THE DISEASE BURDEN ASSOCIATED WITH OVERWEIGHT AND OBESITY

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I. INTRODUCTION

Many epidemiological studies have considered the impact of increasing body weight, body mass index (BMI), and other anthropometric measurements on the risk of chronic disease (1, 2), including coronary heart disease (CHD), type 2 diabetes mellitus (T2DM), hypertension, stroke, and cancers of the breast, endometrium, and colon (3, 4).

Because body fat distribution is linked to obesity and is of particular importance in the etiology of certain chronic diseases, this chapter provides the reader with an overview of the epidemiological evidence linking both excess body weight and body fat distribution to the risk of several chronic diseases in adults. This chapter complements Chapter 1, in which the indicators of obesity are covered in detail, and Chapter 13, which provides a full discussion of the pathophysiology of obesity-related health conditions.

II. WEIGHT, FAT, AND FLUX

1. General and Central Adiposity

Although BMI is commonly employed as the measure of general or overall adiposity in most observational studies, growing evidence suggests that a central (abdominal) fat distribution pattern, as reflected by a higher waist circumference (WC) or waist-to-hip ratio (WHR), may be a better measure of risk than elevated body weight particularly among older adults (5-7). For example, individuals with a higher proportion of abdominal fat have a greater risk of developing CHD (8, 9), T2DM (10-13), and cardiovascular disease (CVD) than those with less abdominal fat. Using WC data from the National Health and Nutrition Examination Survey (NHANES), Li and colleagues observed that the prevalence of abdominal obesity has increased continuously

over the past 15 years (14). Abdominal obesity, as reflected by WHR, presumably contributes to the risk of CVD through its mediated effects on other cardiovascular risk factors, such as hypertension, dyslipidemia, insulin resistance or glucose intolerance, and adipocyte regulation of coagulation and inflammatory pathways (15-17).

Abdominal obesity is one of the key conditions in a cluster of disorders known as the metabolic syndrome, which is additionally characterized by disturbed glucose or insulin metabolism, mild dyslipidemia, and hypertension (18). The metabolic syndrome, discussed in detail in Chapter 9, is associated with increased risk of both T2DM and CVD (19-21). The prevalence of metabolic syndrome is high, with an estimated 47 million Americans affected; the highest prevalence was among adults aged 60 years and older (22). . In addition, the prevalence of metabolic syndrome appears to be increasing among adolescents (23).

Some researchers have suggested that WC or WHR are better predictors of obesity-related health risk than BMI (13, 24, 25). However, both general adiposity, captured by BMI, and abdominal adiposity, captured by WC or WHR, are independent risk factors for certain diseases; each measure may thus contribute distinct information about health risks associated with overweight and obesity (3, 26). Nevertheless, both general and abdominal obesity arise as a consequence of weight gain, and, conversely, both respond to weight loss. Therefore, it is important to elucidate the mechanisms and independent roles of body fat distribution on the etiology of chronic diseases.

2. Weight Flux

Weight fluctuations as a result of repeated failures to maintain weight loss are associated with an increased risk of developing chronic diseases (27-29) and excess mortality (30). A small number of studies suggest that weight fluctuation is associated with increased mortality; however, these findings may reflect inadequate or incomplete measures, or failure to incorporate variables that accurately characterize weight changes. Difficulties in distinguishing changes as weight gain, weight loss, or weight flux with limited time points, together with the need to differentiate between intentional and unintentional weight loss, increase the complexity of examining weight flux in relation to disease risk. In the Chicago Western Electric Company Study, which included multiple weight measures that clearly distinguished weight gain, weight loss, and weight variability, did not find that weight flux predicted increased mortality (31). Findings from the British Regional Heart Study suggested that increased mortality associated with weight loss and weight fluctuation was due to the effects of preexisting disease and smoking rather than the effects of weight loss and weight flux, per se (32).

3. Broad Consequences of Obesity

Clearly, the health consequences and compromised quality of life associated with obesity provide major incentive to address the continuing obesity epidemic. Compared with adults of normal weight, adults with BMI >40 kg/m2 have an approximately 64% higher risk of T2DM, a 54% higher risk of high blood pressure, a 9% higher risk for high cholesterol, a 17% for higher risk for asthma, a 34% higher risk for arthritis, and a 32% higher risk for generally fair or poor

health (Mokdad, Ford et al. 2003). However, despite recognition of these effects, the epidemic of overweight and obesity has not reversed (Flegal, Carroll et al. 2012) and continues to escalate in minority groups (33, 34). Levels are also high in much of the developed and developing world (35). According to data from the continuing NHANES, 65% of American adults are overweight, and a further 35% are obese, with the prevalence varying among the three major racial/ethnic groups in the US (33). The prevalence of obesity has also increased in children in several countries including the US, China, and Brazil and others (36, 37) and others (38). Obesity in children is associated with an increased risk for many obesity-related diseases including T2DM and CVD risk factors (39-41), left ventricular hypertrophy related to hypertension (42), and metabolic syndrome (23), although the utility of a diagnosis of metabolic syndrome in children has been challenged (43, 44).

As the prevalence of obesity increases, it associated economic costs rise in parallel and represent a major burden for national health economies (45). Recent estimates indicate that obesity accounts for 5-10% of health care costs in the US and that the total cost of overweight and obesity to the American economy approaches US $114 billion annually (46).

Fortunately, mounting evidence indicates that many of the health effects associated with obesity can be reversed with weight loss. In the Framingham Heart Study, weight loss was associated with improvements in blood pressure and glucose metabolism (47, 48). Other studies have confirmed that weight loss can improve metabolic risk factors among overweight persons with hypertension, dyslipidemia, insulin resistance, and T2DM (49-52).

III. CARDIOVASCULAR DISEASE RISK FACTORS AND CARDIOVASCULAR DISEASE

1. Cardiovascular Disease Risk Factors

a. Hypertension

Both cross-sectional (1, 53) and prospective (54-56) studies have linked obesity to hypertension. The prevalence of elevated blood pressure dramatically increases with weight gain, particularly among individuals <55 years old (57). Similarly, among postmenopausal women, the risk of developing high blood pressure doubles with either a high BMI or high WHR (9). Recent data from NHANES suggest that, after adjustment for other risk factors (such as age, degree of weight cycling, physical activity, smoking, and alcohol consumption), the prevalence of hypertension monotonically increases with BMI, across all ethnic groups (58). Furthermore, it appears that the prevalence of hypertension increases even with relatively small increases in body weight (59-61). In addition, in hypertensive subjects, being overweight is associated with cardiovascular abnormalities such as increased progression of left ventricular hypertrophy (62, 63). These findings suggest that both general and abdominal obesity are important cardiovascular risk factors via hypertension, and that improvements in hypertension may come about as a result of losing excess adiposity. Indeed, this is borne out in observational and intervention studies. In the Framingham study (64), a weight loss of 6.8 kg or more led to a 28% reduction in the risk of hypertension (relative risk [RR] 0.72; 95% confidence interval [CI]:

0.49 – 1.05) for middle-aged adults, and a 37% reduction for older adults (RR 0.63; 95% CI: 0.42 – 0.95). The same study reported that sustained weight loss over 4 years resulted in a 22% reduction in hypertension risk among middle-aged adults (RR 0.78; 95% CI: 0.60 – 1.03) and a 26% reduction (RR 0.74; 95% CI: 0.56 – 0.97) in older adults. These observational studies are corroborated by clinical intervention trials, which consistently observe that weight loss effectively lowers blood pressure (49, 65-67). In addition to a reduction in blood pressure, weight loss and exercise may induce favorable changes in left ventricular structure that are related to cardiovascular events (68). Given that high blood pressure represents one of the most common modifiable risk factors for CVD, obesity-related hypertension, if reversed with weight loss, could reduce CVD risk at the population level.

b. Dyslipidemia

Dyslipidemia is characterized by elevated total cholesterol and triglyceride levels, normal to elevated low density lipoprotein (LDL) cholesterol, reduced high density lipoprotein (HDL) cholesterol, and elevated low-density apolipoprotein B (69). Several observational studies (1, 3, 70-72) have reported associations between body weight and plasma lipoproteins. In the Framingham Heart Study, weight gain over a 26-year follow-up period was associated with adverse lipid profiles, while weight loss was associated with improvements in cholesterol (73). Other studies have found that changes in body weight are associated with changes in lipid concentrations (74-77). Findings from the Framingham Offspring Cohort provide further evidence that BMI has a significant, linear association with total cholesterol, LDL cholesterol, and triglyceride concentrations, and is inversely associated with HDL cholesterol in non-smoking men and women (3). The latter observation is consistent with other studies (1, 3, 77, 78). In contrast to weight gain, weight loss and exercise may result in lower LDL cholesterol and triglyceride levels, decreases in the total cholesterol-to-HDL cholesterol ratio, and increases in HDL cholesterol levels (79-81). Furthermore, cohort (82, 83), case-control (84, 85), and intervention studies (86) have found that dyslipidemia, represented by high LDL and low HDL cholesterol levels, as well as high triglyceride-to-HDL cholesterol ratio and small LDL particle size in the presence of hypertriglyceridemia, are strongly associated with CVD risk (87, 88). Data from the 2003-2004 NHANES survey indicated that 37% of Americans with CVD or related co-morbidities have an abnormal lipid profile in line with hallmarks of dyslipidemia (89). This unfavorable lipid profile often coincides with obesity in adults (90).

c. Hyperinsulinemia

Insulin resistance is a condition characterized by increased insulin production and impaired glucose tolerance (22), and is among the most frequent of metabolic abnormalities observed in conjunction with central or visceral abdominal adiposity (91, 92). Insulin resistance may underlie a number of other metabolic disorders including hypertension, hyperglycemia, hypertriglyceridemia, and hypercholesterolemia (93, 94). As mentioned above, the clustering of these risk factors is commonly referred to as the metabolic syndrome, discussed in detail in Chapter 9. It is worth noting that although each individual risk factor confers only a small increase in CVD risk, the overall impact on CVD risk is substantial due to the co-aggregation of these risk factors (95).

Increasing central obesity has been independently associated with insulin resistance, hyperinsulinemia, and a progressive rise in insulin and glucose concentrations (as responses to an oral glucose tolerance test [OGTT]) (96-98). Some have proposed that central obesity, through several as yet unknown pathways, promotes insulin resistance and hyperinsulinemia which subsequently contributes to the development of general obesity (99). The accumulation of free fatty acids as a result of central adiposity is associated with oxidative stress and the impairment of microvascular function (100, 101). Central obesity may also induce insulin resistance through release of inflammatory cytokines such as interleukin (IL)-6, which in turn impair insulin action in diverse tissues (102, 103). Alternatively, insulin resistance in obesity may be attributable to both a decrease in insulin receptors and intracellular post-receptor defects in insulin action (104-106). Furthermore, abnormal secretion of several adipocyte hormones such as leptin (107, 108), adiponectin (108), and ghrelin (109), which are primarily regulated by insulin-induced changes of adipocyte metabolism, may be potential targets for managing obesity and insulin resistance (110).

Insulin resistance has been associated with weight gain in some (111, 112), but not all observational studies (113, 114). In young adults, weight gain over a 7-year follow-up period was positively associated with concentrations of fasting glucose and insulin (115). Wilson and colleagues found that weight gain over 16 years predicted the development of features of the insulin resistance syndrome (116). However, it has been proposed that insulin resistance is an adaptation for maintaining stable weight, such that the oxidation of fat tends to be favored over its storage and over the oxidation of glucose (117, 118). Data from several observational studies of different ethnic groups support this hypothesis that higher fasting insulin is associated with lower weight gain (113, 119, 120), with ethnicities displaying differences in adiponectin and leptin concentrations (121). Interestingly, data in children indicates that hyperinsulinemia and insulin resistance may favor weight gain (122).

In women, the body fat distribution pattern often changes with progression through menopause (123, 124). Greater increases in WC and WHR in post-menopausal women compared to women who remain pre-menopausal for a longer time may contribute to increased risk of chronic disease, such as T2DM. Van Pelt, et al. (125) reported in a large cohort of healthy post-menopausal women that WC was significantly associated with hyperinsulinemia and elevated triglyceride concentrations despite a normal range of BMI (24-28 kg/m2). Furthermore, it appears that the combination of insulin resistance and the accumulation of visceral adipose tissue in the abdominal compartment contribute to the most unfavorable metabolic risk profiles in post-menopausal women (126).

2. Cardiovascular Disease

a. Obesity and CHD risk

At the population level, obesity is observed to be a well-defined and consistent hazard for CHD (127-130). As described above, obesity is strongly linked to cardiovascular risk factors including diabetes, hypertension, and dyslipidemia. In fact, these risk factors may represent intermediate steps in the causal pathway between obesity and CHD risk. Over the years there has been

considerable debate over whether adjustment for these risk factors in statistical models predicting CVD risk is desirable or whether such adjustments represent “over control,” thereby introducing, rather than controlling for, bias (131, 132). Observational studies that have not controlled for such “intermediate” risk factors have observed positive associations between BMI and CHD (133-136). Evidence from two large prospective cohorts with long follow-up-the Nurses’ Health Study, and the Health Professionals Follow-up Study-indicates that the RR of CHD is 2.48 (95% CI: 2.20 – 2.80) and 2.13 (95% CI: 1.82 – 2.48) times greater in women and men, respectively, among individuals with BMI of greater than or equal to 30 kg/m2 compared to those with a normal BMI (18.5 – 22.9 kg/m2) (134). Correspondingly, weight loss has been observed to reduce predicted long-term CHD risk (137), as has increased physical activity levels (138).

A study from a multinational cohort of 5,661 men found that almost 60% of the 10-year coronary risk in this population was attributable to a BMI >25 kg/m2 (139). Although this study did not control for hypertension or dyslipidemia, the authors observed that systolic blood pressure and total cholesterol increased sharply with elevated BMI among men with WHR less than 0.95, and was high at all levels of BMI among men with WHR exceeding 0.95. Further evidence that abdominal obesity also plays an important role in CHD risk is provided by the results of a case-control study on 29,972 subjects from 52 countries which reported that for both men and women in all regions of the world, abdominal obesity increased the population attributable risk of myocardial infarction (one of the most common CHD events) to 80.2%, from 75.8% attributable risk due to hypertension, diabetes, and dyslipidemia (140).

First acknowledged in 1998 (141), the American Heart Association (AHA) continues to recognize obesity as an independent CHD risk factor (142). Evidence from recent studies support the AHA’s statement that obesity increases the risk of CHD events (15, 143-145). However, as discussed in this chapter, other CHD risk factors such as hypertension, dyslipidemia, and diabetes might explain some of the association observed between obesity and CHD (145). Supporting this, observational studies that control for one or more coronary risk factors in analyses report that while BMI remains independently associated with CHD risk, the association tends to be attenuated (127, 128, 146).

While findings from studies in young and middle-aged adults support a generally direct relation between BMI and CHD risk (147-149), a direct relation between BMI and CHD risk has not been consistently observed in cohorts of older individuals (>60 years) (150-152). Rimm and colleagues (151) found that among men <65 years old, the risk of CHD increased 3-fold (RR 3.44; 95% CI: 1.67 – 7.09) for men with a BMI >33.0 kg/m2 compared with lean men (BMI <23.0 kg/m2), yet in older men the risk was substantially lower (RR 1.26; 95% CI: 0.37 – 4.30) between the same extreme categories. Other prospective studies have reported a lack of association between BMI and coronary disease among older populations (150, 153). Most recently, Wannamethee, et al. (2011) found no significant association between BMI and heart failure in men ages 60-79 without pre-existing CHD (152). These age-related differences in obesity and CHD risk may reflect selective mortality due to early onset CHD incidence among overweight persons, changes in the relative proportion of fat free and lean body mass with age (154), or weight loss due to subclinical disease (155).

b. Body Fat Distribution, Weight Change, and CHD Risk

As discussed above, a growing body of evidence indicates that abdominal visceral adiposity may have more significant health consequences than overall adiposity. This is seen in relation to CVD incidence and mortality as well (156-161), due perhaps to abdominal adiposity's stronger association with cardiovascular risk factors (162). A positive association between abdominal visceral fat and pathological changes of the coronary arteries may indicate that coronary atherosclerosis occurs even before individuals are clinically diagnosed with CHD (163). Rexrode and colleagues (164) reported that after adjustment for BMI and other cardiac risk factors, women with a WHR >0.88 were 3 times more likely to develop CHD than women with a WHR <0.72, during an 8-year follow-up. In this same cohort, WC was also significantly associated with increased risk of CHD, even after controlling for BMI (164). Another population-based cohort of 67,334 female subjects found that WHR was positively associated with the incidence of CHD in both younger and older women, while BMI was only related to CHD among women 55 years old and younger(165). Several other longitudinal studies have observed associations between abdominal obesity and CHD among middle-aged and older women (15, 166) and men (167). In a large prospective study of 29,122 men, Rimm, et al. (151) observed BMI was a strong predictor of CHD risk in men <65 years old, whereas after age 65, WHR was a more consistent predictor of risk among men. However, another prospective study found that abdominal obesity was an independent risk factor for CHD in middle-aged men (168). Interestingly, Rexrode, et al. (169) found a modest relationship between abdominal obesity, as measured by either WHR or WC, and risk of CHD both in middle-aged and older men. These associations were reduced substantially when BMI was accounted for. The availability of measures of abdominal obesity, such as WHR or WC, may complement BMI in cardiovascular risk assessment (170, 171). Further, within BMI categories, defining specific thresholds of WC or WHR may provide added information on the roles of overall and abdominal obesity in CVD risk.

With respect to weight gain, data from the Nurses' Health Study suggest that even modest weight gain (4-10 kg), compared to stable weight during adulthood, increases CHD risk by 27% (172). It has been estimated that for every kilogram increase in body weight, the risk of developing CHD in women increases by 3.1% (173). Fluctuations in body weight have also been associated with CHD risk (28, 29). In the Framingham Heart Study, individuals whose body weight fluctuated, as reflected in large relative standard error of the regression coefficient, experienced more CHD events than individuals who maintained a stable weight (174).

Rapid weight gain and high weight in childhood is also associated with CHD later in life. Individuals born with a low birth weight who gain weight rapidly after 1 year of age have an elevated risk of developing CHD in later in life (175, 176). Longitudinal studies in children and adolescents have observed an increased risk of CHD in adulthood with higher BMI during childhood (177-179). In the Nurses' Health Study, weight gain from age 18 to age 55 was significantly associated with future risk of CHD after adjustment for BMI (180). Increasing prevalence of elevated BMI in children could have important ramifications on CHD rates of the future, resulting in substantially higher morbidity and mortality (181).

3. Obesity, Body Fat Distribution, and Risk of Stroke

In contrast to the epidemiological studies linking obesity and CHD risk, fewer studies have examined the association between obesity and stroke incidence and mortality (182-185). Evidence of an association between general obesity and risk of stroke is conflicting, but the majority of study findings suggest that a higher BMI is associated with higher stroke incidence (183, 184, 186, 187), although some studies report no association (188-190). Risk appears to vary with type of stroke (ischemic, hemorrhagic, or total). In the Nurses' Health Study, the risk of ischemic stroke was directly related to BMI; women whose BMI was >32 kg/m2 had over twice the risk (RR 2.4; 95% CI: 1.6 – 3.5) of ischemic stroke compared to those with a BMI <21 kg/m2 (183). In contrast, the risk of hemorrhagic stroke was inversely related to obesity in the same cohort, with the highest risk among the leanest subjects. Using a similar methodology in a large prospective study of men, Walker, et al. (190), reported no association between BMI and incidence of total stroke, of which approximately 70% was ischemic stroke. However, other studies have demonstrated a significant association between BMI and risk of stroke among men (191-193), including total stroke and ischemic stroke.

A graded, significant association was observed between abdominal obesity, as captured by WHR or WC, and stroke, indicating they may be a better predictors of stroke than BMI (185). Men with a WHR >0.98 were twice as likely to suffer a stroke compared to men with a WHR <0.89 (190). In women, these associations appear to be less consistent (15, 194). Significant associations between WHR and stroke incidence have been reported in other observational studies as well (194-196).

IV. DIABETES

1. Obesity and T2DM

Approximately 300 million people in the world have diabetes, with the number predicted to rise above 435 million by the year 2030 (197). In the US alone, 33 million Americans are predicted to have T2DM by 2021 (198). The link between obesity and T2DM is supported by evidence from both cross-sectional (57, 199-201) and prospective cohort studies (202-205). These reports have consistently upheld a strong positive association between BMI and T2DM. It is estimated that 64-74% of new T2DM cases in the US could be prevented if BMI was maintained at levels <25 kg/m2 (206). While other obesity-related conditions, such as high blood pressure and dyslipidemia, have declined across all BMI groups over the past 40 years, the prevalence of diabetes across these groups has remained stable within this time frame (82). Studies have observed that the risk for developing diabetes increases exponentially in both men and women with increasing BMI (9, 57, 207, 208). Data from the Nurses' Health Study suggests that compared to a women with a BMI <23.0 kg/m2, the RR of T2DM increases 8-fold when BMI is 25.0-29.9 kg/m2, 20-fold when BMI is 30-34.9 kg/m2, and 39-fold when BMI exceeds 34.9 kg/m2 (209). A prospective study of 27,270 men observed an increased risk of T2DM across BMI quintiles, with the most dramatic increase among those in the highest quintile categories of BMI (i.e., those individuals with a BMI >25.4 kg/m2) (13).

2. Body Fat Distribution, Weight Change, and T2DM

Other independent predictors of risk of T2DM, besides BMI include WHR (9, 12, 199, 210), WC (10, 210-212), weight gain or loss, and duration of obesity (47, 213, 214). Folsom and colleagues (9) observed in a study of 31,702 women that a high WHR markedly elevated diabetes risk, regardless of BMI. In contrast, Chan, et al. (203) reported that WHR was only weakly associated with risk of T2DM in a study of 51,529 men after controlling for BMI, while WC remained an independent predictor of T2DM. A more recent 13-year follow-up study confirmed the observation that WC is a more accurate predictor of T2DM than WHR in men (13). Lean and colleagues (1998) found that among men and women with a large WC (greater than or equal to 102 and greater than or equal to 88 inches, respectively) the risk of developing T2DM increased 4.5- and 3.8-fold, respectively (212).

Prospective studies have shown that weight gain, even when modest, increases the risk of developing T2DM (207, 213, 215-217). Estimates suggest that for every kilogram increase in body weight the risk of developing T2DM rises by 5.4% (207). Wannamethee and colleagues (213) examined the association between weight change and incident T2DM in a cohort of middle-aged British men over a 12-year period. After adjustment for age, initial BMI, smoking, physical activity, high blood pressure, and report of CHD, the risk of developing T2DM increased 1.6-fold among those who gained substantial weight (>10%) compared to men who maintained a stable weight. A steady increase in T2DM risk has been observed for men and women who gain weight after adolescence (203, 204).

Given these associations, weight loss followed by weight maintenance is recommended for the prevention and management of T2DM (215), and weight loss has been associated with a lower risk of T2DM (204, 213). Several epidemiological studies report that weight loss is associated with a reduced risk for T2DM among those at high risk of developing the disease (i.e., individuals who are severely obese, or with impaired glucose tolerance [IGT] or impaired fasting glucose [IFG]) (218-220). One intervention study observed that for every kilogram of weight loss in individuals with impaired glucose tolerance, the risk of developing T2DM fell by 16% (220). Wing, et al. (221) reported that a modest weight loss of 4.5 kg over 2 years, as a consequence of a lifestyle intervention including diet and/or exercise, reduced the risk of developing T2DM by 30% relative to no weight loss over the same 2 years. In the Multiple Risk Factor Intervention Trial (MRFIT), a large, randomized controlled trial in which 12,866 middle-aged men at risk for CVD were assigned to counseling (to reduce saturated fat, cholesterol, and calorie intake; to stop smoking; and to increase physical activity), or to usual care, and followed for 6-7 years, researchers observed that weight loss reduced the risk of developing T2DM, but only among non-smokers. In smokers, the risk of developing T2DM unexpectedly increased, but the study authors attributed the increased risk to weight gain following smoking cessation (222).

V. CANCER

In contrast to CVD and T2DM, obesity receives less attention as a risk factor for many cancers. However, in countries where obesity prevalence has increased rapidly, such as the US, an estimated 3% of all new cancers may be attributable to obesity (223). Elevated body weight has

been linked with increased risk of some cancers, including cancers of the colon, esophagus kidney, pancreas, and gallbladder, and in women cancer of the breast and reproductive system (Research 2007). The relationship between some site-specific cancers and obesity is multi-factorial and complex, and the exact mechanisms whereby obesity elevates cancer risk is not clearly understood. Changes in endocrine function due to an increase in fat mass likely contributes to the development of some cancers, as a consequence of adipocytes affecting the regulation of hormones, growth factors, and pro-inflammatory factors (224, 225).

1. Breast Cancer

A complex relationship exists between obesity and breast cancer risk (226). Although some prospective studies have found that increased weight or BMI is associated with increased breast cancer risk among post-menopausal women (9, 227-230), others have found little or no association (231, 232). In contrast, among pre-menopausal women, most cohort studies have found either no association (233-235) or an inverse association between BMI and breast cancer risk (231, 236-239). One explanation for this apparent interaction between obesity and menopausal status on breast cancer risk is that obesity exerts different effects on circulating endogenous sex steroid hormones among post-menopausal women (240, 241). Endocrine interaction with tumor progression is an active area of research, given the modulating effects of fat mass on hormone regulation which appear to be particularly relevant to breast cancer. Adiponectin, an adipocyte-secreted hormone, has some ability to decrease the proliferation rate (242, 243) or tumor size (244) of some breast cancer cell types. Adiponectin is down-regulated in obesity, potentially reducing tumor-suppression in obese individuals. Conversely, another adipokine, leptin, is up-regulated in obese adults and elevated levels have been found to have some synergistic effect on certain breast cancer tumor cell lines, both directly and via modulation of the estrogen system, positively enhancing cancer proliferation in human tissue samples (244-246). Other predictors, such as a high fat diet (247), height (232, 248), body fat distribution (5, 9, 249-251), and weight change during adulthood (252-256) have been linked to breast cancer in post-menopausal women. In the Nurses' Health Study (5), central adiposity determined by WC and WHR was associated with an increased risk of post-menopausal breast cancer, with the greatest elevation in risk evident among post-menopausal women who were not receiving hormone replacement therapy (228, 229, 257).

2. Endometrial Cancer

Although endometrial cancer is less common in the US population than breast cancer, a greater number of endometrial cancer cases are attributable to obesity due to the strength of the association. Obesity and central adiposity are strongly related to endometrial cancer in both pre- and post-menopausal women (258), with an estimated 34-56% of endometrial cancer cases attributable to elevated BMI (259). Several cohort (260-264) and case-control studies (265-269) have found positive associations between endometrial cancer and excess weight, particularly among older women (9, 270, 271). Less consistently than BMI, other measures of obesity such as WC (272), waist-to-thigh ratio (273), and fat accumulation (subcutaneous or visceral) (274) have been positively associated with endometrial cancer, independent of BMI. Possible inflammatory and endocrine pathways between obesity and endometrial cancer are proposed

mechanisms currently being investigated (275-277).

3. Colon Cancer

Colorectal cancer is the fourth most common cancer in the world in both men and women, and the second most common cancer in developed countries (278). The incidence of colon cancer is higher in obese adults compared to those in the healthy weight range (279). Cohort studies have consistently found a strong, positive relationship between BMI and risk of colon cancer, particularly in men (280-283), with weaker associations found in women (284-286). Murphy, et al. (286) examined the association between BMI and colon cancer mortality over a 12-year follow-up in 496,239 women and 379,167 men and found that the relative risk of colon cancer mortality increased linearly across all categories of BMI in men, but not in women. The authors suggested that the greater tendency for abdominal or central adiposity in men may be one reason for the observed gender differences. Some observational studies have reported a strong, positive association between obesity and colon cancer in pre-menopausal women, but results have been inconsistent in post-menopausal women or those taking hormone replacement therapy (287, 288).

Some observational studies found that body fat distribution, as determined by WHR or WC, is an important independent risk factor for colon cancer (9, 289, 290). In the Health Professionals Follow-up Study, both WC and WHR were strong colon cancer risk factors, independent of BMI (289). In this cohort, after accounting for BMI, a 3-fold risk (RR 3.41; 95% CI: 1.52 – 7.66) of colon cancer was seen for men with a WHR greater than or equal to 0.99 compared to those with a WHR <0.90. Similarly, a 2-fold higher risk (RR 2.6; 95% CI 1.33-4.96) was seen in men with a WC greater than or equal to 43 inches compared to men with a WC <35 inches. Furthermore, some evidence suggests that the effects elevated BMI and WC may differ for cases of cancer occurring in the proximal or distal colon (285).

Recent studies on the adipocyte-modulated hormones leptin and adiponectin have shown possible relevant interactions between fat mass and cancer progression. Leptin tissue concentrations are elevated in those with increased adiposity in some cell lines of colon cancer (291). Tumor angiogenisis (292) and tumor migration and metastases (293) are enhanced in the presence of elevated leptin levels. Conversely, adiponectin, which is inversely associated with obesity, has been shown to inhibit growth and induce apoptosis in some cancerous colorectal cells (294, 295).

4. Kidney Cancer

Several risk factors for renal cell cancer have been identified, including obesity, cigarette smoking, hypertension, and certain occupational exposures (296). While the mechanisms by which most of these risk factors contribute to the development of kidney cancer remain largely unknown, there is convincing evidence that obesity is a potential cause (258). Based on evidence from case-control studies, obesity represents one of the more consistently observed risk factors for renal cell carcinoma (297-300). Prineas & Folsom (Prineas, Folsom et al. 1997) prospectively examined the association between risk factors and renal cell carcinoma in 35,192

post-menopausal women over a 7-year follow-up period and found that WHR, weight at age 18, and the amount of weight gained between ages 18 and 50 years, were all independent predictors of renal cell carcinoma. A prospective study with a 25-year follow-up found that the risk of renal cell cancer was almost double among Swedish men with a BMI greater than or equal to 27.8 kg/m2 compared to those with a BMI less than or equal to 21.8 kg/m2, suggesting that even small excesses in body weight increase risk of renal cell cancer among men [Strom, 1995]. A study among Norwegian men and women observed an increased risk of renal cell carcinoma in both sexes with increasing BMI (Chow, Gridley et al. 2000). Whether there are obesity-related sex differences in the risk of kidney cancer is unclear, but some results indicate that renal cell cancer is more prevalent in women (227, 299, 301) than in men (302-304). A meta-analysis of 28 studies found that 27% of renal cell cancer cases among men and 29% of cases among women could be attributed to overweight and obesity (305).

5. Other Cancers

Obesity may play a role in the development of cancer in other tissues. For instance, obesity has been linked to increased risk of esophageal adenocarcinomas (EA), one of two major esophageal cancer types, in both cohort (306) and case-control studies (307). The increased risk of EA associated with elevated BMI may be higher in men; however, at least one study reported values of 1.76 (95% CI: 1.03-3.02) in men, but 2.13 (95% CI: 0.97-4.71, approaching statistical significance) in women, after adjustment for smoking and alcohol consumption (308).

The landmark American Cancer Society study, a 13-year prospective cohort study of 750,000 US men and women, established that gallbladder cancer mortality rates were significantly higher among overweight women, but not overweight men (Lew and Garfinkel 1979). Several subsequent investigations have corroborated these early findings. Studies report that the incidence of gallbladder cancer is positively associated with body weight (227, 309), particularly among women (284, 310). Based on current evidence, it would appear that body fatness is a probable cause of gallbladder cancer, and individuals with a history of gallstones-for which the obese are at higher risk (311)-are more likely to develop gallbladder cancer (258).

Worldwide, prostate cancer is the second most common cancer in men (258). While some observational studies have suggested that body weight is associated with an increased risk of prostate cancer (312-314), the vast majority of studies have found no consistent link between obesity and prostate cancer (315-317). Findings from some observational studies suggest that obesity may be associated with a more advanced form of prostate cancer (318, 319). Interestingly, prostate-specific antigen (PSA) levels, one of the methods used to diagnose prostate carcinoma, are inversely associated with BMI (320). Furthermore, 15% of biopsy-detected prostate cancer occurs in men with normal PSA levels (321). Misclassification of the diagnosis of prostate cancer due to improper diagnostic methods may be one of the possible explanations for the inconsistent association between obesity and prostate cancer (322). Recent laboratory and clinical studies on variance in endocrine levels due to increased fat mass on the progression of cancer have shown weak relationships at high levels in some subgroups of men (323, 324) suggesting that while obesity and body fatness might play a part in prostate cancer, there are other, more causal factors.

VI. MORBID CONDITIONS ASSOCIATED WITH OBESITY

Several additional diseases and health conditions are associated with overweight and obesity.

1. Gallbladder disease

Analyses of NHANES III data indicate a 7.1% prevalence of gallstones, the most prevalent form of gallbladder disease within the US (325). The vast majority of cases are cholesterol gallstones (326). Sex-specific differences in risk for gallbladder disease are striking, with prevalence much higher in women than in men (327), and important differences exist across racial/ethnic groups within each sex (326). However, increased BMI is a recognized risk factor for gallstones and gallbladder disease (311). Men of all ages and women >55 years old experience elevated risk with increasing degrees of obesity (57). In addition, younger overweight or obese women are also at risk of gallstones compared to normal weight women in the same age group. Grodstein, et al. (328) reported that compared to women with BMI <21 kg/m2, relative risk of symptomatic gallstones increases to 2.8 (95% CI: 1.8 – 4.3) in those with a BMI of 25-27 kg/m2, to 6.1 (95% CI: 3.6 – 10.0) in women with a BMI >36 kg/m2. Risk of gallstones for women who had major weight gain (>15 kg) after the age of 18 was 3-fold higher compared to women who remained weight-stable (328). Furthermore, overweight and obesity are associated with a significantly higher risk for symptomatic gallbladder disease (329). In middle-aged men and women studied prospectively over a 10-year period, risk of developing gallstones increased across obesity classes similarly for men and women, with those individuals in the highest obesity class at 3-fold greater risk (330).

Ironically, weight loss in obese persons has also been shown to be an independent risk factor of gallstones and gallbladder disease (327). In a systematic review of the effects of weight loss on gallstone formation in obese patients, Everhart (331) found that 10-25% of men and women may develop gallstones within four months of starting a hypocaloric diet, with one-third going on to develop symptoms of gallbladder disease.

Overall, obesity has been consistently shown to be a powerful risk factor for the development of gallbladder disease in women (311). While men in the US have a lower prevalence of gallstones (326), some studies suggest that abdominal obesity is a strong predictor for gallstone incidence in men, independent of BMI (332, 333). These findings suggest that abdominal obesity may be a better predictor than BMI in men. Furthermore, the presence of metabolic syndrome was associated with a >3-fold increase in the odds of gallstone disease (odds ratio [OR] 3.2; 95% CI: 1.7-6.0) (334).

2. Sleep Apnea and Respiratory Problems

As described in greater detail in Chapter 13, obese patients suffer from a variety of respiratory complications such as obstructive sleep apnea (OSA) (335, 336), obesity hypoventilation syndrome (337), symptoms of dyspnea, and possible increased risk of asthma (337, 338). In studies of individuals with morbid obesity, in those with a mean BMI >40 kg/m2, the prevalence of OSA was estimated to vary between 40% and 90% (339). A large population-based study

reported that for BMI >28 kg/m2, the prevalence of excessive daytime sleepiness, which is considered to be a cardinal sign of sleep apnea, increased in an exponential manner (340, 341). In the Wisconsin Sleep Cohort Study, an increase of 1 standard deviation in BMI was associated with a 4-fold increase in risk of OSA (342). Further evidence suggests visceral adiposity and increased neck circumference are important risk factors for OSA (343, 344). Several dietary intervention studies have found that weight loss has been associated with improvements in sleep-disordered breathing (336, 337, 345). Given that OSA is an important risk factor for hypertension (346), CVD (347), stroke (348), and T2DM (349), weight loss can simultaneously reduce sleep breathing disorders and other morbid health conditions in obese patients (336).

Inflammatory, immunologic, genetic, and mechanical mechanisms have been proposed to explain the association between obesity and asthma (350). NHANES data from 2001-2002 and 2003-2004 indicate that current asthma prevalence increases along with excess weight in women, with a less linear but still positive association in men. In obese and extremely obese women, current asthma prevalence was estimated at 11.1% and 14.9%, respectively, compared to 6.7% in normal weight women. In men, the prevalence of current asthma is 6.3% in obese and 14.5% in extremely obese men compared to 6.1% in those of normal weight (351). The directionality of the relation is difficult to establish in cross-sectional studies, given that obese patients may gain weight as a result of reduced physical activity. In a longitudinal analysis based on 89,061 women aged 27-44 years from the Nurses' Health Study, BMI and weight gain were both significantly and prospectively associated with the development of adult-onset asthma after controlling for other risk factors including age, race, smoking, physical activity, energy intake, hysterectomy status, birth weight, and duration of breastfeeding (352). In this study, nurses who gained more than 25 kg since the age of 18 had the highest risk for the development of asthma (RR 4.7; 95% CI: 3.1-7.0) compared to those who remained weight-stable. Chen and colleagues (353) examined the relationship between obesity and asthma in 17,605 Canadians participating in the National Population Health Survey and found that the prevalence of asthma increased with increasing BMI in women, but not in men. Increasing BMI and female sex were among the significant predictors of asthma prevalence in a population-based case-control study with 2,788 asthma cases and 39,637 controls (354). The study also found that the odds of having asthma increased with increasing BMI, with the greatest increase among individuals with a BMI of 40-60 kg/m2 (OR 2.8; 95% CI: 2.3-3.5), after adjusting for possible confounders including physical activity. Furthermore, several studies have demonstrated that weight loss can improve lung function (355, 356). In this ongoing field of research, studies in diverse populations are still required to confirm that obesity is a significant risk factor for asthma.

3. Osteoarthritis

Obesity is a potent risk factor for osteoarthritis, particularly in weight-bearing joints such as the hip and knee (357-360). Although it is now recognized that the risk factors for the development of osteoarthritis and the risk factors for the progression of the disease may not be the same, obesity may contribute as a risk factor for both its development and progression (361). Two possible mechanisms may account for the observed association between obesity and

osteoarthritis: the mechanical effects on the joint of increased load (362) and/or systemic effects such as overall bone mineral density or inflammatory effects (363, 364). It has been suggested that the ostensible association between obesity and osteoarthritis is spurious due to reverse causation (i.e., arthritis reduces activity and this in turn results in obesity). However, it is more likely that the association is more complex, and that there are causal factors operating in both directions. That obesity leads to osteoarthritis has been observed in prospective studies (365, 366), in addition to cross-sectional (367, 368), and case-control studies (369, 370). A prospective cohort of 39,023 Australians found a 3-4 fold increase in risk of knee or hip replacement associated with body weight (hazard ratio [HR] 3.44; 95% CI: 2.83 – 4.18), BMI (HR 3.44; 95% CI: 2.80 – 4.22), fat mass (HR 3.51; 95% CI: 2.87 – 4.30), and percentage fat (HR 2.99; 95% CI: 2.46 – 3.63) (371). Abdominal adiposity, including WC (HR 2.77; 95% CI: 2.26 – 3.39) and WHR (HR 1.46; 95% CI: 1.21 – 1.76) were less strongly associated with risk of knee or hip replacement, perhaps adding to the evidence that overall weight-bearing load, rather than body fat distribution, is mechanically impacting joint health (371).

A large population-based case-control study in England (369) with cases identified prior to surgical treatment for primary knee osteoarthritis and appropriately matched controls, reported ORs of 2.5 (95% CI: 1.8 – 3.6) and 6.6 (95% CI: 4.4 – 10.5) for overweight and obese cases, compared to respective controls. In this study, higher risk with increasing BMI was observed. The authors emphasized the public health implications of these strong risks in the face of this relatively common disease; based on their analyses, they estimated that 24% of cases of knee osteoarthritis could be avoided if overweight and obese individuals reduced their weight by 5 kg, or until their BMI was within the healthy weight range (369). Accordingly, weight loss has been recommended as one of the standard, non-pharmacologic therapies for osteoarthritis in overweight patients (372, 373). In light of the recommendation, a meta-analysis which reviewed randomized, controlled trials undertaken on the effects of weight loss on osteoarthritis concluded that disability reduction could be predicted from weight loss (374).

Unlike the strong association demonstrated between obesity and knee osteoarthritis, the reported associations between obesity and hip osteoarthritis are weaker (375) or less consistent (376, 377). This difference may reflect discrepancies in the methods for measuring hip osteoarthritis based on clinical findings (such as hip pain) or radiological description (378). Nevertheless, a recent publication from a cohort study of 265,725 participants showed a relationship between increasing BMI throughout the lifespan and total hip replacements due to primary osteoarthritis (379). This relationship was particularly evident in subjects with a high BMI as young adults, a finding that has been observed in other studies (370, 380). Further epidemiological studies are needed to support the link between obesity and hip osteoarthritis.

4. Cataract

Age-related cataract is a major global public health problem (381, 382). In the US, 29.0-34.3% and of adults 50 years old and older in 5 states reported having a cataract in 2005 (383). Although the etiology of a cataract is multi-factorial and differs depending on its location in the lens, obesity appears to be one potential risk factor that may influence its development (382). Schaumberg and colleagues (384) have observed that BMI and WHR in men are each

independently positively associated with cataract occurrence. Several plausible mechanisms exist through which obesity may increase the risk of cataract. For example, elevated body weight is associated with higher blood lipid levels, glucose intolerance, and insulin resistance, 3 conditions linked with the development of cataracts (385). The epidemiological evidence linking BMI and cataract has been inconsistent (386). Most recent large-scale studies associate an elevated BMI with an increased risk of certain cataract types (384, 387, 388), particularly posterior subcapular (PSC) cataract (382, 388-390). A small study in women observed that relative to women with fasting glucose concentrations <7.0 mmol/L, women with T2DM were 4 times as likely to have PSC cataract (OR 4.1; 95% CI: 1.8 – 9.4) (389). In addition, women with BMI >30 kg/m2 or WC >89 cm have higher odds of PSC cataract compared to those with BMI <25 kg/m2 (OR 2.5; 95% CI: 1.2 – 5.2) or WC <80 cm (OR 2.3; 95% CI: 1.0 – 5.2) (389). Results from the Nurses' Health Study and the Health Professionals Follow-up Study (388) identified that the increased risk of incident PSC cataract from an elevated BMI was independent of risk factors, including T2DM. However, the mechanisms underlying the association may still be attributable to other obesity-related conditions such as reduced glycemic control or undefined inflammatory mechanisms. Overall, excess adiposity appears to be associated with some types of cataract, particularly PSC cataract, but the role of obesity in eye disease requires additional research, including etiological differences between PSC and other forms of cataract, and whether obesity is an independent risk factor for eye disease or mediated by other disease pathways.

VII. ALL-CAUSE MORTALITY

It is difficult to comprehensively assess the overall impact of obesity on human health in the context of population-based investigations. One approach is to examine all-cause mortality. From a methodological perspective, this avoids the issue of competing risk factors and misclassification of cause of death. The downside of this approach is that it only accounts for the most severe outcome of disease: death.

Because of the relative ease of conducting observational studies, the early population-based literature on the health consequences of obesity provided much insight into the relationship between obesity and mortality (391-394). However, these studies contained several methodological flaws that threatened their validity, such as failure to account for smoking, failure to eliminate the first several years of follow-up, and over-adjustment for potentially mediating variables, thereby attenuating the observed association between weight status or BMI and mortality (132). More recent studies have sought to address these design limitations. In a comprehensive analysis of 5 large prospective studies representing the mortality experience of just under one million participants, findings were remarkably consistent: the relative risk of death first rises at a BMI between 25 kg/m2 and 29 kg/m2. At BMIs in excess of 30 kg/m2 (obesity), a 40-60% elevation in risk is observed, and at BMIs >35 kg/m2 (obesity classes 2 and 3) the relative risk of death doubles (395). The number of excess deaths attributable to obesity (BMI greater than or equal to 30 kg/m2) in 2000was estimated at 111,909 (396).

While excess body weight is clearly associated with increased risk of mortality, the optimal body weight to minimize mortality risk is equivocal. Whereas morbid obesity has been clearly linked to

higher mortality rates (395, 397), the relation between low to moderate body weight and all-cause mortality is less clear (398). Several observational studies have reported a U- or J-shaped association between overweight and mortality (399-401), while other studies have observed a gradual increase in mortality with increasing weight, particularly among non-smokers (95, 402). Furthermore, some investigators have questioned whether the recommended BMI cut-off points for determining overweight and obesity are applicable for identifying health risks associated with adiposity independent of ethnicity status (403). In a study of 527,265 men and women, although an increased risk of death was observed among those individuals in the highest and lowest BMI category, upon further restriction to healthy non-smokers, the risk of death was associated with overweight and obesity status only (399). Thus, although the shape of the curve defining the relationship between BMI and mortality is debatable, observational studies have consistently demonstrated that adults with a BMI >30 kg/m2 have higher mortality rates (395).

The role of age in the association between obesity and mortality continues to be controversial. The debate was initially sparked when the 1990 USDA Dietary Guidelines for Americans, which presented separate BMI standards for adults over and under the age of 35, were revised in 1995 to recommend a single guideline that did not vary with age. The Dietary Guidelines also recommended that after adult height was attained, adults should not gain >10 pounds throughout adulthood (404) . However, within a 10-year period, the incidence of major weight gain (greater than or equal to 12 pounds) was 3.9% among men and 8.4% among women (405). Evidence was sought to establish whether the lowest point of the U-shaped weight-mortality curve, taken to define optimal weight, changed with age. Test of this hypothesis was complex for two reasons: 1) the aforementioned methodological complexity of the relationship between health and weight confused the issue; and 2) there were a limited number of datasets with adequate data to properly address the question (406). In an analysis of mortality of approximately 62,000 men and 262,000 women enrolled in the American Cancer Society's Cancer Prevention Study I, based on self-reported height and weight at baseline, there was no evidence of a shift in the optimal BMI for health below age 75. It was observed that with increasing age, the weight-mortality U-curve became more shallow, however (407). This flattening of relative risk occurs because the mortality rate of the entire population increases markedly with age so that on a relative scale, risk of death due to obesity with advancing age appears to lessen. Stevens subsequently emphasized that on an absolute scale (such as risk difference), the excess number overweight persons continues to increase with age (406). Adding to the debate, Flegal, et al. (408) suggested that the estimate of deaths attributable to obesity in the US does not necessarily represent the total US population because of exclusions to control for baseline health status and the under-representation of older adults. Flegal, et al. suggest that a weighted-sum method would provide more accurate and precise age-specific estimates of the mortality risk for older adults (408). Hu, et al. (409) reported concerns that the arguments by Flegal and colleagues did not take into account chronic, long-term obesity, as the relative risk calculated from the oldest age groups would not reflect the true long-term impact of obesity on mortality. Regardless of the absolute number, there is little controversy that obesity contributes substantially to excess, and deferrable, mortality.

VIII. CONCLUSIONS

The health consequences of obesity are substantial, with T2DM, CVD, and gallbladder disease among the more common obesity-related diseases. More recent evidence points to differential roles for body fat distribution patterns, in addition to excess overall adiposity, in elevating risk of many major chronic diseases. The large numbers of children entering adulthood overweight, together with increased weight gain in adulthood, portend an enormous burden in terms of human suffering, lost productivity, and health care expenditure in the coming decades. It is additionally important to note that this review did not include a discussion of the considerable psychosocial consequences of obesity. Given the magnitude and prevalence of obesity within the population, individual approaches discussed in the remaining chapters will likely need to be reinforced, supported, and extended by integrated environmental and policy approaches.

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