	3.5 (2.9-4.1)
						30-34.9	11.2 (9.3-13.6)
						≥35	23.4 (19.4-33.2)

Table 1 continued on next page

Table 1. Continued

Burke et al. (2003)* San Antonio Heart Study		St. Onge et al. (2004)† NHANES III		Janssen et al. (2004)† NHANES III	
MEXICAN-AMERICANS		**WOMEN**		**WOMEN**	
BMI	RR	BMI	RR (95%CI)	BMI	RR (95%CI)
<25	1.0	18.5-20.9	1.0	18.5-24.9	1.0
≥25-29.9	2.7	21-22.9	3.68 (1.89-7.19)	25-29.9	2.51 (1.70-3.70)
≥30-34.9	5.1	23-24.9	7.51 (3.90-14.46)	30-34.9	4.27 (3.06-5.93)
≥35	6.8	25-26.9	18.58 (10.10-34.17)		
NON-HISPANIC WHITES		**MEN**		**MEN**	
BMI	RR	BMI	RR (95%CI)	BMI	RR (95%CI)
<25	1.0	18.5-20.9	1.0	18.5-24.9	1.0
≥25-29.9	4.0	21-22.9	2.97 (1.24-7.15)	25-29.9	2.49 (1.81-3.44)
≥30-34.9	10.1	23-24.9	4.95 (2.13-11.54)	30-34.9	5.08 (3.56-7.27)
≥35	11.2	25-26.9	9.88 (4.29-22.75)		

* Confidence intervals not reported
† Relative risk of the metabolic syndrome, which includes diabetes, hypertension, and dyslipidemia

Table 2. Relative risk (and 95% confidence intervals) of different forms of cancer

	Calle et al. (2003)[†]				Calle & Kaaks (2004)[*]		
	MEN		WOMEN				
Colorectal cancer	BMI	RR (95%CI)	BMI	RR (95%CI)	Colorectal cancer (men)	BMI	RR
	18.5-24.9	1.0	18.5-24.9	1.0		25-29.9	1.5
	25-29.9	1.20 (1.12-1.30)	25-29.9	1.10 (1.01-1.19)		≥30	2.0
	30-34.9	1.47 (1.30-1.66)	30-34.9	1.33 (1.17-1.51)			
	35-39.9	1.84 (1.39-2.41)	35-39.9	1.46 (0.94-2.24)			
Breast cancer	N/A		BMI	RR (95%CI)	Colorectal cancer (women)	BMI	RR
			18.5-24.9	1.0		25-29.9	1.2
			25-29.9	1.34 (1.23-1.46)		≥30	1.5
			30-34.9	1.63 (1.44-1.85)			
			35-39.9	1.70 (1.33-2.17)			
Uterine cancer	N/A		BMI	RR (95%CI)	Postmenopausal breast cancer (women)	BMI	RR
			18.5-24.9	1.0		25-29.9	1.3
			25-29.9	1.50 (1.26-1.78)		≥30	1.5
			30-34.9	2.53 (2.02-3.18)			
			35-39.9	2.77 (1.83-4.18)			
Ovarian cancer	N/A		BMI	RR (95%CI)	Endometrial cancer (women)	BMI	RR
			18.5-24.9	1.0		25-29.9	2.0
			25-29.9	1.15 (1.02-1.29)		≥30	3.5
			30-34.9	1.16 (0.96-1.40)			
			35-39.9	1.51 (1.12-2.02)			
Kidney cancer	BMI	RR (95%CI)[‡]	BMI	RR (95%CI)	Kidney cancer (men and women)	BMI	RR
	18.5-24.9	1.0	18.5-24.9	1.0		25-29.9	1.5
	25-29.9	1.18 (1.02-1.37)	25-29.9	1.33 (1.08-1.63)		≥30	2.5
	30-34.9	1.36 (1.06-1.74)	30-34.9	1.66 (1.23-2.24)			
	35-39.9	1.70 (0.99-2.92)	35-39.9	1.70 (0.94-3.05)			

Table 2 continued on next page

	Calle et al. (2003)[†]				Calle & Kaaks (2004)[*]		
	MEN		WOMEN				
Non-Hodgkins lymphoma	NS		BMI	RR (95%CI)	Esophageal adenocarcinoma (men and women)	BMI	RR
			18.5-24.9	1.0		25-29.9	2.0
			25-29.9	1.22 (1.06-1.40)		≥30	3.0
			30-34.9	1.20 (0.95-1.51)			
			35-39.9	1.95 (1.39-2.72)			
Pancreatic cancer	BMI	RR (95%CI)	NS		Pancreatic cancer (men and women)	BMI	RR
	18.5-24.9	1.0				25-29.9	1.3
	25-29.9	1.13 (1.03-1.25)				≥30	1.7
	30-34.9	1.41 (1.19-1.66)					
	35-39.9	1.49 (0.99-2.22)					
Prostate cancer	BMI	RR (95%CI)	N/A		Gallbladder cancer (men and women)	BMI	RR
	18.5-24.9	1.0				25-29.9	1.5
	25-29.9	1.08 (1.01-1.15)				≥30	2.0
	30-34.9	1.20 (1.06-1.36)					
	35-39.9	1.34 (0.98-1.83)					
Multiple myeloma	BMI	RR (95%CI)[‡]	NS		Gastric cardia adenocarcinoma (men and women)	BMI	RR
	18.5-24.9	1.0				25-29.9	1.5
	25-29.9	1.18 (1.01-1.39)				≥30	2.0
	30-34.9	1.44 (1.10-1.89)					
	35-39.9	1.71 (0.93-3.14)					
Leukemia	BMI	RR (95%CI)	NS				
	18.5-24.9	1.0					
	25-29.9	1.14 (1.02-1.28)					
	30-34.9	1.37 (1.13-1.67)					
	35-39.9	1.70 (1.08-2.66)					

[*]Confidence intervals not reported
[†]p for trend = $p<0.001$ unless otherwise noted
[‡]$p=0.002$
N/A = Not Applicable
NS = Not Significant

Table 3. Relative risk (and 95% confidence intervals) of cardiovascular disease

Willet et al. (1995)* Nurses' Health Study		Rimm et al. (1995)* Health Professionals Follow-up Study		Janssen et al. (2004)† NHANES III		Field et al. (2001)‡ Nurses' Health Study Health Professionals Follow-up Study	
WOMEN		**MEN**		**WOMEN**		**WOMEN**	
BMI	RR	BMI	RR (95%CI)	BMI	RR of hypertension	BMI	RR of hypertension
<21	1.0	<23	1.0	18.5-24.9	1.0	<25	1.0
21-22.9	1.19 (0.98-1.44)	23-24.9	1.18 (0.86-1.63)	25-29.9	1.92 (1.56-2.35)	25-29.9	1.7 (1.6-1.8)
23-24.9	1.46 (1.20-1.77)	25-28.9	1.49 (1.11-2.00)	30-34.9	3.01 (2.28-3.98)	30-34.9	2.1 (1.9-2.2)
25-28.9	2.06 (1.72-2.48)	29-32.9	1.97 (1.35-2.88)			≥35	2.3 (2.1-2.6)
≥29	3.56 (2.96-4.29)	≥33	3.06 (1.76-5.32)	BMI	RR of hypercholesterolemia	BMI	RR of hypercholesterolemia
				18.5-24.9	1.0	<25	1.0
				25-29.9	2.26 (1.80-2.82)	25-29.9	1.1 (1.1-1.2)
				30-34.9	1.87 (1.46-2.38)	30-34.9	0.9 (0.9-1.0)
						≥35	0.7 (0.6-0.7)
						BMI	RR of heart disease
						<25	1.0
						25-29.9	1.4 (1.2-1.5)
						30-34.9	1.5 (1.3-1.7)
						≥35	1.5 (1.3-1.8)
				MEN		**MEN**	
				BMI	RR of hypertension	BMI	RR of hypertension
				18.5-24.9	1.0	<25	1.0
				25-29.9	1.75 (1.44-2.11)	25-29.9	1.7 (1.6-1.8)
				30-34.9	2.99 (2.33-3.84)	30-34.9	2.7 (2.4-3.0)
						≥35	3.0 (2.3-3.9)
				BMI	RR of hypercholesterolemia	BMI	RR of hypercholesterolemia
				18.5-24.9	1.0	<25	1.0
				25-29.9	1.57 (1.25-1.97)	25-29.9	1.3 (1.2-1.3)
				30-34.9	1.70 (1.20-2.41)	30-34.9	1.2 (1.1-1.3)
						≥35	1.3 (1.1-1.6)
						BMI	RR of heart disease
						<25	1.0
						25-29.9	1.5 (1.4-1.7)
						30-34.9	2.0 (1.7-2.3)
						≥35	2.2 (1.5-3.1)

Table 3 continued on next page

Table 3. continued

Lean et al. (1999)[†] Monitoring Cardiovascular Health in the Netherlands Project		Wilson et al. (2002)[†] Framingham Heart Study	
WOMEN		**WOMEN**	
BMI	RR of hypertension	BMI	RR of hypertension
<25	1.0	18.5-24.9	1.0
25-29.9	1.95 (1.57-2.43)	25-29.9	1.75 (1.54-2.00)
≥30	4.75 (3.72-6.07)	≥30	2.75 (2.32-3.27)
BMI	RR of hypercholesterolemia	BMI	RR of hypercholesterolemia
<25	1.0	18.5-24.9	1.0
25-29.9	1.52 (1.29-1.79)	25-29.9	1.35 (1.20-1.52)
≥30	1.38 (1.10-1.72)	≥30	1.16 (0.99-1.36)
MEN		**MEN**	
BMI	RR of hypertension	BMI	RR of hypertension
<25	1.0	18.5-24.9	1.0
25-29.9	2.89 (2.27-3.68)	25-29.9	1.46 (1.24-1.75)
≥30	5.88 (4.43-7.79)	≥30	2.21 (1.75-2.79)
BMI	RR of hypercholesterolemia	BMI	RR of hypercholesterolemia
<25	1.0	18.5-24.9	1.0
25-29.9	1.58 (1.33-1.88)	25-29.9	1.19 (1.04-1.37)
≥30	2.22 (1.76-2.81)	≥30	1.11 (0.88-1.38)

[*]Cardiovascular disease defined as coronary heart disease
[†]Cardiovascular disease defined as hypertension and hypercholesterolemia
[‡]Cardiovascular disease defined as hypertension, hypercholesterolemia, and heart disease