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THE RELATIONSHIP OF BODY FAT DISTRIBUTION PATTERN TO METABOLIC SYNDROME IN THE US AND TAIWAN

By

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ABSTRACT

THE RELATIONSHIP OF BODY FAT DISTRIBUTION PATTERN TO METABOLIC SYNDROME IN THE US AND TAIWAN

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The purposes of this study were: 1) to determine whether percent bodyfat (%BF) added to the predictive power of waist circumference (WC) to assess risks for modified metabolic syndrome (MMS, where WC was omitted as a criteria) and/or each metabolic co-morbidity by gender; and 2) to examine how the odds ratio (OR) for MMS and each co-morbidity differed by distribution patterns of %BF in overweight men and women with normal or high WC in the United States and Taiwan. Two national survey datasets, NHANES III from the U.S. and NAHSIT from Taiwan, were used. A total of 960 males and 676 females non-Hispanic White Americans (BMI between 25 and 30 kg/m^2) and 291 males and 312 females Taiwanese (BMI between 24 and 27 kg/m^2) met these criteria. Percent BF was divided into 4 categories based on the 50^{th} percentile split for %BF and WC as normal vs high ($\geq$102 cm for men, 88 cm for women in the U.S. and 90cm, 80 cm in Taiwan, respectively). Odds Ratios (OR) equations were derived from logistic regression models for MMS and metabolic co-morbidities [high triglycerides (TG) $\geq$150 mg/dL, low HDL (<40 mg/dl for male and <50 mg/dl for female), high blood pressure (BP>85/135 mm Hg) and impaired fasting glucose

(IFG≥100 mg/dL)]. The lower 50th percentile of %BF with normal WC in the sample was used as the reference.

Results: In non-Hispanic whites, WC was the strongest positive predictor for MMS and metabolic co-morbidities. WC was independent of gender, except for low HDL and high blood pressure in men. The risk for MMS increased with increasing WC, but not always with increasing BF, for people with BMI 25<30. White males with high WC and %BF had the highest risk for MMS (OR=2.1) and for high TG (OR= 1.8). White females with high WC but normal %BF had the highest OR for MMS (OR= 2.2) and for impaired fasting glucose (OR= 3.8).The relation of WC and %BF to MMS and co-morbidities were weaker in the Taiwanese sample but similar to NHANES in that adding %BF to WC did not increase the ability to predict MMS.

Conclusion: Percent BF provided no advantage over WC in assessing obesity-related metabolic risks in the Non-Hispanic white US or in the Taiwanese samples. The relationship of fat distribution patterns to the risk for MMS differed somewhat by gender for both staples. Males with higher %BF and high WC had the greatest risk for MMS, high TG. In women, %BF was associated with decreased risk for high serum TG, low HDL, and high fasting glucose and MMS syndrome when adjusted for WC.

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CHAPTER 1

INTRODUCTION

INTRODUCTION

Results from the 2003 to 2004 National Health and Nutrition Examination Survey indicate that an estimated 66.3% of U.S. adults are either overweight or obese (Ogden, Carroll et al., 2006). Obese individuals are at high risk of hypercholesterolemia, hyperglycemia, hyperinsulinemia, type 2 diabetes, cardiovascular disease (CVD), hypertension, stroke, and some cancers. In 2003 alone, the medical costs attributable to obesity and related diseases in the USA were estimated at about $75 billion (Finkelstein, Fiebelkorn et al., 2004). The increasing prevalences of obesity have been reported in Asian countries as well, such as China, Taiwan, Japan, and Korea (Gu, Reynolds et al., 2005; Kim, Ahn et al., 2005). As the prevalence of obesity increases worldwide along with concomitant risks for chronic, metabolic diseases (WHO, 2000; Jacob et al., 2000), health professionals search for improved ways to target those at greatest risk for the diseases with high medical costs in these diverse populations.

The rapidly increasing prevalence of obesity and related diseases are associated with a cluster of risk factors called metabolic syndrome (MS) or Syndrome X. The concept of MS was introduced in the 1980's as the co-occurrence of cardiovascular risk factors, such as abdominal obesity, atherogenic dyslipidemia (elevated triglyceride, small LDL particles, low HDL cholesterol), raised blood pressure, insulin resistance (with or without glucose intolerance), and prothrombotic and proinflammatory states (Alberti and Zimmet,

1998). Although MS is well known, the criteria for clinical diagnosis of MS varies around the world with at least three recognized professional and medical organizations reporting slightly different clinical criteria for diagnosis (**Table 1**). These diagnostic differences confound a clear diagnosis, research on etiology, and cross-cultural comparisons in risk trends.

Table 1. Criteria for diagnosis of Metabolic Syndrome by NCEP ATP III[1], WHO[2] and AACE[3]

	ATP III	WHO	AACE
Prerequisite	None ***[Fasting glucose ≥100 mg/dL as risk factor below]***	Insulin resistance, identified by 1 of the following: • Type 2 diabetes, • Impaired fasting glucose • Impaired glucose tolerance With normal fasting glucose levels (<110 mg/dL), glucose uptake below the lowest quartile for background population under investigation under hyperinsulinemic, euglycemic conditions	None ***[Fasting glucose 110-126 mg/dL as risk factor below]***
Risk factors	• Abdominal obesity, as waist circumference men >102 cm (>40 in) women >88 cm (>35 in) • Triglycerides ≥150 mg/dL • HDL cholesterol Men <40 mg/dL Women <50 mg/dL • Blood pressure ≥130/≥85 mmHg • Fasting glucose ≥100 mg/dL	• BMI >30 kg/m^2 and/or waist:hip ratio >0.9 in men, >0.85 in women • Triglycerides ≥150 mg/dL • HDL cholesterol <35 mg/dL in men, <39 mg/dL in women • Blood pressure ≥140 / 90mmHg • Urinary albumin excretion rate ≥20 µg/min OR albumin:creatinine ratio ≥30 mg/g	• Overweight/obesity BMI >25 kg/m^2 • Triglycerides ≥150 mg/dL • HDL cholesterol Men <40 mg/dL Women <50 mg/dL • Elevated blood pressure >130/85 mm Hg • Fasting glucose 110-126 mg/dL • 2-Hour postglucose challenge >140 mg/dL • Polycystic ovary syndrome • Sedentary lifestyle • Advancing age
Diagnostic Criteria	**3 of 5** of the listed risk factors are present	Prerequisite plus **2** other risk factors sufficient for diagnosis of metabolic syndrome	Diagnosis depends on clinical judgment based on risk factors

1. The National Cholesterol Education Program's Adult Treatment Panel III report (NCEP., 2001; Grundy, Cleeman et al., 2005)
2. World Health Organization(Alberti, 1998; Alberti and Zimmet, 1998)
3. The American Association of Clinical Endocrinologists(Einhorn, Reaven et al., 2003)

The three definitions shown in **Table 1** are similar in that all use four metabolic risk criteria for elevated triglycerides (TG), low high density lipoproteins (HDL), high blood pressure or hypertension, and impaired fasting glucose. However, the anthropometric criteria differ among all three. The National Cholesterol Education Program's Adult Treatment Panel III Report (NCEP, 2001) focused on waist circumference (WC), the World Health organization (WHO) focused on body mass index (BMI, where BMI=wt in kg/ht in m^2) and/or waist to hip ratio (WHR), and the American Association of Clinical Endocrinologists (AACE) used BMI. Even the BMI cut-offs for risk differ among these three sets of criteria. Such differences suggest a need for more research to elucidate the relationship of anthropometric variables to metabolic complications in order to generate useful anthropometric indicators for specific target populations.

In people of predominantly European descent, the risk for developing MS increases strikingly at a BMI$\geq$25 (Ford, Giles et al., 2002). In a recent study, Park et al. reported that the prevalence of MS in normal-weight (BMI=18.5–24.9), overweight (25.0–29.9), and obese ($\geq$30) men were 4.8%, 22.8%, and 60.2%,respectively. Prevalence rates were similar for U.S. women. Studies have shown, however, that individuals with greater degrees of central adiposity develop this syndrome more frequently than those with peripheral body fat distribution (Kissebah, Vydelingum et al., 1996). In all populations, current studies showed that both increased total and abdominal adiposity are risks for cardiovascular disease. The total amount of body fat and the amount of abdominal fat are highly inter-correlated (Han TS, 1997), but the relative

contribution of each individual compartment to metabolic risks has not yet been established, especially for different populations. It is evident that MS relates to the degree of obesity, but it also appears to be critically dependent on body fat distribution.

Anthropometric Indices (AI), such as BMI, waist circumference (WC), skinfold measurements, and percent body fat (%BF) predicted by Bioelectrical Impedance Analysis(BIA), are commonly used for screening obesity. BMI and WC are the most widely used indicators of overweight and obesity and are useful surrogate indicators of adiposity because they are simple, associated with body adiposity, and relatively unaffected by body height (Heymsfield, Allison et al., 1995). Many researchers have investigated whether BMI is better than WC or vice versa for predicting risk for morbidities and mortality (Janssen, Katzmarzyk et al., 2002; Katzmarzyk, Church et al., 2005). Since BMI and WC are highly correlated and depend upon the age, gender, and racial structure of the study sample, one or the other will perform better, and the magnitudes of their association with related diseases often differ by a small amount. Janssen et al. analyzed national health survey data from the US and reported that WC, not BMI, best explained the obesity-related health risk (Janssen, Katzmarzyk et al., 2004). BMI is an imperfect indicator for MS for the following reasons. First, BMI cannot distinguish between fat and fat-free mass, i.e., a person may be overweight but not overfat, or normal weight, yet overfat. Secondly, BMI cannot distinguish truncal from peripheral body fatness (Gallagher, Visser et al., 1996). Another limitation for BMI is that the universal cutoff points for BMI do not apply equally

well for all racial groups (Deurenberg et al., 1998). Obesity defined by WHO criteria is BMI ≥30.0, but this cut-point results in a MS prevalence of only 2-3% of the Japanese population, in contrast to 10-20% in Europe and the US (Shiwaku, Nogi et al., 2005).

The advantages of WC include its high correlation with BMI (Lean, Han et al., 1995) and with total body fat (Lean, Han et al., 1996), and its association with cardiovascular disease risk factors independent of BMI (Janssen, Heymsfield et al., 2002). Studies indicated that health risk increases in a graded fashion when moving from normal weight to obese BMI categories and that within each BMI category, individuals with high WC values are at a greater health risk than those with normal WC values (NIH, 2000). Although WC is a criterion for the diagnosis of MS by ATPIII, the limitation of using WC to indicate adiposity is that it cannot distinguish between the content of abdominal subcutaneous fat and intra-abdominal visceral fat. It is the latter which is hypothesized to pose the greatest risk for MS because it lies in the etiological pathway for the disease. Also, WC only indicates primarily regional adiposity and not total body adiposity. In addition, there is evidence that Asians should use smaller cut-points for waist circumference than those for people of European descent in predicting increased metabolic risk (Yagalla, Hoerr et al., 1996; Wildman, Gu et al., 2004).

Bioelectrical Impedance Analysis (BIA) holds promise as another screening indicator for body composition, because it is inexpensive, easy to use, free of observer bias and relatively precise when correctly used (Lukaski, Bolonchuk et al., 1986; Roubenoff and Kehayias, 1991). Studies have shown

that percent body fat measured by BIA had statistically significant linear relationships with body fat measured by dual-energy x-ray absorptiometry (DEXA) (Bolanowski and Nilsson, 2001). However, BIA loses its accuracy in severely obese persons and can be of limited usefulness for tracking changes in total body fat in persons losing weight (NIH, 1998). Theoretically, BIA estimates total body adiposity rather than body mass and should provide more precise information about obesity as related to metabolic disease. Whether the use of BIA for adiposity is better than BMI when combined with WC to predict obesity-related metabolic risk is still unclear. As more than 60% of the US population is either overweight or obese, it is difficult for health professionals to target those at greatest risk for CVD in this group. Apparently, no single anthropometric indicator can precisely target those with highest risk. A combination of two or more screening indices should be able to help health professionals target those in the greatest risk for MS and clarify whether the regional or total adiposity contribute most to the etiology of MS.

As indicated earlier, racial and ethnicity variation in metabolic risks complicate the determination of body adiposity and its distribution to metabolic risks. In the U.S., Ford et al. reported age-adjusted prevalence of MS as 23.7%, with the ethnic specific prevalence highest in Mexican Americans and lowest in blacks. The prevalence of MS of Asian Americans in the US is unknown due to insufficient sample size in both the National Health and Nutrition Examination Survey (NHANES) III and NHANES 1999-2000. Researchers have recently argued that it is precisely because people of Asian descent appear to have

greater central body fat deposition, that the BMI cutpoints for these populations should be >23 rather than >25 for defining overweight (Ota, Takamura et al., 2002; Kim, Ahn et al., 2005; Shiwaku, Nogi et al., 2005). One study also showed (Deurenberg-Yap, Chew et al., 2002) that for the same percent body fat, the BMI of Singaporean Chinese, Malays, and Asian Indians are about 3 kg/m^2 lower than that of Caucasians. In Asian ethnic groups, specifically Chinese, Korean, Indian, Paskistani, and Bangladeshi, the risk of hypertension, diabetes and hypercholesterolemia starts to increase rapidly at levels of BMI and WC well within the acceptable range of BMI or WC for Europeans (Deurenberg, Yap et al., 1998; Deurenberg-Yap, Chew et al., 2002; Kim, Suh et al., 2004; Pan, Flegal et al., 2004). Such complications appear to be associated also with both abdominal fat distribution and total body fat adiposity. However, the relative effect of total fat and of abdominal fat to MS and to specific metabolic disorders within various populations still needs to be clarified. Comparative studies between populations of European and Asian descent can help to delineate the differences in amount and distribution of body fat between these groups. Such comparisons are important because the WHO definitions for overweight and obesity were established using data primarily from those of European descent (WHO, 1995), yet people of Asian descent appear to exhibit metabolic risks at lower anthropometric cutpoints and as a population, are increasing rapidly around the globe.

Research purpose

There is an increasing threat of obesity as a global epidemic. Current evidence demonstrates a high correlation between abdominal obesity and metabolic syndrome, as well as elevated percent body fat and cardiovascular risks at relatively low levels of BMI. Such trends and associations require that appropriate measures be undertaken to prevent and manage obesity complications among diverse population groups.

The purpose of this study was to identify the anthropometric indicators, waist circumference and percent body fat, with the best predictive power to target those at highest risk of metabolic syndrome related disorders[1] (MSRD) in diverse populations. The literature reviewed suggests that different patterns of body fat distribution have different relative risks associated with metabolic syndrome[2] and MSRD. The study sample will be narrowed to people who are only overweight, but not obese (BMI 25-29.9). There were several reasons to choose this narrowed range of BMI. 1) For public health screening purposes, it is better to target those in overweight rather than those already obese. 2) The wide variation in body fat distribution that exists at a limited range of BMI can help determine the effect of total fat and abdominal fat to metabolic risks more precisely than by using the entire range of BMI's. 3) At BMI>30, there are few people with either normal

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[1] Includes elevated triglycerides (≥150 mg/dl); low HDL cholesterol (≤40 mg/dl in men, ≤50 mg/dl in women); high blood pressure (≥ 130/85 mmHg); and impaired fasting glucose (≥110 mg/dl).

[2] For the purposes of this study, MS will be defined as 2 or more of 4 risk indicators: TG ≥150 mg/dl, HDL <40 in men and <50 in women, blood pressure ≥ 130/85 mmHg, and fasting glucose≥110 mg/dl as defined by ATP III (NCEP, 2001), excluding the WC used here as a predictor.

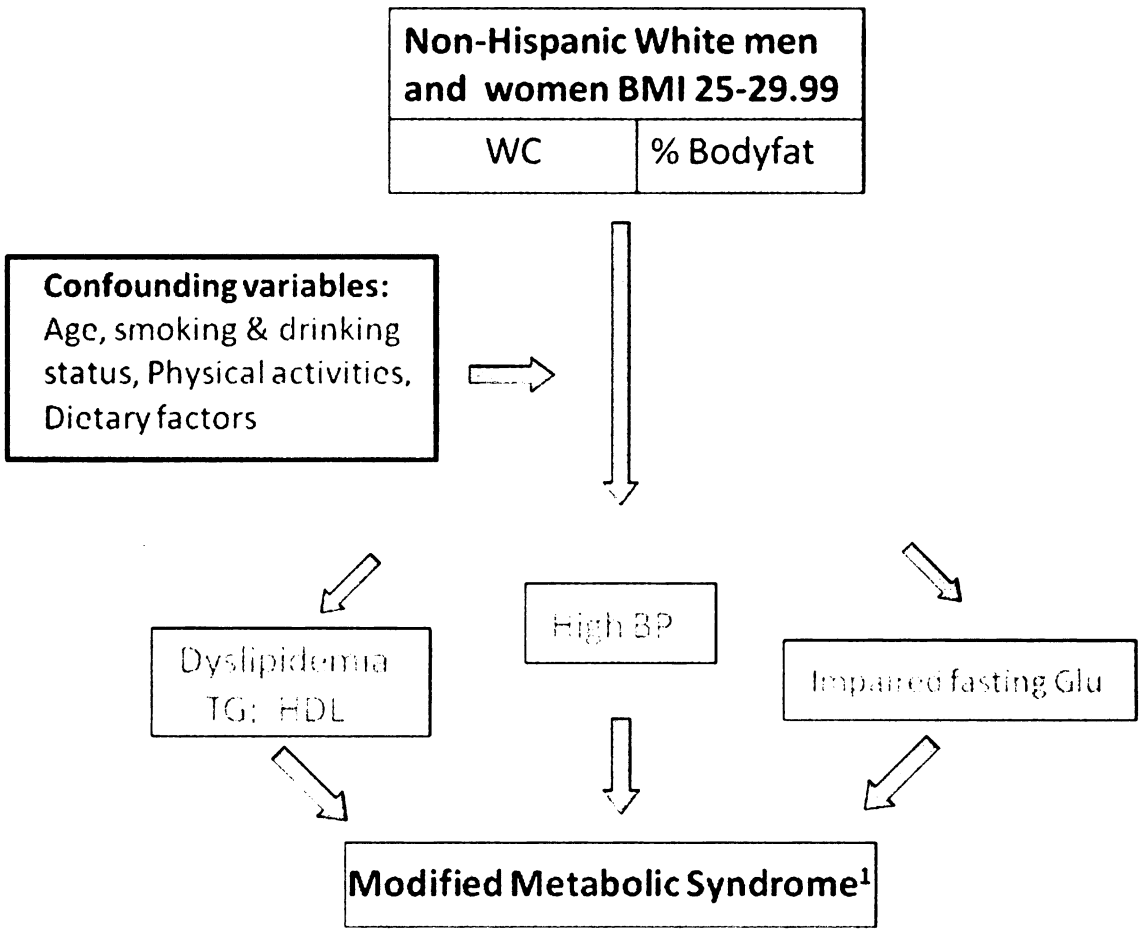
waist circumference or body fat percentile categories. 4) Finally, studies have shown that south Asians, Taiwanese, and Japanese have a much higher prevalence of MS compared to the US population at this lower level of BMI and the prevalence of BMI>30 is less than 4% in these countries (Deurenberg-Yap, Chew et al., 2002; Lin, Yen et al., 2003; Kim, Suh et al., 2004).It is expected that the prevalence of each body fat distribution pattern will differ by race/ethnicity and possibly by gender, resulting in different prevalences of metabolic risks within the same BMI interval.

The **specific aims** and accompanying hypotheses for this study follow for individuals within the defined BMI interval of overweight, 25-29.9.

Aim 1. To determine whether percent body fat assessed by Bioelectrical Impedance Analysis adds to the predictive power of waist circumference in risk for modified metabolic syndrome and/or each metabolic syndrome related disorder (elevated triglycerides, low HDL cholesterol, high blood pressure, impaired fasting blood glucose) in non-Hispanic white, overweight (BMI 25-29.9) men and women (NHANES III). **Figure 1.1** illustrates the conceptual model for this aim.

H1.$_1$: Both waist circumference and percent body fat predict risk for modified metabolic syndrome and/or each metabolic syndrome related disorder in overweight non-Hispanic white men and women.

H1.$_2$: Percent body fat adds to the predictive power of waist circumference to detect risk for modified metabolic syndrome and/or each metabolic syndrome related disorder in overweight non-Hispanic white men and women (NHANES III).



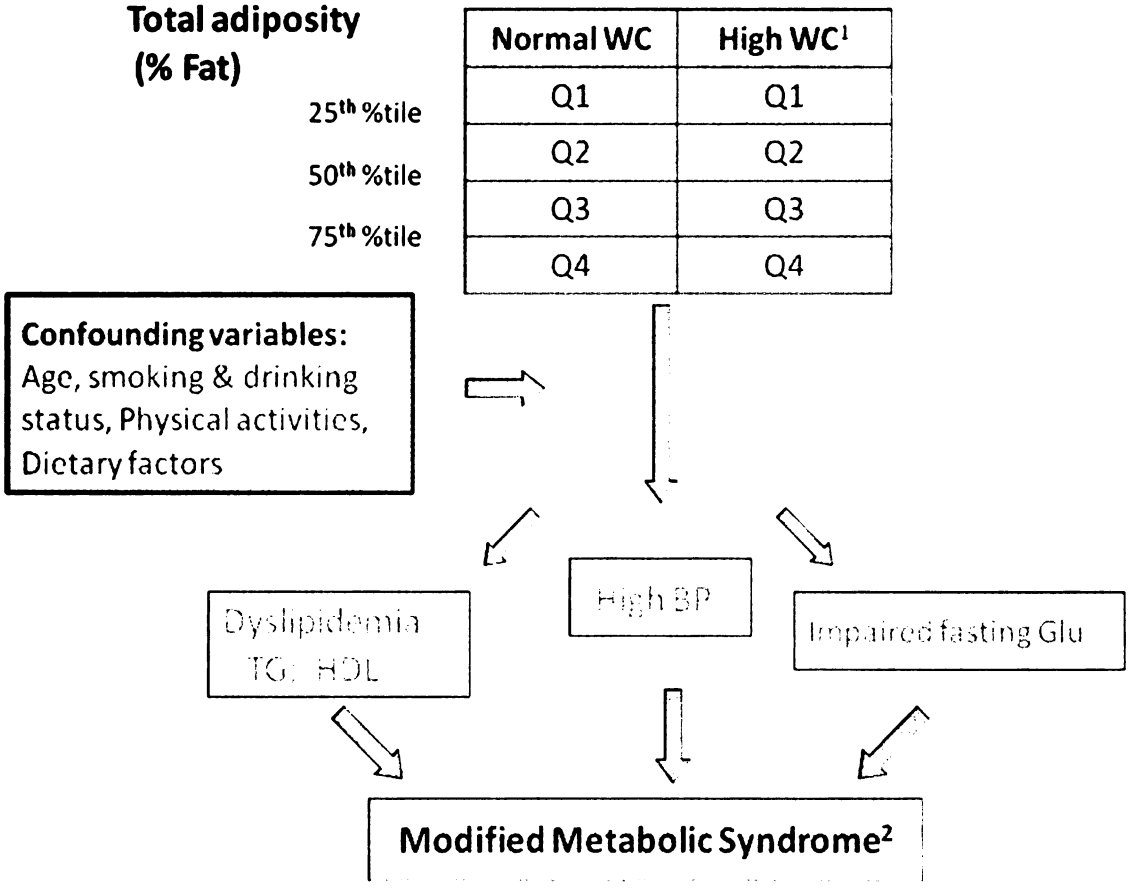
[1] Based on NCEP ATPIII Criteria but not including high WC, i.e. having 2 or more of following abnormalities: Triglycerides ≥150 mg/dL; HDL: Men <40 mg/dL Women <50 mg/dL; Blood pressure ≥130/≥85 mmHg; Fasting glucose ≥100 mg/dL.

Figure 1.1 Conceptual Model for **H1.$_1$**, **H1.$_2$**, and **H3.$_1$**

Aim 2. To determine whether body fat distribution modifies the effect of percent body fat and waist circumference on modified metabolic syndrome and each metabolic syndrome related disorder differ in overweight non-Hispanic white men.

H2.$_1$: For each percent fat quartile, those with high waist circumference will have higher risk than those with normal waist circumference for modified metabolic syndrome and each metabolic syndrome- related disorder in

overweight non-Hispanic white men and women Figure **1.2.** illustrates the conceptual model for $H2_{.1}$, where the overweight sample is categorized into one of *eight* groups by percent body fat and waist circumference.



[1] WC: Waist Circumference, High: >102 cm in men, > 88 cm in women.

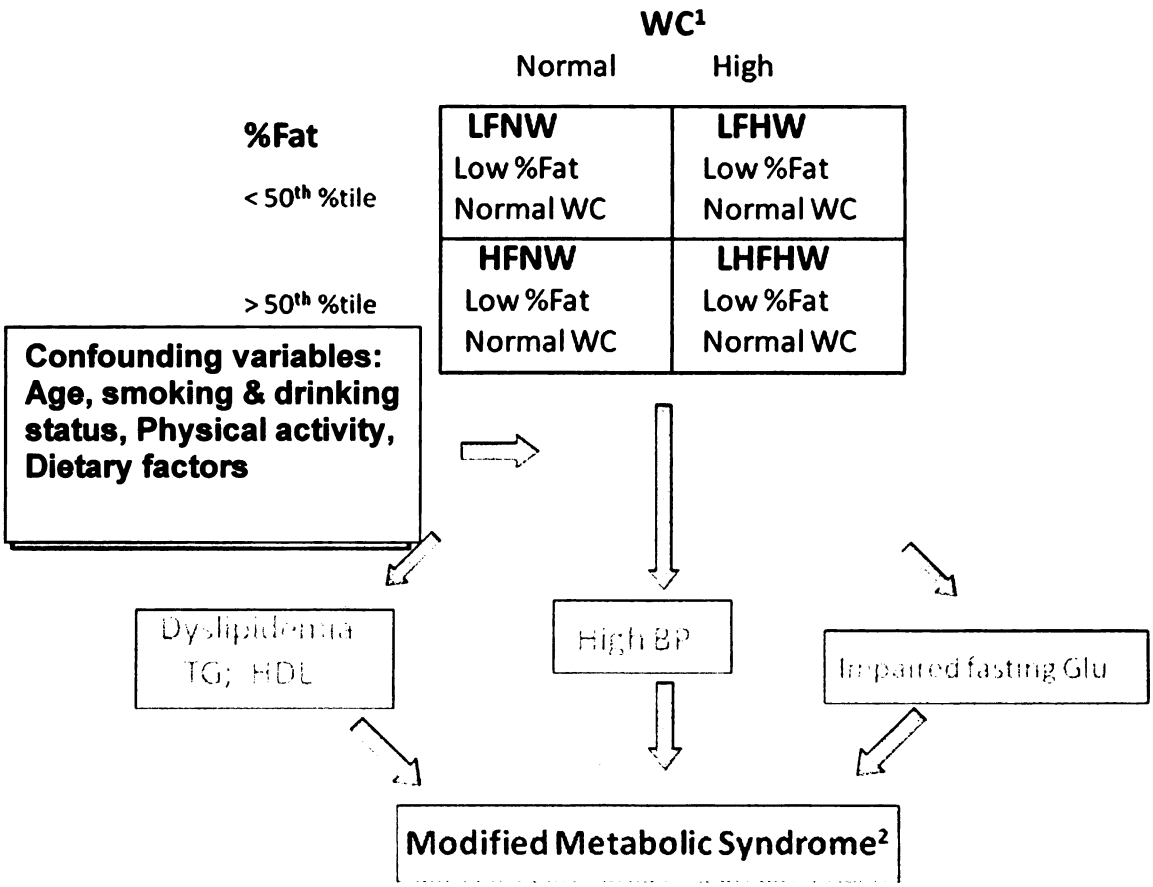
[2] Based on NCEP ATPIII Criteria but not including high WC, i.e. having 2 or more of following abnormalities: Triglycerides ≥150 mg/dL; HDL: Men <40 mg/dL Women <50 mg/dL; Blood pressure ≥130/≥85 mmHg; Fasting glucose ≥100 mg/dL.

Figure 1.2 Conceptual model for $H2_{.1}$

$H2_{.2}$: Those with high body fat (>50th %tile), and high waist circumference (HFHW) will have higher risk for modified metabolic syndrome and each related disorder compared to those with low body fat (≤50th %tile) and high waist circumference (LFHW), high body fat (>50th %tile) and normal waist

circumference (HFNW) and low body fat ($\leq 50^{th}$ %tile) and normal waist circumference (LFNW) in overweight non-Hispanic white men and women.

Figure 2.2. illustrates the conceptual model for $H2._2$, where the overweight sample is categorized into one of *four* groups by WC (normal vs. high) and median split for body fat.



[1] WC: Waist Circumference, High: >102 cm in men, > 88 cm in women.

[2] Based on NCEP ATPIII Criteria but not including high WC, i.e. having 2 or more of following abnormalities: Triglycerides ≥150 mg/dL; HDL: Men <40 mg/dL Women <50 mg/dL; Blood pressure ≥130/≥85 mmHg; Fasting glucose ≥100 mg/dL.

Figure 1.3 Four anthropometric categories based on two anthropometric measures: waist circumference (WC) and percent body fat (% fat) in overweight people (BMI=25-29.9). The quartiles of adiposity are specific to the non-Hispanic white (**$H2_{.2}$**) or Taiwanese sample (**$H3_{.2}$**) by gender and for those who are overweight.

Aim 3. To determine the predictive power of waist circumference and percent body fat to detect the risk for modified metabolic syndrome and/or each metabolic syndrome related disorder in overweight Taiwanese men and women using data from the Nutrition and Health Survey in Taiwan 1993-1996 (NAHSIT).

$H3._1$: Both percent body fat and waist circumference predict risk for modified metabolic syndrome and/or each metabolic syndrome related disorder (elevated triglycerides, low HDL cholesterol, high blood pressure, and impaired fasting blood glucose) in overweight Taiwanese men and women (See previous Figure 1.1).

$H3._2$ Those with high body fat (>50^{th} %tile) and high waist circumference (HFHW) will have higher risk for modified metabolic syndrome and each metabolic syndrome related disorder compared to those with low body fat (≤50^{th} %tile) and high waist circumference (LFHW), high body fat (>50^{th} %tile) and normal waist circumference (HFNW) and those with both low body fat (≤ 50^{th} %tile) and normal waist circumference (LFNW) in overweight Taiwanese men and women.

There are two expected outcomes of this study. First, findings should result in evidence for using two to three anthropometric indicators together (instead of just BMI or waist circumference) to screen for metabolic risks in diverse populations. This is important because preventing obesity is easier and less costly to manage than treating massive obesity or metabolic disorders (Finkelstein, 2001). Secondly, the relative contribution of total fat vs. abdominal fat to metabolic syndrome risk disorders within various populations should be clarified by the study design and cross population comparisons. This outcome should contribute to the understanding of how the distribution of adipose tissue relates to the etiology of metabolic syndrome in more than one race.

Glossary

Metabolic syndrome: defined as 3 or more of the following: waist circumference ≥ 102 cm in males, ≥ 88 cm in females, triacylglycerol concentration ≥150 mg/dl, HDL cholesterol concentration ≤40 mg/dl in men or ≤50 mg/dl in women, blood pressure ≥ 130/85 mmHg , and fasting glucose concentration ≥100 mg/dL. In this study, the diagnosis of the metabolic syndrome will not include a high waist circumference.

Modified Metabolic syndrome (MMS): defined as two or more of the following: triacylglycerol concentration ≥150 mg/dl, HDL cholesterol concentration ≤40 mg/dl in men or ≤50 mg/dl in women, blood pressure ≥ 130/85 mmHg, and fasting glucose concentration ≥100 mg/dL. In this study, the diagnosis of the metabolic syndrome will not include a high waist circumference.

Metabolic syndrome related disorders (MSRD): include elevated triglycerides (≥150 mg/dl); low HDL cholesterol (<40 mg/dl in men, ≤50 mg/dl in women); high blood pressure (≥ 130/85 mmHg); and impaired fasting glucose (≥100 mg/dl).

High blood pressure: ≥ 130/85 mmHg. Individuals reporting a history of hypertension and current blood pressure medication use were defined as having high blood pressure, regardless of measured blood pressure values.

Impaired fasting glucose: fasting plasma glucose concentration ≥ 100 mg/dl. Individuals also met this criterion if they had a doctor diagnosis of diabetes or were using hypoglycemic medication.

Total body adiposity: Expressed by percent body fat (%BF) from bio impedance analysis (BIA).

Overweight: Having a BMI=25-29.9, in US non-Hispanic men and women; Having a BMI=24-26.9 in Taiwanese men and women.

Normal waist circumference (WC): Having a WC <102 cm in US men and a WC < 88 cm in US women, and having a WC < 90 cm in Taiwanese men and a WC < 80 cm in Taiwanese women.

Education level: In NHANES III education is divided into three categories: ≤8 years, 9 to 12 years, and >12 years of education. In NAHSIT, education was divided into three categories: ≤9 years, 10 to 12 years, and more than 12 years of education. The difference is due to a slight difference between the two educational systems. In Taiwan, middle school goes from grades 7-9 and high school goes from grades10 -12.

Smoking status: Subjects were considered *current smokers* if they smoked cigarettes, cigars, or tobacco at the time of the interview; *previous smokers* if they were not current smokers, but had smoked ≥100 cigarettes in their entire life; and *nonsmokers* if they had smoked less than these amounts.

Alcohol consumption: Subjects were *non-drinkers* if they drank no beer, wine, or liquor in the past month, *moderate drinkers* if they drank 1–15 drinks in the past month, or *heavy drinkers* if they drank >15 drinks in the past month.

Physical activity: This was based on the subject's self- reported frequency of common leisure physical activities within the past month. Activities in NHANES III included walking a mile without stopping, jogging or running, swimming, regular

dancing, aerobic exercise or aerobic dancing, riding a bicycle, calisthenics, garden or yard work, and weight lifting. The activities in NAHSIT included biking, ball games, gymnastics/punching boxing, swimming, aerobic dancing/country dancing, mountain climbing, jogging, walking, gardening, housework. Those people reporting no activity within a weekly period, less than once per week, 2-5 activities/week, or >5 activities/week were divided into 'physically inactive', 'light', 'moderate', and 'physically active' categories, respectively.

Dietary factors: Both surveys assessed dietary intake from one 24 hour dietary recall. The two dietary variables extracted from both for this study were percent of energy from carbohydrate and percent of energy from fat.

CHAPTER TWO

REVIEW OF LITERATURE

The topics covered in this chapter relate to the rationale, significance and methods for this study. The literature reviewed was limited to primarily that published within the last 10 years. Three sections organize this review. First is an in-depth review of metabolic syndrome including the definition, etiology, and associated health complications. Next is a discussion regarding the amount and distribution of body fat as relating to metabolic syndrome and metabolic related disorders in different populations and ethnic groups. Finally, a review of selected anthropometric indices elucidates the strengths and limitations of using different measures and indices to assess the relation of body adiposity to metabolic syndrome.

A. Definition of Metabolic Syndrome

Worldwide, the rapidly increasing prevalence of obesity and related diseases has been associated with a cluster of risk factors called metabolic syndrome (MS), earlier Syndrome X. People diagnosed with this syndrome have an increased risk to develop Type 2 diabetes and/or cardiovascular diseases. Metabolic syndrome is closely linked to a generalized metabolic disorder called insulin resistance in which the normal actions of insulin are impaired (Reaven, 1988). Excess body fat, especially abdominal adiposity, and physical inactivity promote the development of insulin resistance, as well as a genetic predisposition for some individuals (Reaven, 1988).

Over the years, the number of metabolic disturbances associated with metabolic syndrome has increased (Alberti, 1998). Risk factors for cardiovascular disease (CVD) as well as chronic kidney disease are now included in some definitions (Alberti and Zimmet, 1998; Reisin and Alpert, 2005). Currently, there are three different sets of criteria for diagnosing MS, and this section will review the similarities and differences among those that various organizations now accept (**Table 2.1**).

The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) diagnostic criteria for metabolic syndrome are currently recommended and widely used, with minor modifications (NCEP, 2002). The ATP III definition places treatment of metabolic syndrome as a secondary target of risk-reduction therapy, after the primary target of LDL-cholesterol. NCEP ATP III proposed an operational definition of MS to facilitate both diagnosis and preventative interventions. Within this definition, a person must have at least three of the five criteria for a diagnosis. The criteria include: 1) abdominal obesity, as determined by a waist circumference of greater than 40 inches for men and greater than 35 inches for women; 2) triglyceride level of 150 mg/dL or greater; 3) HDL cholesterol less than 40 mg/dL for men and less than 50 mg/dL for women; 4) blood pressure of 130/85 mmHg or greater; 5) and a fasting glucose level of 110 mg/dL or greater. In 2005, NCEP ATPIII updated the definition, thus further lowering the fasting glucose level to 100 mg/dl (Grundy, Cleeman et al., 2005). Because glucose tolerance testing is included within the ATP III MS diagnosis criteria, insulin concentration measurements and parameters for proinflammatory states

are not required. This set of criteria allows for ease of use in clinical practice and requires only readily available clinical data.

A consultation group from the World Health Organization (WHO) established the first international definition of metabolic syndrome in 1999 (WHO, 1999), and recognized CVD as the primary outcome of the metabolic syndrome. The WHO also viewed insulin resistance as a required component for diagnosis defined as one of the four following conditions: 1)type 2 diabetes; 2)impaired fasting glucose (IFG); 3)impaired glucose tolerance (IGT); or 4) (for those with normal fasting glucose values) $\geq$110 mg/dL, a glucose uptake in the lowest quartile for the background population under hyperinsulinemic, or euglycemic conditions. In addition to insulin resistance, at least two additional of the following five risk factors are necessary for a WHO diagnosis of metabolic syndrome: 1) BMI >30 kg/m^2 and/or waist to hip ratio >0.9 inches in men and > 0.85 inches in women; 2) TG >150 mg/dL; 3) HDL cholesterol <35 mg/dL in men and <39 mg/dL in women; 4) BP $\geq$ 140/90 mmHg; and 5) urinary albumin excretion rate $\geq$ 20 µg/min OR albumin: creatinine ratio $\geq$ 30 mg/g. The WHO MS diagnostic criteria use a higher blood pressure cut point than does the criteria used by the ATP III.

Recently, the International Diabetes Federation (IDF) proposed a second international definition of MS that requires the presence of central obesity with specific ethnic cut-points, in addition to two or more of the following factors: 1) serum triglycerides $\geq$150 mg/dl and/or treatment for hypertriglyceridemia; 2) a low serum HDL level of $\leq$50 mg/dl for women and $\leq$40 mg/dl for men and/or treatment for this abnormality; 3) blood pressure elevated to $\geq$130/85 mmHg or previously

diagnosed hypertension; and 4) fasting glucose levels of ≥100 mg/dl or previously diagnosed type 2 diabetes mellitus (International Diabetes Federation, 2005). The IDF appears to acknowledge in their MS definition that central obesity and insulin resistance are important causative factors. The IDF definition builds upon the NCEP criteria, but differs in two key aspects. First, the IDF definition has lowered the threshold for waist circumference from 102 to 94 cm for Europid men and from 88 cm to 80 cm for Europid women. Secondly, waist circumference is a required component of MS under the IDF criteria, rather than an optional component as it with the ATPIII definition by the NCEP.

These three definitions of MS have many similarities yet important differences. Each recognizes the existence of a clinical entity with multiple risk factors for CVD (Reisin and Alpert, 2005) including central obesity, high plasma triglyceride (TG) levels, high-density lipoprotein cholesterol (HDL-C) concentration and essential hypertension with some degree of glucose intolerance. The definitions differ both in the diagnostic criteria and in their usefulness to interpret etiology in cross-cultural comparisons for risk trends.

The NCEP ATP III, WHO and IDF definitions, include patients with diabetes in the metabolic-syndrome population thus limiting the ability to reserve the diagnosis of MS only for patients classified as pre-diabetic and at risk for becoming diabetic (Ninomiya, L'Italien et al., 2004). The WHO is the sole organization with a recommendation to include microalbuminuria in its definition of MS. Incorporating microalbuminuria within the criteria links metabolic syndrome with the risk of developing chronic kidney disease and has been determined to be

valid (Chen, Wildman et al., 2004). All three definitions are in consensus regarding central obesity as the key symptom for MS (Reisin and Alpert, 2005).

The anthropometric criteria, however, differ among all these definitions. The NCEP ATP III Report (NCEP, 2001) and IDF both focus on waist circumference (WC), but IDF proposes stricter criteria including ethnic group specificity. The WHO focuses on Body Mass Index (BMI = wt in kg/ht in m^2) and/or waist-to-hip ratio (WHR). These differences in anthropometric criteria suggest the need for additional research to elucidate the relationship of anthropometric variables to metabolic complications, in order to generate useful anthropometric indicators for specific target populations.

Table 2.1 Criteria for diagnosis of Metabolic Syndrome by NCEP ATP III[1], WHO[2], and IDF[3]

	ATP III[1]	WHO[2]	IDF[3]
Prerequisite	None ***[Fasting glucose ≥110 mg/dL as risk factor below]***	Insulin resistance, identified by one of the following: • Type 2 diabetes, • Impaired fasting glucose • Impaired glucose tolerance • With normal fasting glucose levels (<110 mg/dL), glucose uptake below the lowest quartile for background population under investigation under hyperinsulinemic, euglycemic conditions	Central obesity Central obesity measured by waist circumference with specific cut-points for different ethnic groups
Risk factors	• Abdominal obesity, as waist circumference Men >102 cm (>40 in) Women >88 cm (>35 in) • Triglycerides ≥150 mg/dL • HDL cholesterol Men: <40 mg/dL Women: <50 mg/dL • Blood pressure ≥130/≥85 mmHg • Fasting glucose ≥100 mg/dL	• BMI >30 kg/m^2 and/or Waist: hip ratio Men: >0.9 Women: >0.85 • Triglycerides ≥150 mg/dL • HDL cholesterol Men: <35 mg/dL Women: <39 mg/dL • Blood pressure ≥140 / 90mmHg • Urinary albumin excretion rate ≥20 µg/min OR albumin:creatinine ratio ≥30 mg/g	• TG level: > 150 mg/dL • HDL cholesterol: Men: < 40 mg/dL Women: < 50 mg/dL • Blood pressure >130/85 mm Hg, • Fasting plasma glucose 100 mg/dL and/or previously diagnosed with Type 2 diabetes
Diagnostic Criteria	**3 of 5** of the listed risk factors are present	Prerequisite plus **2** other risk factors sufficient for diagnosis of metabolic syndrome	Central obesity plus any two of the risk factors

1. The National Cholesterol Education Program's Adult Treatment Panel III report (NCEP., 2001; Grundy, Cleeman et al., 2005)
2. World Health Organization(Alberti, 1998; Alberti and Zimmet, 1998)
3. International Diabetes Federation (International Diabetes Federation, 2005)

B. The etiological mechanism of metabolic syndrome

A standardized definition of MS is difficult for a clinical entity that is characterized by a complex pathophysiology, covered briefly in this section. By understanding the metabolic evidence for the various criteria in different definitions of the metabolic syndrome, researchers can design valid studies to detect the risk factors related to metabolic syndrome and to avoid misinterpretation of results from existing and future studies, especially in comparisons across cultures.

1. Clinical symptoms of metabolic syndrome

Table 2.2 shows the spectrum of clinical abnormalities associated with the metabolic syndrome. Abdominal obesity, impaired glucose tolerance, dyslipidemia, and elevated blood pressure are commonly found in patients with metabolic syndrome. Evidence is accumulating that insulin resistance is the underlying factor that links atherosclerosis to the metabolic syndrome (NCEP, 2002; Reaven, 2005). Metabolic syndrome or insulin resistance syndrome is not a disease of itself, but a physiological abnormality that increases the likelihood that one or more of the abnormalities listed in Table 2.2 will be present (Reaven, 2005). Dyslipidemia is a hallmark of the metabolic syndrome and characterized by elevated triglycerides (TG) and low levels of HDL cholesterol. Plasma LDL cholesterol (LDL-C) levels are often normal in patients with the metabolic syndrome. A common finding is that LDL particles are smaller and denser than normal and associated with increased cardiovascular risk (Reilly and Rader, 2003). Additionally, disturbances such as microalbuminuria (WHO, 1997; Groop

and Orho-Melander, 2001) and hyperuricemia are associated with metabolic syndrome. Furthermore, abnormalities in fibrinolysis and blood coagulation concomitant with increased levels of plasminogen activator inhibitor 1 (PAI-1) and fibrinogen have been attributed to the components of the metabolic syndrome. Elevated markers of chronic inflammation have been described in relation to metabolic syndrome (Han, Williams et al., 2002). Besides these abnormalities, individuals with metabolic syndrome are susceptible to other conditions, notably polycystic ovary syndrome, fatty liver, cholesterol gallstones, asthma, sleep disturbances and some forms of cancer (Isomaa, 2003).

Researchers have suggested several etiological mechanisms to explain the clustering of metabolic disturbances and cardiovascular risk factors described in connection with the metabolic syndrome. The predominant underlying risk factors for the syndrome appear to be abdominal obesity and insulin resistance (Grundy, Cleeman et al., 2005). Other associated conditions can be physical inactivity, aging, and hormonal imbalance (Apridonidze, Essah et al., 2005). In the following section of this literature review, insulin resistance is reviewed as the key etiological factor for the increased predisposition to dyslipidemia, hypertension, and central adiposity.

TABLE 2.2 Abnormalities associated with metabolic syndrome and insulin resistance/compensatory hyperinsulinemia (modified from Reaven, 2005 and Isomaa, 2003) (Isomaa, 2003; Reaven, 2005)

	Insulin resistance/ compensatory hyperinsulinemia
Dyslipidemia*	↑ triglycerides ↓ HDL-C ↓ LDL-particle diameter (small, dense LDL particles) ↑ postprandial accumulation of triglyceride-rich lipoproteins
Glucose intolerance*	impaired fasting glucose impaired glucose tolerance type 2 diabetes
Endothelial dysfunction	↑mononuclear cell adhesion ↑ plasma concentration of cellular adhesion molecules ↑plasma concentration of asymmetric dimethylarginine ↓ endothelial-dependent vasodilation
Abnormal uric acid metabolism	↑ plasma uric acid concentration ↓renal uric acid clearance
Procoagulant factors	↑ plasminogen activator inhibitor-1 ↑ fibrinogen ↑levels of von Willebrand factor
Markers of inflammation	↑ C-reactive protein white blood cell count
Others	central obesity* hypertension* microalbumiuria fatty liver disease polycystic ovary syndrome hemodynamic changes-↑ renal sodium retention sleep disordered breathing

*Denotes core cluster of MS; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein

2. Insulin resistance and dyslipidemias

Insulin resistance- related dyslipidemia includes elevated serum triglycerides and decreased high-density lipoprotein (HDL). Summarized in Figure 2.1 is some of the considerable evidence that resistance to insulin-stimulated glucose uptake leads to a compensatory increase in plasma insulin concentration enhanced hepatic very low-density (VLDL) triglyceride (TG) secretion and hypertriglyceridemia. For example, in individuals with normal insulin secretory function, particularly non-diabetics, there is a relatively linear and positive relationship between measures of insulin resistance and plasma insulin concentration (Hollenbeck, Chen et al., 1984; Hollenbeck and Coulston, 1987; Reaven, 1988). The more insulin resistant an individual is, the greater the magnitude of hyperinsulinemia. In addition, resistance to insulin-stimulated glucose uptake is positively associated with VLDL-TG secretion rate and plasma TG concentration in both normal triglyceridemic and hypertriglyceridemic individuals (Reaven, 1993). Increased triglyceride levels are implicated as an underlying cause of the production of small, dense LDL cholesterol particles that are more easily oxidized, hence more atherogenic, and less readily cleared from the blood (Howard and Howard, 1994).

Insulin inhibits the release of FFA (non-esterified free fatty acids) from adipose tissue and people with insulin resistance release FFA in the blood thus contributing to dyslipidemia. FFAs are in plasma as the products of lipolysis of triglycerides stored in adipose tissue and are the main substrates for energy metabolism in the fasting state when insulin and serum glucose levels are

relatively low (Reaven and Laws, 1999). When insulin concentration increases, usually during the fed state, it primarily suppresses plasma FFAs by inhibiting the action of hormone-sensitive lipase (HSL). HSL causes breakdown of adipocyte triglycerides into FFAs and glycerol. Plasma FFAs are also the major substrates for liver triglyceride synthesis (Reaven and Laws, 1999). Insulin can decrease plasma FFAs by promoting their re-esterification in adipose cells for storage as triglycerides (Wolfe and Peters, 1987; Coppack, Evans et al., 1992).

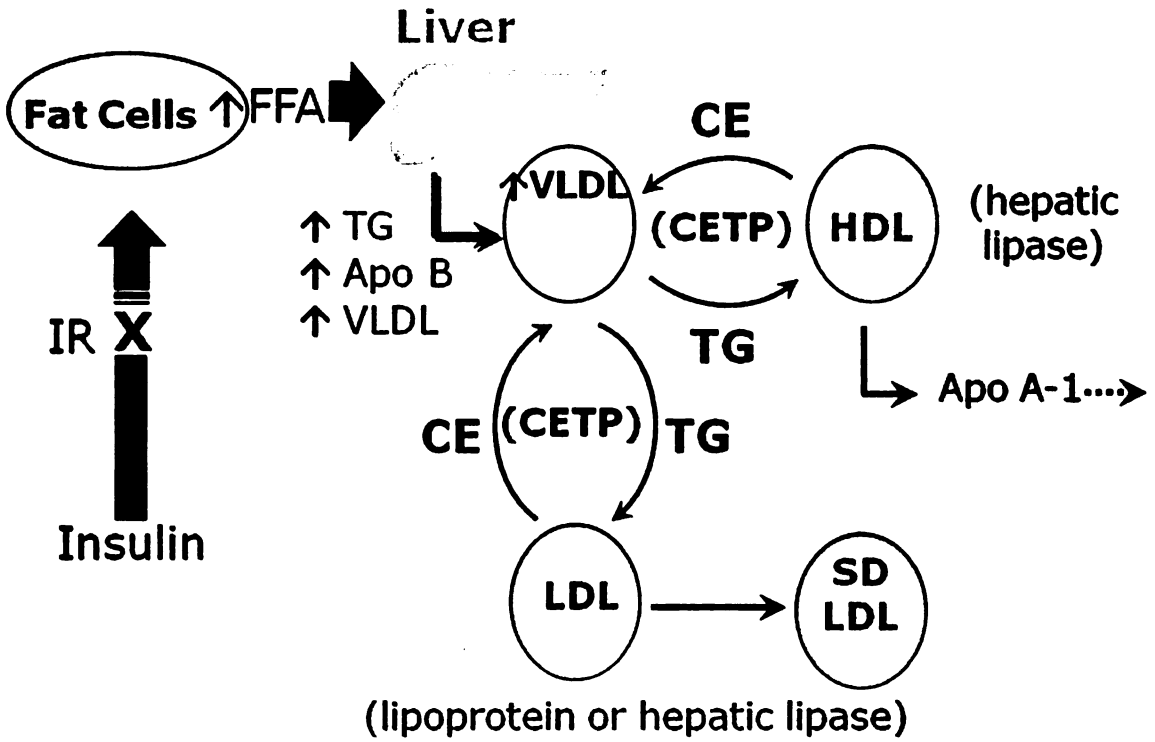
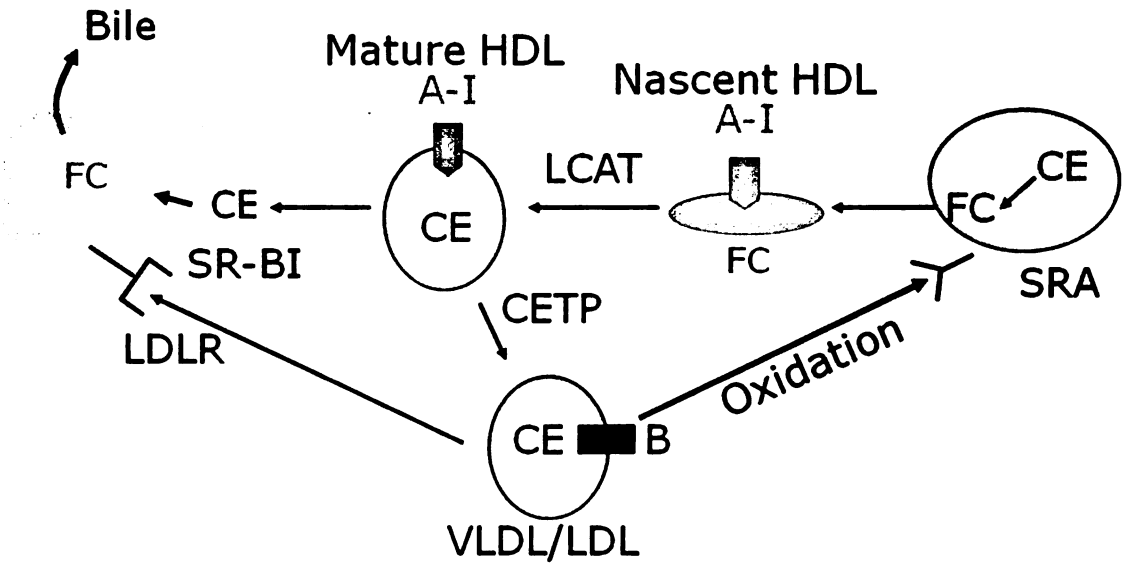


Figure 2.1 Mechanisms Relating Insulin Resistance and Dyslipidemia Modified from Lipid Online Slide Library (Rader, 2007)
FFA: Free fatty acids; VLDL: very Low-density lipoprotein; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; SDLDL: small dense low density lipoprotein; TG: triglyceride: ApoB: Apoprotein B; CE: cholesterol ester; CETP:cholesterol ester transfer protein

Many studies have demonstrated impaired FFA suppression in those with insulin resistance (Byrne, Wareham et al., 1994). Byrne and colleagues showed that FFA suppression is impaired in people with impaired glucose tolerance compared to those with normal glucose tolerance. Yki-Jarvinen and Tasknen demonstrated parallel impairment in insulin-stimulated glucose uptake and insulin suppression of lipolysis in hypertriglyceridemic diabetic and non-diabetic subjects (1988). Finally, with type 2 diabetes researchers have extensively documented a defect in insulin suppression of FFA level (Bierman, Dole et al., 1957; Kashyap, Magill et al., 1970; Reaven and Laws, 1999).

In insulin resistant subjects, day- long increases in plasma insulin (muscle insulin resistance) and FFA concentrations, due to adipose tissue insulin resistance, act on an insulin sensitive liver and stimulate hepatic TG synthesis (Olefsky, Farquhar et al., 1974; Reaven, 2005). A consequence of hepatic TG synthesis is an increase in very-low-density lipoprotein (VLDL) synthesis and secretion, ultimately leading to hypertriglyceridemia (Ginsberg and Huang, 2000). Insulin resistance also decreases lipoprotein lipase activity, the major mediator of VLDL clearance that might also contribute slightly to elevated triglycerides. Low levels of HDL-C are predominately found in certain populations, such as those who smoke, are physically inactive, or who have type 2 diabetes, metabolic syndrome, obesity, or hypertriglyceridemia (NCEP, 2001). Low HDL-cholesterol concentrations in insulin- resistant or hyperinsulinemic persons are partly due to the cholesterol ester transfer protein (CEPT) transferring of cholesterol from HDL to VLDL (Swenson, 1991) (**Fig 2.2**). The higher the VLDL pool size, the greater

the transfer rate from HDL to VLDL and the lower the resulting HDL-cholesterol concentration.



CETP = cholesteryl ester transfer protein; LDL = low-density lipoprotein; LDLR = low-density lipoprotein receptor; VLDL = very-low-density lipoprotein

Figure 2.2. Role of CETP in HDL Metabolism. Modified from Lipid Online Slide Library (Rader, 2007)

Several studies have investigated the effects of insulin resistance on lipoprotein abnormalities (Abbott, Lillioja et al., 1987; Laakso, Sarlund et al., 1990; Laws and Reaven, 1992). In some dyslipidemic individuals, HDL particles may be transformed to dysfunctional, lipid-poor, small HDLs with diminished residence time in the plasma compartment. For instance, in moderate hypertriglyceridemia, cholesterol ester transfer protein (CETP) activity preferentially targets elevated levels of triglyceride-rich VLDL, leading to VLDL enrichment with cholesterol but also equally enhanced TG content in HDL (Guerin, Le Goff et al., 2001). Hepatic lipase hydrolyzes triglyceride-enriched HDL

from small dense HDL. Such small dense HDL of abnormal composition (high triglyceride/cholesterol) has a shorter half-life in plasma than large HDL, and, as a result, HDL levels decrease (Lewis and Rader, 2005). Small dense HDL particles in hypertriglyceridemic states also exhibit impaired anti-oxidative activity versus larger HDL particles, as demonstrated recently in a study that compared patients with the metabolic syndrome from matched, normolipidemic healthy controls (Hansel, Giral et al., 2004).

These complex mechanisms are the means by which prolonged insulin resistance can lead to dislipidemia. Individual differences in genetic susceptibility likely also play important roles. The next section reviews the hypothesized mechanisms for insulin resistance and hypertension.

3. Insulin resistance and hypertension

The most complicated relationship between insulin resistance or hyperinsulinemia and CVD relates to the role of essential hypertension. The prevalence of insulin resistance among patients with hypertension is less in those with hypertriglyceridemia or hyperglycemia (Bonora, Kiechl et al., 1998). No more than half of patients with essential hypertension are also insulin resistant (Zavaroni, Mazza et al., 1992), yet this subset of patients are at greatest risk for CVD (Sheu, Jeng et al., 1992; Jeppesen, Hein et al., 2001). For example, patients with essential hypertension with electrocardiograph evidence of ischemic changes are more glucose intolerant and hyperinsulinemic compared with a normotensive control group or a hypertensive patient with a normal electrocardiogram (Sheu, Jeng et al., 1992). Measurement of insulin-mediated

glucose disposal has demonstrated that patients with essential hypertension and ischemic electrocardiograph changes were insulin resistant, and dyslipidemic changes associated with insulin resistance/hyperinsulinemia were present in these individuals compared with normotensive individuals or hypertensive patients with normal electrocardiograms electrocardiogram (Sheu, Jeng et al., 1992; Reaven, 2005).

Although insulin may have a vasodilatory effect, this effect seems to be active in the microvasculature of the skeletal muscle, an important determinant of insulin mediated glucose uptake (Vincent, Barrett et al., 2003). In vivo studies have shown that insulin exerts a different effect on larger arteries and can cause elevation in blood pressure in healthy humans (Arcaro, Cretti et al., 2002). Arcaro et al. demonstrated that exogenous insulin infusion in healthy subjects could cause endothelial dysfunction and diminish endothelium-dependent vasodilation in the large conduit arteries by mechanisms involving the induction of oxidative stress. In the presence of insulin resistance, as in patients with type 2 diabetes, the effect of insulin on the microvasculature in the skeletal muscle is blunted (Baron, 1994).

It is reasonable to postulate that the sympathetic nervous system overrides the normal vasodilatory effects of insulin under more extreme conditions such as obesity, sucrose feeding and hypertension. For example, insulin has been shown to contribute to sodium retention (Nosadini, Sambataro et al., 1993; Ling, Matsunaga et al., 1995), to stimulate the sympathetic nervous systems (Rahmouni, Morgan et al., 2004) and to induce oxidative stress. All these actions

could contribute to the pathogenesis of hypertension in people who are insulin resistant (Tseng, 2006). Recent studies on adipose tissue derived proteins found that renin and angiotensinogen are produced by the adipocyte and might contribute as well to the link between obesity and hypertension (Reaven, Scott et al., 2005).

This section has described some likely mechanisms by which insulin resistance and/or obesity could contribute to the manifestation of hypertension, which is one criterion of MS in all three definitions. Elucidation of these relationships is an active area of research as described next.

C. Impact of total body fat, abdominal fat and visceral fat on metabolic syndrome

Worldwide, the prevalence of obesity is increasing dramatically. Twenty years ago, as documented in NHANES III (1988 to 1991), 42% of men and 52% of women in their fifties were overweight in the U.S. (Kuczmarski, Flegal et al., 1994); and recent estimates from show NHANES 2003-2004 that 78% of men and 68% of women 40-59 years of age were overweight (Ogden, Carroll et al., 2006). Using the criteria of the National Cholesterol Education Program Adult Treatment Panel III (ATPIII), the prevalence of the metabolic syndrome in U.S. adults ≥20 years of age was recently estimated to be 23.7% (Ford, Giles et al., 2002). Prevalence increased with age, reaching 43.5% and 42.1% for those 60–69 and ≥70 years of age, respectively. According to NCEP ATP III, the "obesity epidemic" is primarily responsible for the rising prevalence of metabolic syndrome. Obesity is now known to be linked to insulin resistance, type 2 diabetes, and

cardiovascular disease and contributes to hypertension, high serum cholesterol, low HDL cholesterol, and hyperglycemia. It is abdominal obesity in particular, however, that especially correlates with metabolic risk factors and excess adipose tissue releases several inflammatory factors that exacerbate these risk factors (Grundy, Brewer et al., 2004).

The purpose of this section is to review the relationship of different regions of body fat deposition and the inherent risks for metabolic syndrome. In addition, the critical role that adipose tissue has in the manifestation of the insulin resistance components will be discussed.

1. Abdominal fat vs. peripheral fat in relation to the metabolic syndrome

Many studies have shown that increased body fat adiposity elicits increased insulin resistance. It is increasingly recognized that not only the degree of overweight but also the distribution of body fat is important to the development of insulin resistance and the metabolic syndrome. (Donahue and Abbott, 1987; Ross, Leger et al., 1991; Bjorntorp, 1992). There is considerable evidence that visceral or intra-abdominal fat, which increases with age, is linked to insulin resistance. Adipose tissue, increased FFA turnover, and increased levels of circulating FFA found in those who are obese are also highly associated with insulin resistance (Bjorntarp, 1992). Over the last 10 years the use of computed tomography, a tool used to study regional adipose tissue accumulation, has been used to demonstrate significant positive associations between abdominal visceral adipose tissue deposition and the risk factors of metabolic syndrome (Kvist, Chowdhury et al., 1988).

Abdominal obesity, or "central adiposity", is a preferential deposition of fat in the abdominal region and often involves accumulation of visceral fat. Patients with central adiposity have higher insulin levels and are more insulin resistant than subjects at a similar weight with a peripheral type of obesity (Abate, Garg et al., 1997; Samaras and Campbell, 2000). The importance of central obesity is well recognized in the definitions of metabolic syndrome. Abdominal fat, however, can be subdivided into two compartments: subcutaneous adipose tissue (SCAT) and visceral adipose tissue (VAT) as identified by computed tomography or magnetic resonance imaging scanning (Borkan, Gerzof et al., 1982; Kvist, Chowdhury et al., 1988).

The excess accumulation of VAT appears to play a more significant pathogenic role in metabolic syndrome than does SCAT. The abdominal SCAT is located immediately beneath the skin and on top of the abdominal musculature. Most lower body fat is SCAT, stored primarily in the femoral and gluteal regions (Wajchenberg, 2000; Lafontan and Berlan, 2003). VAT deposits, located in the body cavity beneath the abdominal muscles, are composed of the greater and lesser omentum (peritoneum attached to the stomach and linked with other abdominal organs) and the mesenteric fat. A lesser amount of VAT is located retroperitoneally. In general, VAT accounts for up to 20 percent of total fat in men and 5-8 percent in women. Studies have shown that lean individuals with normal BMIs can also have a significant accumulation of VAT with increased risk factors for cardiovascular disease and diabetes (metabolically obese, but normal weight) (Ruderman, Chisholm et al., 1998; Katsuki, Sumida et al., 2004). Meanwhile,

obese individuals with high BMI but relatively little VAT can present normal metabolic profiles and a few risk factors for metabolic syndrome, cardiovascular disease, and diabetes (Ruderman, Chisholm et al., 1998).

Numerous inherent differences between VAT and SCAT have been found in the last decade. VAT is a major predictor for insulin resistance (Wagenknecht, Langefeld et al., 2003) and metabolic syndrome (Carr, Utzschneider et al., 2004). The "Portal Theory" hypothesized that insulin resistance and related features could arise from VAT delivering FFAs at a high rate directly into the liver via the portal vein (Bjorntorp, 1990; Arner, 1997). This, in turn, would increase hepatic glucose production, reduce hepatic insulin clearance and ultimately lead to insulin resistance, hyperinsulinemia, and hyperglycemia, as well as non-alcoholic fatty liver disease. FFA flux could also lead to enhanced production of triglycerides and apolipoprotein B-rich lipoproteins, both features of insulin resistance syndrome reviewed earlier (Busetto, 2001). Compared to SCAT, VAT adipocytes have a higher rate of lipolysis more readily stimulated by catecholamines and less readily suppressed by insulin (Zierath, Livingston et al., 1998). VAT also releases a larger amount of glycerol than the liver can convert to glucose, thus contributing to hyperglycemia (Kishida, Kuriyama et al., 2000). Other investigators have argued that the "Portal Theory" is inadequate as a sole explanation of VAT's role in metabolic syndrome (Freedland, 2004). The mechanism by which VAT contributes to MS might be due in part to the proteins produced by the adipocytes and will continue to be investigated.

2. Relationship of adipose tissue derived proteins, adipocytokines, to the metabolic syndrome

The investigation of mechanisms for obesity's intimate link to insulin resistance, type 2 diabetes and cardiovascular disease has led to an increased understanding of the complex function of adipocytes. Traditionally considered a passive storage depot for triglycerides, adipocytes are now recognized as a complex and active endocrine tissue secreting numerous immunomodulatory factors that play major roles in the regulation of human metabolism and vascular biology (Wisse, 2004; Hamdy, 2005; Hutley and Prins, 2005). In the last decade, researchers have learned that adipocytes produce several proteins including leptin, adiponectin, resistin ,tumor necrosis factor (TNF)-α, interleukins (ILs), C-reactive protein (CRP), and plasminogen activator inhibitor (PAI)-1. Some of the proteins are classical cytokines and others, including leptin, are structurally related to cytokines (Wisse, 2004). This finding has led to the introduction of the term 'adipocytokines' to describe the wide range of proteins adipose tissue produces (**Table 2.3**). The term adipocytokine also highlights that several proteins produced by adipocytes may act locally as autocrine and paracrine factors rather than remote-acting endocrine factors (Frayn, Karpe et al., 2003). Through the actions of such proteins, the adipocyte itself becomes central to the development of insulin resistance and vascular disease.

For the adipocytokines and leptin, the endocrine function of adipose tissue is well established. In the past decade, the endocrine role of leptin has expanded to include regulation of reproduction (Cunningham, Clifton et al., 1999) and immune

function (Lord, 2002). Leptin exerts an effect on the central nervous system to control satiety, increase energy expenditure, and reduce food intake. Obesity is associated with leptin resistance and increased leptin secretion. Most overweight and obese humans have elevated levels of leptin that do not suppress appetite. This leptin resistance is postulated to be a fundamental pathology in obesity (El-Haschimi, Pierroz et al., 2000; Hutley and Prins, 2005). Leptin helps regulate insulin action within the liver and has anti-inflammatory actions (Klein, Horowitz et al., 2000). Leptin secretion is considerably greater from subcutaneous fat stores than from visceral fat depots (Montague, Prins et al., 1998; Van Harmelen, Reynisdottir et al., 1998).

Adiponectin is an adipocytokine that may have a protective role in the vascular wall (Ouchi, Kihara et al., 1999; Hotta, Funahashi et al., 2001). Adiponectin can accumulate within injured vascular walls (Okamoto, Kihara et al., 2006) and suppress TNFα-induced expression of adhesion molecules in vascular endothelial cells (Ouchi, Kihara et al., 1999). Adiponectin has been strongly implicated in cardiovascular health. Epidemiologic data demonstrates an inverse association between serum adiponectin concentrations, vascular inflammatory markers and manifestations of the metabolic syndrome, including altered CRP, fibrinogen, hypertension, and endothelial function (Shimabukuro, Higa et al., 2003; Schulze, Rimm et al., 2004). Furthermore, reduced levels of adiponectin (hypoadiponectinemia) are associated with higher BMI, decreased insulin sensitivity, less favorable plasma lipid profiles, and increased risk for development of cardiovascular disease (Ryo, Nakamura et al., 2004; Trujillo and Scherer,

2005). The primary mechanisms by which adiponectin enhances insulin sensitivity appears to be through increased fatty acid oxidation and inhibition of hepatic glucose production (Lihn, Pedersen et al., 2005). Other actions of adiponectin include suppression of macrophage to foam-cell transformation in vitro (Ouchi, Kihara et al., 2001) and inhibition of endothelial signaling through cyclic adenosine monophosphate (cAMP). In addition to its effects on the endothelium and vascular wall, adiponectin secretion is reduced in obesity, which further increases insulin resistance and inflammation (Reaven, Scott et al., 2005).

Tumor necrosis factor (TNF-α) is a proinflammatory adipokine that stimulates expression of other inflammatory mediators like leptin and IL-6 (Banks, Forbes et al., 1995; Bullo, Garcia-Lorda et al., 2003). Expression and secretion of anti-inflammatory adiponectin is reduced in response to TNF-α (Kappes and Loffler, 2000). By releasing TNF-α, the adipocyte directly suppresses insulin signaling, induces insulin resistance, and has direct inflammatory effects on the macrophage and the endothelial cell. This promotes the development of atherosclerosis.

Plasminogen-activator inhibitor 1 (PAI-1) is a prothrombotic factor which is found more highly secreted by VAT than abdominal SCAT (Wagenknecht, Langefeld et al., 2003; Fain, Madan et al., 2004; Pantanetti, Garrapa et al., 2004), while leptin is more highly secreted by SCAT (Minocci, Savia et al., 2000). Elevated levels of PAI-1 in inflammatory and obese states are a known risk factor for thrombosis and a predictor for cardiovascular events and mortality (Fay, 2004).

Renin and angiotensinogen are involved in blood pressure control, causing vasoconstriction. The fact that they are produced by the adipocyte may explain the link between obesity and hypertension (Reaven, Scott et al., 2005).

The adipocytes and numerous other adipose tissue-derived molecules described here have an impact on glucose homeostasis, vascular biology, tumor development, lipoprotein metabolism, and inflammation (Rajala and Scherer, 2003). It is now clear that obesity, especially central obesity, dysregulated expression and secretion of adipokines drives a proinflammatory state. Adipokines from VAT can be delivered via the portal system directly to the liver where they can affect hepatic, and ultimately systemic, inflammation. Chronic inflammation contributes to the development of insulin resistance, glucose intolerance, and atherogenesis, all characterizing the metabolic syndrome. Understanding the molecular mechanisms linking obesity with components of the metabolic syndrome represent key foci to determine the connection among obesity, metabolic syndrome and cardiovascular disease.

Table 2.3. Proteins produced by adipose tissue, adipocytokines.

TNF-α
IL-6
IL-1β
Leptin
Adiponectin
Resistin
Acylation-stimulating protein
SAA3
α 1 acid glycoprotein
Pentraxin-3
IL-1 receptor antagonist
Macrophage migration inhibitor factor

Adapted from (Wisse, 2004)

D. Ethnic differences in metabolic risk factors

The prevalence of metabolic syndrome varies by race/ethnicity, by age, and by the definition used for diagnosis as illustrated in **Table 2.4**. Environmental factors, including health-related behaviors, lifestyles, and economic disadvantages likely contribute to some of the race/ethnic disparities in the prevalence of metabolic syndrome. However, because these factors cannot explain all of the racial differences in disease patterns, genetic factors likely operate at the metabolic level and in conjunction with and response to the environment contributing as well to disparities in obesity-related co- morbidities (Cossrow and Falkner, 2004). The aim of the next section of the literature review is to evaluate current studies on the prevalence and variations in metabolic syndrome in different ethnic groups and to explore possible contributions to the disparities.

1. The prevalence of the obesity related metabolic risks in the US

Using the criteria of the NCEP-ATP III with the NHANES III database, updated to the 2000 census, the overall prevalence of the metabolic syndrome in the United States is high, approximately 47 million (23.8%) American adults (Ford, Giles et al., 2002). The risk of metabolic syndrome progressively increases with age, rising from approximately 7% for adults in their 30s to over 40% risk for those who are

Table 2.4. Prevalence of metabolic syndrome in different ethnic groups by different definitions

Studies	Ethnic groups	(n=)	Age	Definition of Metabolic Syndrome								
				ATPII			WHO			Other		
				All (%)	Male (%)	Female (%)	All (%)	Male (%)	Female (%)	All (%)	Male (%)	Female (%)
(Li, Xu et al., 2006)	**Chinese (Urban)**		40-49		14.2	21.3						
			50-59		17.6	23.1						
(Patel, Huang et al., 2006)	**Hong Kong**	2900	>35		14.6	20.9						
	Taiwan	48406			10.7	12.1						
	Thailand	5305			18.5	26.5						
	US	9718			30.9	35.3						
(Tillin, Forouhi et al., 2005)	**European**	2346	40-69		18.4	14.4		18.8	9			
	South Asian	1711			28.8	31.8		46.3	31			
	African-Caribbean	803			15.5	23.4		26.7	26.4			
(Ford, Giles et al., 2002)	**US**	8814	>20	23.7	24	23.4						
	White				24.8	22.8						
	African Am				16.4	25.7						
	Mexican Am				28.3	35.6						
(Chuang, Chen et al., 2004)	**Taiwan**	24329	>20	9.5	10.6	8.1				12.9	15.5	10.5
(Jia, Xiang et al., 2004)	**China, Shanghai**		>20	12			17.1					
(Tan, Ma et al., 2004)	**Singapore**	4723	18-69	12.1	13.1	11.0				18.2	20.0	15.5[a]
	Chinese			9.4	10.8	8.3				14.8	26.2	21.0
	Malay			18.7	17.3	20.0				24.2	29.8	43.2
	Indian			20.4	23.7					28.8	41.4	53.8

Table 2.4. (cont'd)

Studies	Ethnic groups	(n=)	Age	Definition of Metabolic Syndrome								
				ATPII			WHO			Other		
				All (%)	Male (%)	Female (%)	All (%)	Male (%)	Female (%)	All (%)	Male (%)	Female (%)
(Lee, Park et al., 2004)	Korean			6.8								
Choi, 2005	Korea	1230			34.2*	38.7		21.8	19.4			
(Shiwaku, Nogi et al., 2005)	Japanese	368	30-49		13.3	11.5						
	Korean	232			14.2	11.9						
	Mongolian	102			18.6	13.5						

60 years and older. Overall, the prevalence of the metabolic syndrome shows similar patterns within each ethnic group, i.e., increasing with age and BMI. The prevalence of the metabolic syndrome is highest in Hispanics and lower in non-Hispanic whites and African Americans. Cossrow and colleagues found that African Americans exhibit less dyslipidemia compared to Caucasians, but higher rates of coronary heart disease and stroke (Cossrow and Falkner, 2004). The lower prevalence of metabolic syndrome among African Americans might be explained by the two lipid criteria in the ATP III definition of high triglycerides and low HDL cholesterol. Lower prevalence of lipid abnormalization in African Americans might offset their high rates of hypertension and glucose intolerance.

The NHANES 1999-2000 survey demonstrated that the prevalence of co-morbidities for MS was high and increasing for various groups(Hajjar and Kotchen, 2003). Currently, 28.7% of Americans have hypertension (Hajjar & Kotchen, 2003). Non-Hispanic blacks had the highest prevalence of hypertension (33.5%) among race-ethnic groups. Prevalence of hypertension increased with age to 65.4% among those $\geq$60 years and older, and tended to be higher in women (30.1%) than in men (27.1%). Mexican-Americans had the lowest prevalence of hypertension during the same period of time (Hajjar and Kotchen, 2003). The prevalence of the metabolic syndrome using the ATPIII definition was 86% among people with diabetes who were over age 50 in the NHANES 1999-2000 survey (Alexander, Landsman et al., 2003). A lower but still higher-than-average prevalence of the metabolic syndrome was observed in people with impaired glucose tolerance (31%) and impaired fasting glucose

(71%). Prevalence of the metabolic syndrome was 60% greater than that of type 2 diabetes in the same population. Similar differences in glucose tolerance between African-Americans and non-Hispanic whites were found in healthy young adults from the Coronary Artery Risk Development in young adults (Pereira et al., 2002). This finding suggested that the predisposition to abnormalities in glucose tolerance may be more common in African-Americans than in Caucasians (Pereira, Jacobs et al., 2002). Thus, the increased prevalence of MS may be related to an increase in BMI as well as to the aging and increasing ethnic-racial diversity of the U.S. population (Mokdad, Ford et al., 2003; Kim and Beckles, 2004).

2. The prevalence of the obesity related metabolic risks in Asians

Several studies provide evidence to support that insulin resistance could be the biological basis for the racial difference in expression and prevalence of diabetes. Dickinson and colleagues examined possible variations in the evolution of the insulin resistance syndrome across races by comparing Asians and Caucasians (Dickinson, Colagiuri et al., 2002). Young, healthy, lean Asian and Caucasian adults were fed white bread in an amount to provide 75 g of available carbohydrate. Baseline plasma glucose and insulin as well as changes in glucose and insulin concentration were measured for 2 hours post parandial. Mean fasting glucose concentrations were similar between groups, but postprandial glucose was markedly higher in Asian subjects compared with Caucasians, with a two-fold higher mean incremental area under the curve. Insulin responses were similar with a mean area under the curve greater than

two- fold higher for the Asian group. When insulin sensitivity was estimated by the homeostasis model assessment, the Asians were less insulin sensitive than the Caucasians. These results supported the likelihood of racial differences in predisposition to the development of the insulin resistant syndrome. However, cardiovascular fitness levels were not controlled nor matched in this study.

Pan et al. (2002) used data from the Nutrition and Health Survey in Taiwan (NAHSIT) and the US National Health and Nutrition Examination Survey III (NHANES III) to estimate the prevalence rate of the metabolic syndrome defined by NCEP-ATP III guidelines. Findings demonstrated that the risk of increasing BMI for hypertension, diabetes, and hypertriglyceridemia was greater for Taiwanese than for US non-Hispanic whites in the US. As illustrated in **Figure 2.3,** the clustering of high blood pressure (BP), triglycerides (TG) and high-density lipo-protein (HDL-C) with or without large waist circumference was most common for Taiwanese men, while the US non-Hispanic white population showed a more evenly distributed pattern. Most Taiwanese women had a clustering of high HDL, BP and waist circumference, while most white women had a syndrome of high HDL, TG, and waist circumference. Abdominal obesity appeared more prevalent for women than for men across populations. The results of this study showed that the patterns of MS varied by gender and among various ethnic/racial groups. The implications of these different co-morbidity patterns should be considered in cross cultural comparisons.

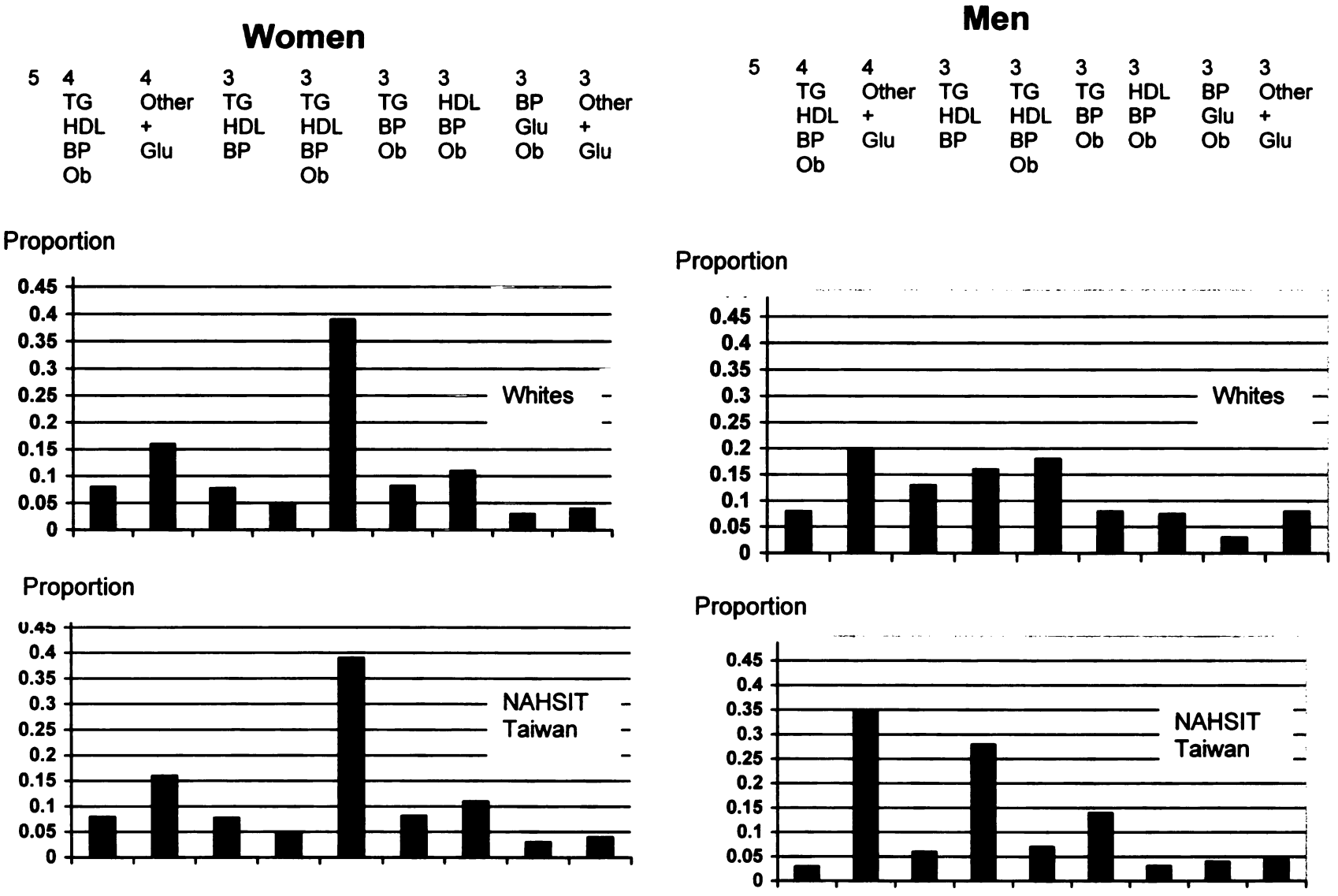


Figure 2.3 Patterns of metabolic syndrome in Taiwanese and in US non-Hispanic whites (TG: hi-triglycerides, HDL: low-high density lipoprotein, BP: high blood pressure, OB: large waist circumference, Glu: high fasting blood glucose). Adapted from (Pan, 2002).

Many Asians have a higher prevalence of metabolic disorders at a lower BMI level compared to their Caucasians counterparts (Pan et al., 2002). It has been debated for years whether the cut point for BMI to define obesity for Asian countries should be set lower than that for populations with predominantly Caucasian and African ancestry (Ota, Takamura et al., 2002; Grundy, Brewer et al., 2004; Kim, Ahn et al., 2005; Shiwaku, Nogi et al., 2005). To this end, investigators have examined the relationship between central body fat deposition in Asians as a contributing risk factor to a higher prevalence of type 2 diabetes and premature CVD.

Recently, it has been found that type 2 diabetes and premature CVD occurs in individuals with lower BMIs in Asians compared to Caucasians (Ota, Takamura et al., 2002; Grundy, Brewer et al., 2004; Kim, Ahn et al., 2005; Shiwaku, Nogi et al., 2005). Bell et al. examined ethnic differences on the strength of the association between BMI and hypertension (Colin Bell, Adair et al., 2002). Cross-sectional data were used from adults aged 30-65 years in China (n = 3,423), the Philippines (n = 1,929), and the United States (n = 7,957). A higher BMI was associated with a higher prevalence of hypertension in all ethnic groups. However, at BMI levels less than 25, prevalence rate increased more in Chinese men and women, but not in Filipino women, compared to non-Hispanic whites. Non-Hispanic blacks and Filipino women had a higher prevalence of hypertension at every level of BMI compared with non-Hispanic whites and Mexican-Americans. These ethnic differences, along with the strength of

association between BMI and hypertension and in underlying prevalence, warrant further investigation of the use of ethnic-specific BMI cutoffs in clinical settings to more accurately identify individuals at risk from obesity (Colin Bell, Adair et al., 2002).

Another study examined Singaporean Chinese, Malays, and Indian populations to determine the risk for selected co-morbidities at various BMI categories and abdominal fat distribution using data from the Singapore National Health Survey (Deurenberg-Yap, Chew et al., 2002). Results demonstrated that at any given body fat percentage, the BMI of Singaporean Chinese, Malays, and Asian Indians was approximately 3 kg/m^2 lower than that of Caucasians.

In Asian ethnic groups, specifically Chinese, Korean, Indian, Pakistani, and Bangladeshi, the risk of hypertension, diabetes, and hypercholesterolemia starts to increase rapidly at levels of BMI and WC well within the acceptable range of BMI or WC for Europeans (Deurenberg, Yap et al., 1998; Deurenberg-Yap, Chew et al., 2002; Kim, Suh et al., 2004; Pan, Flegal et al., 2004). A possible explanation of the difference in risk across races/ethnicities might be that Asians have a higher level of body adiposity at a lower level of BMI or more visceral adiposity distribution compared to Caucasians. Co-morbidities of metabolic syndrome also appear to be associated with both abdominal fat distribution and total body adiposity. The relative effect of total fat and of abdominal fat to MS and to specific metabolic disorders within various populations, however, needs clarification.

Although metabolic syndrome occurs in all populations, the disturbances of lipid metabolism and distribution of body fat that accompanies insulin resistance vary among populations. Genetics and environmental factors all contribute to such disparities in co-morbidities. Varying definitions and age groups used in different studies further complicate the differences. Regardless, cross cultural studies can enhance understanding of etiology, so important to developing effective prevention and treatments. Comparative studies between populations of European and Asian descent can help to delineate differences in amount and distribution of adipose tissue between groups. Such comparisons are important because the WHO definitions for overweight and obesity and NCEP-ATP III definitions for metabolic syndrome were established using data from populations primarily of European descent (WHO, 1995; Pan, 2002). However, people of Asian descent appear to exhibit metabolic risks at lower anthropometric cut-points, and finally, the marked increase in Asian populations around the globe may call for the lowering of their BMI cut-point.

E. Lifestyle factors (diet and physical activity) related to metabolic disorders.

The metabolic syndrome is closely linked to lifestyle factors of energy intake in excess of needs and a sedentary lifestyle. One study showed that middle- aged men engaging in over three hours per week of moderate to vigorous leisure-time physical activity were half as likely as sedentary men to have MS (Laaksonen, Lakka et al., 2002). This risk reduction was similar in two

prospective studies for the development of diabetes following lifestyle interventions for obese subjects with impaired glucose tolerance (Tuomilehto, Lindstrom et al., 2001; Diabetes Prevention Program Research Group, 2002).

Due in a large part to findings like these, the revised NCEP-ATP III report targeted lifestyle interventions for prime consideration to reduce risk for metabolic syndrome (Grundy, Cleeman et al., 2005) . Weight management, increased physical activity, and dietary moderation were all recommended to reduce risk for atherosclerotic cardiovascular disease (Grundy, Cleeman et al., 2005). The following section will review the current evidence for the salutatory effect of healthy diet and physical activity on the etiology of insulin resistance and the metabolic syndrome.

1. Weight reduction

It is commonly observed that the probability of having metabolic abnormalities, including metabolic syndrome, increases with the level of obesity. The association between increased prevalence of obesity and metabolic syndrome reflects the importance of adiposity as a contributor to insulin resistance and metabolic syndrome. Recent clinical trials and observational epidemiologic studies demonstrate the importance of lifestyle changes—such as decreased intake of energy and dietary fat—to sustain weight loss, as well as regular physical activity to improve insulin sensitivity, glucose tolerance and to reduce the risk of cardiovascular disease (Ross, Janssen et al., 2004; Janssen, Katzmarzyk et al., 2005).

Several researchers have emphasized that dietary treatment for metabolic syndrome should primarily focus on weight reduction to improve both insulin sensitivity and other aspects of the metabolic syndrome (Riccardi and Rivellese, 2000; Riccardi, Aggett et al., 2004; Reaven, 2005). Evidence from observational and clinical trials of lifestyle interventions indicates that even moderate, sustained weight loss can substantially improve insulin action and reduce the risk of type 2 diabetes. The Finnish Diabetes Prevention Study used an intensive lifestyle modification and middle-aged, overweight subjects with impaired glucose tolerance demonstrated reduced risk for diabetes of 58% over 3.2 years of follow-up, accompanied only by a moderate weight reduction of 3.5 Kg (Tuomilehto, Lindstrom et al., 2001). The Finnish intervention included a diet low in saturated and trans fats and high in fiber with regular moderate physical activity. Hermansen reported similar results in a review of weight reduction and blood pressure interventions (Hermansen, 2000). Most randomized control studies demonstrated that even a modest weight loss of 3-9% was associated with a significant reduction in systolic and diastolic blood pressure, roughly 3mmHg, in overweight and obese people.

Most recently in the Diabetes Prevention Program, 3,234 individuals with impaired glucose tolerance were randomly assigned to receive intensive lifestyle intervention, metformin, or a placebo (Ratner et al., 2005). Goals of the intensive lifestyle modification program were to achieve and maintain a weight reduction of at least 7% of initial body weight through consumption of a healthy, low-calorie, low-fat diet and to engage in moderately intense physical activity for at least 150

min/week. After three years of annual assessments, the lifestyle interventions improved CVD risk factor status compared to the placebo and metformin therapy (Ratner, Goldberg et al., 2005). Findings from these studies demonstrate that changes in diet and physical activity can reduce the risk for the co-morbidities of the metabolic syndrome.

2. Relationships of dietary factors and metabolic syndrome

a. Dietary Fat

Consumption of energy-dense and/or high fat diets is strongly and positively associated with overweight and obesity. This in turn impairs insulin sensitivity, particularly when excess adiposity is located in the abdominal region (Feskens, Virtanen et al., 1995). Insulin sensitivity is not only affected by the amount of dietary fat, but also by the quality of dietary fat (Riccardi and Rivellese, 2000). Epidemiological evidence and intervention studies reviewed here clearly show that high intakes of saturated fats significantly worsened insulin-resistance, while those of monounsaturated and polyunsaturated fatty acids improved it through modifications in the composition of cell membranes reflecting dietary fat composition (Riccardi, Giacco et al., 2004).

Astrup and colleagues conducted a meta-analysis of 16 ad libitum low-fat dietary interventions to review the role of dietary fat on body fatness. The results showed that a 10 percent reduction of total Kilocalories from fat would be

expected to decrease mean body weight of the population by 2.5 Kg (Astrup, Grunwald et al., 2000; Frayn and Vessby, 2000). Furhtermore, such a reduction in fat would reduce the obesity prevalence from 20% to 10%, which is an important public health impact.

In a large, geographically based sample of Hispanic and non-Hispanic whites in southern Colorado, high total and saturated fat intakes were associated with hyperinsulinemia independent of age, gender, ethnicity, BMI, waist circumference, total energy intake, or participation in vigorous physical activity (Marshall, Bessesen et al., 1997). Findings from the Dutch and Finnish cohorts of the Seven Countries Study, a 30-year follow-up survey, supported a role for dietary fat in glucose intolerance and the development of type 2 diabetes (Feskens, Virtanen et al., 1995). Although the regression coefficients were small, habitual intake of total and saturated fat higher than the average was positively associated with diabetes incidence 30 years later, adjusting for age, cohort, BMI, and energy intake.

A recent multi-center study demonstrated that a shift from a diet rich in saturated fatty acids to a diet rich in monounsaturated fat improved insulin sensitivity in healthy people (Riccardi, Giacco et al., 2004). Rasmussen conducted randomized multi-center clinical trial with 162 healthy, normotensive subjects assigned to one of two isoenergetic diets: rich in monounsaturated fatty acids (MUFA diet), or rich in saturated fatty acids (SFA diet) (Rasmussen, Vessby et al., 2006) . After three months, those on the MUFA-rich diet had a significantly lower diastolic blood pressure (DBP) compared to those on the SFA-rich diet.

Interestingly, the favorable effects of MUFA on DBP disappeared at a total fat intake above the median of 37% total energy. Although the type of fat, rather than the amount of fat, in the diet might be more important in terms of determining health outcomes, it is noteworthy that a reduction on blood pressure from a MUFA- rich diet is lost when the total fat intake is high.

Positive correlations between changes in dietary total and saturated fatty acids and changes in total, LDL, and HDL cholesterol were in a meta-analysis of 37 dietary intervention studies observed (Yu-Poth, Zhao et al., 1999). In free-living subjects, plasma total cholesterol decreased by 24 mg/dl (10%) compared to baseline, LDL cholesterol by 19 mg/dl (12%), and triglycerides by 15 mg/dl (8%) in Step I diet interventions of 10% saturated fat and 300 mg cholesterol. In Step II diet interventions of 7% saturated fat and 200 mg cholesterol, total cholesterol decreased from baseline by 32 mg/dl (13%), LDL cholesterol by 25 mg/dl (16%) and triglycerides by 17 mg/dl (8%). However, HDL cholesterol decreased by 7% in response to Step II but not Step I dietary interventions (Yu-Poth, Zhao et al., 1999).

b. Dietary carbohydrate

Three aspects of dietary carbohydrate might be relevant to the relation of dietary carbohydrate to risk for metabolic syndrome. Findings from studies investigating the replacement of dietary carbohydrate for fat, dietary fiber, and the glycemic index have all been suggestive. Some of the research on these aspects of carbohydrate and risks for co-morbidities of metabolic syndrome are reviewed in this section.

Until recently, the prudent diet recommended for all Americans contained approximately 15% of total energy from protein, 25%-30% from fat, and 55%-60% from CHO (Gardner and Kraemer, 1995), an approach aimed at decreasing saturated fat intake. The rationale for this recommendation was to reduce CVD risk by keeping low-density lipoprotein cholesterol (LDL-C) concentration as low as possible (Gardner and Kraemer, 1995). The problem with the prudent diet approach was that replacing saturated fat with carbohydrate in isocaloric diets might require more insulin secretion to maintain glucose homeostasis. As a result, insulin resistant individuals will have a greater degree of compensatory hyperinsulinemia (Reaven, 2005).

Although the beneficial effects of low-fat and high-CHO diets on LDL-C concentrations are not lost in insulin resistant individuals, this dietary modification in an insulin resistant person might increase postprandial plasma glucose, insulin levels, and triglycerides and decrease HDL cholesterol (Garg, Bantle et al., 1994; Garg, 1998). There is considerable evidence that increasing dietary intake of CHO accentuates the postprandial accumulation of TG-rich lipoproteins (Chen, Coulston et al., 1995; Abbasi, McLaughlin et al., 2000; Kim, Abbasi et al., 2001). Thus, the predictable effect of low fat/high CHO diets in insulin resistant and hyperinsulinemic individuals will be both an increase in fasting plasma TG concentration and accentuation of the daylong accumulation of TG-rich remnant lipoproteins. Two meta-analyses have shown that low-fat/high-CHO diets result in lower HDL-C concentrations (Mensink and Katan, 1992; Gardner and Kraemer, 1995). There is also an independent relationship between insulin

resistance and hyperinsulinemia and HDL-C concentration (Laws and Reaven, 1992).

Studies have demonstrated a reduced risk of type 2 diabetes with increased intakes of dietary fiber, especially cereal fiber. In a cohort of 42,759 men followed for six years, cereal fiber was inversely associated with type 2 diabetes risk. Similar findings were observed in a large cohort of women, where the relative risk of the extreme quintiles of cereal fiber intake was 0.72 (CI, 0.58-0.90, P trend=.001) (Salmeron, Manson et al., 1997). Data from the Nurses' Health Study supported a role of whole grains in protection against the development of type 2 diabetes (Liu, Manson et al., 2000; Liu, Manson et al., 2000). Comparing the highest to the lowest quintiles of whole grain intake, and adjusting for age and energy intake, the relative risk was 0.62 (95% CI: 0.37, 1.04; P: for trend = 0.07), whereas increased consumption of refined grains was associated with elevated risk of diabetes.

Manipulation of the glycemic index has been suggested to limit the metabolic consequences of the conventional low-fat/high-CHO diets. The rationale for the concept of the glycemic load is that if carbohydrate digestion and absorption are slowed then carbohydrate-rich foods will induce rapid perturbation of the metabolic steady fasting state (Riccardi and Rivellese, 2000). The glycemic index (GI) quantifies the glycemic response produced by a standard amount of a carbohydrate-containing food relative to the response produced by the same amount of carbohydrate from white bread or glucose (Costacou and Mayer-Davis, 2003; Wolever, 2003). The product of the glycemic index and the carbohydrate

content of a food (glycemic load, GL) is an indicator of the quality as well as the quantity of dietary carbohydrate. Although the glycemic index has been criticized for its quantitative approximation, it nevertheless differentiates among the carbohydrate-rich foods as 'fast' or 'lente' depending on the rate of digestion and absorption, which clinical studies have shown as having divergent effects on most of the cardiovascular risk factors clustered in the metabolic syndrome (Gustafsson, Asp et al., 1993; Jenkins and Jenkins, 1995). The detrimental effects of a high-carbohydrate diet on plasma glucose/insulin, triglyceride/HDL, or fibrinolysis occur only when carbohydrate foods with a high GI are consumed, while they are diminished when the diet is largely based on fiber-rich, low-GI foods (Garg, Bantle et al., 1994; Frost, Leeds et al., 1999; Jenkins, Kendall et al., 2000).

Based on the studies in this section, it appears that replacement of saturated fat with MUFA and/or PUFA, rather than CHO, will lower LDL-C concentrations and not lead to a significant increase in plasma insulin concentrations and the manifestations of the metabolic syndrome. However, as mentioned before the anti-athrogenic effect of a MUFA-rich diet seems to be lost at a high total fat intake (Rasmussen, Vessby et al., 2006). Furthermore, diets high in fiber from whole grains and diets with a low glycemic load have been found to have beneficial effects on plasma glucose and insulin. Aspects of all these factors together likely relates to the beneficial effects of the food pattern called the Mediterranean diet reviewed next on risk for the metabolic syndrome.

c. Mediterranean diet pattern

Although some dietary factors have been linked to individual features of the metabolic syndrome, endorsement of an entire dietary pattern, the Mediterranean diet, has come from the scientific advisory committee of the American Heart Association for its ability to reduce or halt the progression of cardiovascular disease and co-morbidities of the metabolic syndrome (Robertson and Smaha, 2001; Esposito, Marfella et al., 2004). Evidence for beneficial health effects of the Mediterranean diet emerged from the classic studies of Keys that showed diets enriched in monounsaturated fat (MUFA) related to reduced incidence of coronary heart disease (Keys, 1997). The Lyon Diet Heart Study showed that a Mediterranean-type diet reduced the rate of recurrence after an initial myocardial infarction (de Lorgeril, Salen et al., 1999). Recently, Esposito et al. conducted a randomized, single-blind trial to determine the dietary effect on metabolic syndrome (Esposito, Marfella et al., 2004). For two years, randomly assigned patients with metabolic syndrome followed either a Mediterranean-style diet of daily consumption of whole grains, fruits, vegetables, nuts, and olive oil or a prudent diet (carbohydrates, 50%-60% kcal; proteins, 15%-20% kcal; total fat, <30% kcal). Those patients on the Mediterranean-style diet demonstrated greater improvement of endothelial function and a significant reduction of markers of systemic vascular inflammation compared to those on the prudent diet.

Food aspects of the Mediterranean diet other than MUFAs that might be beneficial are low intake of alcohol and high intakes of antioxidants and polyphenols. Alcohol intake in excess (more than 30 g/d) can increase both

plasma triglyceride and blood pressure levels (Kiechl, Willeit et al., 1996). Increased oxidative stress might contribute to endothelial inflammation that could play a role in the etiology of both diabetes and CVD. Thus, interest has focused on the ability of antioxidant vitamins and polyphenols (from fruits, vegetables, and whole grains) to protect against inflammation (Riccardi and Rivellese, 2000).

3. Relationship of exercise and metabolic syndrome

Regular physical activity has many benefits, including a reduced risk of cardiovascular and all-cause mortality (Ekelund, Haskell et al., 1988). Benefits of physical activity have been attributed to improved weight control, reduced LDL cholesterol, and increased insulin sensitivity in a dose-response fashion(Kelley and Goodpaster, 2001). Using data from NHANES III Park et al. demonstrated that physical inactivity significantly predicted the prevalence of metabolic syndrome (Park, Zhu et al., 2003) . In a separate NHANES III analysis, strong and significant inverse associations were reported between physical activity and self-reported stroke and angina/myocardial infarction (Ford and Giles, 2000).

Increased glucose tolerance was seen after oral and intravenous glucose loading (Reaven and Laws, 1999) prior to both acute exercise and physical training. For young, middle- aged, and older adults, several epidemiological studies have reported significant associations between physical activity/cardiorespiratory fitness with insulin resistance and other components of the metabolic syndrome (Eriksson, Taimela et al., 1997; Siscovick, Fried et al., 1997; Mayer-Davis, D'Agostino et al., 1998). Within the population-based Kuoppio study, men who engaged in at least moderate-intensity ($\geq$4.5 metabolic

equivalents [METs]) leisure time physical activity of <1.0 hr/wk were 60% more likely to have metabolic syndrome (WHO definition) than those engaging in ≥3.0 hr/wk, even after adjustment for confounding variables (age, socio-economic status, smoking, and alcohol consumption) (Laaksonen, Lakka et al., 2002).

Two intervention studies deserve attention. Among African American and Caucasian sedentary participants recruited for the Health Risk Factors Exercise Training and Genetics Family Study, prevalence of the metabolic syndrome (ATPIII) decreased to 11.8% from 16.9% after 20 weeks of exercise training (Katzmarzyk, Leon et al., 2003). Of 105 participants with the metabolic syndrome at base line, 30.5% (32 participants) were no longer classified as having the metabolic syndrome after the exercise training. No sex or race differences in the efficacy of exercise in treatment were observed. In the Da Qing Study in China, participants with impaired glucose intolerance were assigned to a dietary, exercise, or diet-plus-exercise intervention group. The six-year incidence of diabetes ranged from 41-46% across the intervention groups compared to 67.7% in the control group (Pan, Li et al., 1997). Diabetes risk was reduced by 31%, 46%, and 42% in the diet, exercise, and diet-plus-exercise interventions, respectively. Ross and Katzmarzyk found that men and women with high cardiorespiratory fitness had smaller skinfold thicknesses and less abdominal fat (by waist circumference) for a given BMI compared with men and women with low fitness levels (Ross and Katzmarzyk, 2003).

The exercise induced enhancement of insulin action in muscle is predominantly due to local contraction-dependent mechanisms (Dela, Mikines et

al., 1992). Insulin increases muscle blood flow and this effect tends to increase with training (Dela, Mikines et al., 1992), whereas muscle blood flow may be reduced by inactivity. It is also known that the risk of having insulin resistant syndrome is higher in those with lower levels of cardiorespiratory fitness (Farrell, Cheng et al., 2004) and that overweight and obese individuals have lower levels of fitness than normal weight individuals (Farrell, Braun et al., 2002). Furthermore, recent studies have demonstrated that physically fit men and women, when compared with physically unfit men and women, have a lower amount of total and abdominal fat for a given BMI (Ross and Katzmarzyk, 2003; Janssen, Katzmarzyk et al., 2004). Thus, cardiorespiratory fitness may play an important role in explaining the increased risk of morbidity and mortality associated with metabolic syndrome across levels of body weight.

Lifestyle therapies are first-line interventions to reduce the metabolic syndrome and individual metabolic risk factors (Grundy, Cleeman et al., 2005). The major lifestyle interventions include weight loss in overweight or obese subjects, increased physical activity, and modification of an atherogenic diet **(Table 2.5).** These changes will produce a reduction in all of the metabolic risk factors simultaneously. In the long run, the greatest benefit for those with the metabolic syndrome will be derived from an effective lifestyle intervention.

The accumulation of evidence demonstrating that obesity and physical inactivity, both modifiable, are the most important contributors in the development of metabolic syndrome (Franz, Bantle et al., 2002). Therefore, it is important to include dietary factors and physical activity within analytic models of risk

exposures and atherosclerotic cardiovascular disease outcomes, especially in studies where dietary factors and physical activity measurements are available and have been previously related with the study variables of interest.

Table 2.5. Treatment of Lifestyle Risk Factors for Long-Term Prevention of atherosclerotic cardiovascular disease
or Prevention/Treatment of Type 2 Diabetes

Theraputic Target and Goals of Therapy	Therapeutic Recommendations
Abdominal obesity Goal: Reduce body weight by 7-10% during first year of therapy. Continue weight loss thereafter to extent possible with goal to ultimately achieve desirable weight (BMI<25kg/m2)	Consistently encourage weight maintenance/reduction through appropriate balance of physical activity, caloric intake, and formal behavioral programs when indicated to maintain/achieve waist circumference of <40 inches in men and <35 inches in women. Aim initially at slow reduction of ~7-10% from baseline weight. Even small amounts of weight loss are associated with significant health benefits.
Physical inactivity Goal: Regular moderate-intensity physical activity; at least 30 min of continuous/intermittent (preferably 60 min) 5 d/wk, but preferably daily	In patients with established CVD, assess risk with detailed physical activity history and/or exercise test, to guide preparation. Encourage 30-60 min moderate-intensity aerobic activity (eg, brisk walking), preferably daily, supplemented by increase in daily lifestyle activities (eg, pedometer step tracking, walking breaks at work, gardening, household work). Higher exercise times achieved by accumulating exercise throughout day. Encourage resistance training 2d/wk. Advise medically supervised programs for high risk patients (eg, recent acute coronary syndrome or revascularization, CHF).
Atherogenic diet Goal: Reduce intakes of saturated fat, *trans* fat, cholesterol	Recommendations: Saturated fat <7% of total calories; reduce *trans* fat; dietary cholesterol <200mg/d; total fat 25-35% of total calories. Most dietary fat should be unsaturated, simple sugars should be limited.
BMI indicates body mass index; CVD cardiovascular disease, and CHF, congestive heart failure.	

Adapted from (Grundy, Cleeman et al., 2005).

F. Methods use to assess body fatness.

Obesity- related studies have used different anthropometric indices to assess body fatness, including body mass index (BMI), waist circumference (WC), waist-to-hip ratio (WHR), percent body fat measured by bioelectrical impedance analysis (BIA), and subscapular thickness or triceps skin fold (TSF) measurement. However, specificity and adequacy of these indicators is still controversial because they are indirect and do not allow a precise assessment of body composition (Deurenberg, Yap et al., 1998; Prentice and Jebb, 2001). Direct and accurate measurement of adiposity relies on complex technologies such as dual energy X-ray absorptiometry (DEXA) or computed tomography that has little epidemiological applicability due to high costs and methodological efforts needed. This part of the literature review will focus on the definitions and uses BMI, WC, and BIA as well as their limitations and strengths. Important considerations of using these measures as indicators to interpreted obesity and related risk factors will be discussed.

1. Body Mass Index (BMI)

Body mass index, or Quetelet Index, is a statistical measure of the weight of a person scaled according to height. It was invented between 1830 and 1850 by the Belgian polymath Adolphe Quetelet (Quetelet, 1973). BMI is defined as the individual's body weight (Kg) divided by the square of their height (m^2). BMI became popular in the late 1980s, as obesity started to become an issue of concern in Western society. Most medical professionals have been educated in its

use, and BMI has made significant progress into general public awareness and is gaining acceptance by the mass media (Seidell, Kahn et al., 2001).

The main assumption of BMI is that body mass, adjusted for stature squared, is closely associated with body fatness and consequent morbidity and mortality(Bray, 2003). Because BMI does not measure the fat mass or percentage of fat, the Expert Committee of WHO proposed classification of BMI in terms of degrees of overweight rather than degrees of obesity, with the cut-off points 25, 30, and 40 based principally on the association between BMI and mortality (WHO, 1995). National Institutes of Health (NIH) and the World Health Organization (WHO) then adopted similar body weight guidelines for overweight and obesity (WHO, 1998; DHHS, 2000). According to the WHO, a BMI of ≥ 25.0 is classified as overweight and a BMI of ≥ 30.0 as obesity.

BMI has been used extensively to classify obesity highlighting associated health risks. Based on NHANES III data, Park et al. (2003) reported a prevalence of metabolic syndrome in 4.8%, 22.8%, and 60.2% of normal-weight (BMI: 18.5–24.9), overweight (25.0–29.9), and obese (≥ 30) men in the US population, respectively. The same prevalence pattern were also found in US women (Park, Zhu et al., 2003). The Asia Pacific Cohort Studies Collaboration (Ni Mhurchu, Rodgers et al., 2004), using individual participant data from 33 prospective studies in the Asia-Pacific region, showed that there were continuous positive associations between baseline BMI and the risks of ischemic stroke, hemorrhagic stroke, and ischemic heart disease (IHD), with each 2 kg/m^2 lower BMI associated

with a 12% lower risk of ischemic stroke, 8% lower risk in hemorrhagic stroke, and 11% lower risk of IHD.

BMI is moderately correlated with body fatness but does not quantify total body adiposity (Kuczmarski and Flegal, 2000). Because the BMI is dependent only upon net weight and height, it makes simplistic assumptions about distribution of muscle and bone mass, and thus may overestimate adiposity on muscular individuals, e.g. athletes, while underestimating adiposity on those with less lean body mass, e.g. the elderly (Prentice and Jebb, 2001). This raises concerns about over diagnosis of obesity and hence inappropriate attempts at weight reduction. Moreover, for those with normal BMI (BMI=18.5-24.9) but with higher total percent of body fat, physically inactive people may underestimate their risks for obesity related disorders. Tanaka et al., using the sample of white people aged from 17 to 60 y from the Quebec Family Study, showed that normal BMI males with elevated adiposity had higher prevalence of risk factors than did normal BMI males with less adiposity, and the prevalence in the former was rather similar to that seen in overweight males (Tanaka, Togashi et al., 2002).

As discussed in the early part of this literature review, people with central adiposity have higher insulin levels and are more insulin resistant than subjects at a similar weight with a peripheral type of obesity. BMI does not take into account the distribution of fat in the body. Studies have shown that lean individuals with normal BMIs can also have a significant accumulation of VAT with increased risk factors for cardiovascular disease and diabetes (metabolically obese normal weight) (Ruderman, Chisholm et al., 1998; Katsuki, Sumida et al., 2004). Aging is

accompanied with a progressive increase in body fat and decrease in lean body mass. This occurs even in individuals who manage to maintain a constant BMI as they become older. Thus, the relationship between BMI and body fat is age-dependent (Prentice and Jebb, 2001). Because body fat is more likely to be deposited in the abdominal cavity with increasing age, it is claimed that BMI becomes a poor indicator of overall and abdominal fatness in older persons (Seidell and Visscher, 2000).

In recent years there has been an increasing awareness that certain ethnic groups display a very different relationship between BMI and body fat compared to that described for Caucasians. The universal cutoff points for BMI do not apply equally well for all racial groups. Many Asian races, such as Indian and Chinese, tend to carry a proportionately higher fat mass for a given BMI than Caucasians (Deurenberg-Yap, Chew et al., 2002; Deurenberg-Yap and Deurenberg, 2003; Wildman, Gu et al., 2004). Data from the Singapore National Nutrition Survey showed that at any given percent body fat, the BMI of Singaporeans (consisting mainly Indian, Malay, and Chinese) was about 3kg/m^2 lower than that of Caucasians. In fact, the BMI cutoff points for overweight and obesity were based on mainly those for Caucasians. Many Asian countries established their own cut-offs; Singapore used BMI 23 and 27 as the cut-off for overweight and obesity (Deurenberg-Yap, Chew et al., 2002), Taiwan used 24, 27(Yeh, Chang et al., 2005) respectively. Japan uses BMI greater or equal to 25 as an obesity cut point (Kanazawa, Yoshiike et al., 2002).

The BMI has been an invaluable tool to the backbone of the obesity classification system and surveillance statistics. Even though BMI are available to describe overweight for the medical management and treatment of overweight and obesity, BMI alone should not be considered diagnostic. Additional risk factors should be assessed, including the presence of abdominal obesity based on a measure of waist circumference and the presence of concomitant risk factors or comorbidities, such as hypercholesterolemia or diabetes (Kuczmarski and Flegal, 2000).

2. Waist Circumference

Increased risk of cardiovascular disease has been found in individuals presented with distribution of excess fat in the abdominal region. There is no standard measure of abdominal obesity that is widely accepted at present. Waist circumference (WC) has long been used as a surrogate measure of total abdominal adiposity. Lean et al. (1995) first proposed the use of waist circumference (WC) as part of clinical cardiovascular risk assessments and interpretation of health risks associated with adiposity. Lean et al. (1995) have found that WC $\geq$ 102 cm for men or $\geq$ 88 cm for women identified subjects with body mass index $\geq$ 30. According to their results, Lean et al. suggested men with waist circumference $\geq$ 94 cm and women with waist circumference $\geq$ 80 cm should gain no further weight (waist action level 1), and men with waist circumference $\geq$ 102 cm and women with waist circumference $\geq$ 88 cm should reduce their weight (waist action level 2). The International Diabetes Foundation

(IDF) currently identifies WC limit as one of the necessary requirements for the diagnosis of metabolic syndrome (Zimmet, Alberti et al., 2005). Recommendations are based on ethnic origin; for men: Europids $\geq$ 94 cm, South Asians and Chinese $\geq$ 90, Japanese $\geq$ 85; for women: Europids, South Asian and Chinese $\geq$ 80 cm (Zimmet, Alberti et al., 2005).

The majority of current studies agree that waist circumference (WC) is probably a better indicator of abdominal fatness and cardiovascular disease than either BMI or waist-to-hip ratio (WHR)(Reeder, Senthilselvan et al., 1997; Dobbelsteyn, Joffres et al., 2001). In the NHANES III study and in population studies from Canada, Hong Kong, and Japan, WC was more closely related to metabolic risk factors than was BMI (Ho, Lam et al., 2003; Zhu, Wang et al., 2003; Janssen, Katzmarzyk et al., 2004). Besides identifying individuals with cardiovascular disease risk factors, the WC measure has several advantages over both BMI and WHR. Simplicity, low cost, acceptable accuracy, and ease of interpretation have led to the use of WC measurement compared to BMI and WHR in a clinical setting. It requires only the use of a tape measure, alleviating the expense of the equipment and space needed to measure height and weight. A single measurement (WC) as opposed to the ratio of two measures (WHR), is less susceptible to measurement and calculation errors (Dobbelsteyn, Joffres et al., 2001). Studies have shown a correlation between the change in WC and abdominal fat mass for women and visceral fat mass for men and women (Ross, Janssen et al., 2004) and a decrease in WC has been reported to correlate with

improvements in glucose metabolism. For these reasons, WC is an easy and cost-effective field measure.

However, WC is not without limitations in public health applications (Seidell, Kahn et al., 2001). The limitation of WC is the inability to differentiate subcutaneous adipose tissue from visceral adipose tissue. WC is a direct measure of length rather than of area or volume. Defining fat distribution in the abdominal region based on WC requires transformation of length into separate area or volume (He, Engelson et al., 2004). Circumferences reflect internal as well as subcutaneous adipose tissue and are influenced by variation in muscle and bone. Waist circumference has been shown to be highly correlated with intra-abdominal and total fat mass.

Although many investigators believe that waist circumference serves as a surrogate for visceral fat, it still has a substantial contribution from metabolically different subcutaneous fat (Misra, Wasir et al., 2005). Waist circumference seems to quantify subcutaneous fat better than visceral fat (Bonora, Micciolo et al., 1995). Furthermore, correlation of waist circumference to visceral fat depends on sex and ethnicity because it is weaker in women and blacks (Weinsier, Hunter et al., 2001). Weinsier et al. studied 46 white and black women during a weight loss program and found that white women lost more intraabdominal adipose tissue ($p < 0.001$) and less subcutaneous abdominal adipose tissue ($p < 0.03$) than did black women. In this study, changes in waist circumference correlated with changes in intraabdominal adipose tissue in white women but not in black women. Investigators concluded that waist circumference was not a suitable surrogate

marker for tracking changes in the visceral fat compartment in black women (Weinsier, Hunter et al., 2001).

The lack of a standard protocol for measurement for WC is unfortunate. WC varies between subjects in relation to bone landmarks, muscle, adipose tissue, or may be difficult to identify in obese subjects. In the Taiwan National Nutrition and Health Survey (NAHSIT) and Canadian Heart Health Surveys (CHHS), WC was measured at the visible narrowing of the waist after a normal exhalation, or in extreme cases of obesity, at the level of the 12th rib (Wang, Thornton et al., 2000; Yeh, Chang et al., 2005). In Japan's national nutritional survey, the WC was measured at the height of the navel (Nishimura, Nakagami et al., 2007), but in the diagnostic criteria of the International Diabetes Foundation (IDF) it was measured at the midpoint between the subcostal margin and the margin of the supracristal plane (Zimmet, Alberti et al., 2005). In the United States, technicians in NHANES III measured WC immediately above the iliac crest (DHHS, 1997). Several papers reported considerable difference among different WC measure protocols (Wang, Thornton et al., 2003; Bigaard, Spanggaard et al., 2005). In Wang's study, there was a statistically significant difference (-1.7 cm) between WC measured immediately above the iliac crest (as in NHANES) and WC measured at the narrowest waist (as in the CHHS) in men. In women, the difference between measurement of WC at the iliac crest and narrowest waist was -4.6 cm. These discrepancies in the position of WC measurement make comparisons with other studies difficult. There is an urgent need to establish a single, universal bone

landmark to make the measurement of WC highly reliable and reproducible (Seidell, Kahn et al., 2001).

It must be acknowledged that BMI and WC are highly correlated with each other, at least within the ranges typically observed in industrialized societies. Because of this close correlation, it is difficult to separate the effects that each may have on health (Seidell, Kahn et al., 2001) . The U.S. NIH has recommended a two-tiered classification system using both BMI and WC (NIH, 2000). BMI and WC might be useful as a first step in determining health risks that can be confirmed by more complex and costly tests, such as blood analyses or physiologic challenges.

3. Percent body measured by bioelectrical impedance analysis (BIA)

Obesity is characterized by an excess amount of body fat, to the extent that heath may be impaired. Obesity as excess body fat was defined if percent body fat was greater than 25% in male and 35% in female subjects (WHO, 1995). However, the direct measurement of the body's fat mass is only possible via dissection and chemical analyses. Even indirect techniques like computed tomography (CT) and dual-energy x-ray absorptiometry (DEXA) remains a significant challenge for most body composition techniques. Several instruments have been developed to measure total body fat and its distribution, such as computer tomography (CT), magnetic resonance imaging (MRI) and dual-energy X-ray absorptiometry (DEXA). In general, these techniques are more accurate methods than anthropometric measurements for the assessment of body fat. But

these research techniques are not useful tools in large populations because of the high initial capital investment, the need for a highly trained technical staff, and the high annual maintenance and service costs (Ellis, 2001). Bioelectrical impedance analysis (BIA) promises at least one measure of body composition that can be applied to large populations. BIA is inexpensive, easy to use, free of observer bias, and precise (Lukaski, Bolonchuk et al., 1986; Roubenoff and Kehayias, 1991).

Bioelectrical impedance analysis (BIA) evaluates the electrical conductivity characteristics of the human body (Foster and Lukaski, 1996). In particular, single-frequency BIA evaluates resistance (the pure opposition of tissues to the flow of electrons), reactance (related to the capacitance of cell membranes, tissue interfaces, etc.), and phase angle (the shift between current and voltage). From a nutritional standpoint, resistance (even if more associated with height in different indexes) is considered to be related to total body water while phase angle probably reflects the variability in body cell mass and the ratio intracellular water/extracellular water (Foster and Lukaski, 1996). BIA measures of resistance and impedance are proportional to body water volume, if body electrolyte status is normal, and to the length of the conductor or stature (eg, stature^2/ resistance). Based on the principles of BIA measurement, to estimate the volume of total body water (TBW), three assumptions are used: the whole body acts like a cylindrical conductor, the conductor's length is proportional to the subject's height and the reactance component of the voltage signal can be disregarded (Ellis, 2001). BIA uses regression analysis to derive prediction

models to estimate TBW and fat-free mass (FFM) (Guo, Roche et al., 1989; Chumlea and Guo, 1994).

A large number of BIA equations in the literature predict FFM. These equations vary in the parameters included in the multiple regression equations and their applicability to various subjects. Early BIA equations (before 1987) only included height^2/resistance. Later equations include other parameters, such as weight, age, gender, reactance, and anthropometric measurements of the trunk and/or extremities to improve the prediction accuracy. Currently, the equations for men and for women are as follows (Zhu, Wang et al., 2003):

Men:

FFM (kg) = -10.68 + 0.65 - S^2/R + 0.26 x weight + 0.02 x R

Women:

FFM (kg) = -9.53 + 0.69 x S^2/R + 0.17 x weight + 0.02 x R

%BF = 100 - [(weight - FFM)/weight]

where S^2/R is stature squared divided by resistance (cm^2/Ω).

The use of BIA has increased because the equipment is portable and safe, the procedure is simple and noninvasive, and the results are reproducible and rapidly obtained (Kyle, Bosaeus et al., 2004). BMI and percent body fat measured by BIA are highly correlated. Studies have shown that the correlation coefficients between BMI and BIA are from 0.75 to 0.95 in different gender and age groups (Nagaya, Yoshida et al., 1999). As previously reported, high BMI and high percent body were strongly associated with high serum TC/HDLC ratio and

TG, and low serum HDLC rather than high serum TC and LDLC. Nagaya et al. compared the BMI and percent body fat measured by BIA found that percent body fat by BIA was best correlated with the serum indices, except for serum HDLC in both sexes (Nagaya, Yoshida et al., 1999).

Using the BIA measured values from NHANES III sample compared to the percent body fat determined by DXA, hydrostatic weighing, or data collected using other reference body composition methods in other studies. The means reported for the systematic differences among body composition methods and the between-method limits of agreement are approximately 2.0 kg for FFM and 3 –5% for percent body fat and should be considered when interpreting the data or making inferences (Chumlea, Guo et al., 2002).

Although the daily precision of BIA is good, the accuracy for the assessment of an individual's body fatness remains unclear, due to body dehydration and temperature. In conclusion, body fat can be determined by BIA provided that hydration is normal and BIA equations used are applicable to the study population, with regard to gender, age, and ethnic group (Kyle, Bosaeus et al., 2004).

It is now accepted that the distribution of body fat is an important determinant of metabolic abnormalities, possibly more so than the degree of excess weight as measured by BMI, nor the percent body fat measured by BIA (Walton, Lees et al., 1995). In particular, intraabdominal obesity or visceral fat is strongly associated with metabolic disturbances and insulin resistance (Pouliot, Despres et al., 1994), which could not be distinguished by simple WC

measurement. A combination of two or more screening indices should be able to help health professionals target those in the greatest risk for MS and clarify whether the regional or total adiposity contribute most to the etiology of MS.

CHAPTER THREE

METHODS

Study design

This study was a cross-sectional secondary data analysis of adults classified as overweight, but not obese (BMI 25-29.9 in US and BMI 24-27 in Taiwan). Data were obtained from two representative national health surveys, one from the US (for non-Hispanic whites) and one from Taiwan (for those of Chinese ancestry). The association and contribution of abdominal and total body adiposity to the risks for modified metabolic syndrome and related disorder (elevated triglycerides, low HDL cholesterol, high blood pressure, and impaired fasting glucose) were assessed in both samples. Subjects were divided into eight different anthropometric categories based on their waist circumference and percent body fat **(Figure 1.1).** The odds ratio were calculated to determine the odds of different body fat distribution patterns to modified metabolic syndrome and each of the metabolic syndrome- related disorders and to compare the race/ethnicity-specific differences across the non-Hispanic white and Taiwanese populations. The main outcome measures were the presence of modified metabolic syndrome (defined using NCEP ATP III guidelines, as two of four disorders, not including high waist circumference), serum triglyceride (TG), low high-density lipoprotein cholesterol (HDL), high blood pressure (BP), and elevated

fasting blood glucose, controlling for demographic factors, physical activity, and energy from fat or from carbohydrates.

Subjects and Datasets

Two data sets were used in this study; NHANES III data were used to examine Aim 1 and 2 for non-Hispanic whites. Both NHANES III and Nutrition and Health Survey in Taiwan (NAHSIT) data were used to determine racial differences (for non-Hispanic whites compared to Taiwanese) in body fat distribution in modified metabolic syndrome and metabolic syndrome related disorders. Third National Health and Nutrition Examination Survey (NHANES III) 1988–1994 (DHHS, 1996). The National Center for Health Statistics (NCHS) conducted this survey to obtain nationally representative information on the health and nutritional status of the US population. NHANES III was conducted at 89 locations in 2 phases: 1988–1991 and 1991–1994. NHANES III used a stratified, multi-stage probability cluster sampling, with each respondent's data weighted by the probability of being sampled. The results are representative of the US non-institutionalized population, two months of age or over from the 50 states and the District of Columbia (NCHS., 2007).

In NHANES III, standardized medical examinations were completed in mobile centers that traveled to 89 pre-selected sites in the continental U.S. The medical examinations included a blood chemistry panel and measurements of blood pressure, plasma lipid and glucose concentrations, and anthropometric measurements. Besides the medical examination, the NHANES III staff

conducted surveys in households, administering questionnaires to families, adults and children. The household surveys included questions about demographics, socioeconomic factors, dietary intakes, and health histories. The number of sampled persons for this survey were 39,695 with 33,994 (86%) of these interviewed and 30,818 (78%) both interviewed and examined (DHHS, 1996). This NHANES III survey received human subject approval from the Centers for Disease Control and Prevention. Details of the survey design and questionnaires are published in the NHANES III Plan and Operation Reference Manual (DHHS, 1997). The present study used data from the NHANES III instead of NHANES 1999-2000 for two reasons. First, the protocol was nearly the same in both NHANES III and NAHSIT, because the NAHSIT followed the NHANES III design and procedures. Secondly, NHANESIII had the timeframe most comparable to that of the NAHSIT.

Nutrition and Health Survey in Taiwan (NAHSIT), 1993-1996.

The NAHSIT was an island-wide survey in Taiwan of non-institutionalized residents four years and older selected by a multi-stage complex sample design (Pan, Yeh et al., 2003). A complex sampling scheme was used in th NAHSIT survey, parallel to that of the NHANESIII. The 359 townships or city districts in Taiwan were classified into seven strata according to their geographical locations and degree of urbanization. A total sample of 9,961 participants was obtained from door-to-door interviews, for a 74% response rate. Among those interviewed, 64.9% (6,464 individuals) participated and completed the physical examination. The survey consisted of two parts: The health component included questionnaires

on lifestyle, disease history and measurement of blood pressure, electrocardiogram, biochemical values, clinical signs, oral glucose tolerance test, and anthropometric measures. Clinical data and anthropometric measurements were obtained from a physical examination carried out in temporary clinics set- up in the neighborhood of the survey sites. The dietary and nutrition component included interviews for 24-hour dietary recalls, food frequency, nutrient supplements, vegetarian diets, nutrition-related knowledge/attitude/practices, and biochemical measurements for nutritional indicators. Details on the design and operation of the survey have been published (Lin, Yen et al., 2003; Pan, Flegal et al., 2004).

Analytic samples. The original data were retrieved from the NHANES III CD ROM (NCHS., 1998) and the NAHSIT data downloaded from http://srda.sinica.edu.tw/webpages/nahsit/index.htm. In this study, subjects from both surveys were limited to those aged 20-74 years of age and having a BMI=25-29.9 in NHANES III and BMI=24-27 in NAHSIT, respectively. To compare the specific racial differences in metabolic syndrome related disorders, only non-Hispanic whites were included from the NHANES III survey and only those of Chinese descent were included from the NAHSIT. In NAHSIT, the aboriginal island population, accounting for approximately 1.7% of the total sample, was excluded from this study. Most of the aborigines live in the mountainous areas and are thought to resemble the Malayo-Polynesians in their genetic make-up (Lin, Yen et al., 2003) differing from the main population of

Taiwan who immigrated from mainland China in several waves over the last 200 years.

Participants' data included anthropometric variables, blood pressure, socioeconomic status, lifestyle-related information, blood studies and body composition values from bioelectric impedance analysis (BIA). Further exclusion criteria were any participants with missing data values, who consumed food or beverages other than water within six hours before the venipuncture, and women pregnant or lactating at baseline. Sample sizes from NHANES and NAHSIT were approximately 1600 and 1000, respectively. Before analyzing the data, approval from the university's Institutional Review Board was obtained (Appendix 2).

Procedures

Three types of variables and categories of data were included in the analyses and are shown in **Table 3.1.** A detailed description of how measurements for these variables were collected and analyzed is found in **Appendix 1**.

Dependent variables were developed from the NHANES III and NAHSIT's medical examination data for serum triglycerides (TG), and high density lipoprotein (HDL), systolic and diastolic blood pressures, and fasting plasma glucose. Metabolic syndrome- related disorders were defined according to the latest National Cholesterol Education Program guidelines (NCEP ATP III) (NCEP., 2001). That is, dyslipidemia was defined as high TG (serum TG $\geq$150 mg/dL) and low HDL cholesterol (<40 mg/dL in men and <50 mg/dl in women). High blood pressure was defined as systolic blood pressure $\geq$130 mm Hg,

diastolic blood pressure ≥85 mm Hg, or reports of a history of hypertension or currently taking blood pressure medication, regardless of measured blood pressure values. Impaired fasting glucose was defined as fasting plasma glucose concentration ≥100 mg/dl (Grundy, Cleeman et al., 2005), previous physician's diagnosis of diabetes, or use of hypoglycemic medication. Modified metabolic syndrome (MMS) was defined as having two or more of these disorders.

Although the National Cholesterol Education Program guidelines include high waist circumference as a component of the metabolic syndrome, in this analysis the diagnosis of the metabolic syndrome does not include a high WC, hence the name Modified Metabolic Syndrome. Waist circumference was used instead as a predictor of the Metabolic Syndrome (Okosun, Liao et al., 2000; Janssen, Katzmarzyk et al., 2004). Individuals who reported currently using anti-hypertensive or anti-diabetic medication (insulin or hypoglycemic oral agents) were defined as having hypertension or high fasting glucose regardless of measured blood pressure and plasma glucose values.

Independent variables in this study included WC and percent body fat (%BF) as determined from bioelectrical impedance. WC and %BF were used to construct the eight anthropometric categories according to normal and high values for WC and quartiles of percent body fat (%BF). The cutpoints were 102 cm for men and 88 cm for women for the normal and high WC (NCEP, 2002). In this study, BMI was calculated as the weight of the individual in kilograms divided by the height in meters squared. Based on BMI, subjects were limited to those classified as

overweight with a BMI of 25–29.9, for both men and women (NIH, 1998). This definition is also consistent with those of the World Health Organization (Lean, Han et al., 1995).

Covariates from the demographic and lifestyle data included age, education, gender, race, smoking and alcohol drinking status, and physical activity. Dietary covariates were the percent of energy from total carbohydrates and from fat extracted from the 24-hour dietary recall in each survey

The covariate definitions for the NHANES data are described in the following paragraphs. The definitions for smoking and drinking are identical in NAHSIT to NHANES.

Smoking was categorized as current, past, or never. Subjects were considered current smokers if they smoked cigarettes, cigars, or tobacco at the time of the interview; previous smokers if they were not current smokers, but had smoked $\geq$100 cigarettes in their entire life; and nonsmokers if they had smoked less than those amounts (Janssen et al., 2004). For this study, alcohol consumption was graded as non-drinker, if subjects drank zero drinks of beer, wine or liquor in the past month, moderate drinker if they drank 1–15 drinks, or heavy drinkers if they drank >15 drinks.

Physical activity was based on the subject's self- reported frequencies involving common leisure physical activities in the past month in both data sets. The activities in NHANES III included: walking a mile without stopping, jogging or running, swimming, regular dancing, aerobic exercise, aerobic dancing, riding a bicycle or exercise bicycle, calisthenics, garden or yard work, or weight lifting. The

activities in NAHSIT included: riding a bicycle, ball games, gymnastics, punching/boxing, swimming, aerobic dancing/country dancing, mountain climbing, jogging, walking, gardening, or housework. Respondents engaging in no activity in a weekly period, less than one activity/week, 2-5 activities/week, and greater than 5 activities/week were divided into 'Physically inactive', 'light', 'moderately', and 'physically active' categories, respectively (Janssen, Katzmarzyk et al., 2004). Construction of rank order variables in NAHSIT from continuous data for education and income are described in **Appendix 1**. Education level from NHANES data was divided into three categories: ≤8 years, 9 to 12 years, and more than 12 years of education. Dietary factors will use the energy intake from carbohydrate and fat as covariates. Carbohydrate and fat were expressed as a percentage of total energy, as one relevant measure of dietary composition that might relate to risk of metabolic related disorders.

Statistical Analyses

Statistical analyses were conducted using the Statistical Package for the Social Sciences, SPSS for Windows, version 14.0 (SPSS Inc., Chicago, IL, USA,). All analyses were carried out with SUDAAN version 9 (Research Triangle Institute, Research Triangle Park, NC), to account for the effect of the complex sampling design in statistical testing and to derive means and standard errors. Variance estimation for the statistics computed by SUDAAN used the Taylor series linearization method or replication methods such as Jackknife. Missing values were handled separately for each metabolic disorder in the

analysis. A p-value <0.05 was used to detect statistical significance. Descriptive analyses included mean, standard deviation and standard error of the mean for estimates of BMI, WC, %BF, TG, HDL, systolic and diastolic blood pressure and fasting blood glucose. Values were calculated for each sex and racial-ethnic group.

For Aim 1, an adjusted Wald test (Zhu, Wang et al., 2003) was used to compare prevalence of modified MS, high TG, low HDL, hypertension and impaired fasting glucose between high and normal waist circumference and quartile categories of body fat. The data were age and sex standardized to the 1980 US population and design effect-adjusted standard errors were computed. Multiple logistic regression analysis was used to determine the association of waist circumference and percent body fat to the risk of modified metabolic syndrome and each of the metabolic syndrome related disorders. This regression was also to determine whether the percent body fat adds to the predictive power of waist circumference to detect risk for modified metabolic syndrome and/or each metabolic syndrome related disorder.

For Aim 2, anthropometric combinations were created based on high or normal waist circumference and quartile of percent body fat to compare the odds ratios for the modified metabolic syndrome and each of the metabolic syndrome related disorders using multiple logistic regression analysis for men and women adjusted by age, education, smoking, drinking habits, dietary factors, and physical activity status. The reference cut-points for waist circumference was set below 102 cm for men and below 88 cm for women. The reference group was those

with normal waist circumference (WC) and having body fatness falling in the 50th percentile (LFNW). The main comparisons of interest for odds ratios were three groups: those with high body fat (>50th %tile) and high waist circumference (HFHW); those with low body fat (≤50th %tile) and high waist circumference (LFHW); and those with high body fat (>50th %tile) and normal waist circumference (HFNW) and low body fat (≤50th %tile)

For Aim3, **H3.$_1$** and **H3.$_2$**, the prevalence of the modified metabolic syndrome and each of the metabolic syndrome-related disorders were determined for the Taiwanese people. The adjusted Wald Chi-square test was used to evaluate the statistical significance of the prevalence rate. H3.$_3$, logistic regression was used to compare the prevalence rate ratios (odds ratios) in each of the four body fat distribution categories for modified metabolic syndrome and each of the metabolic syndrome related disorders across gender groups. The dependent variables were presence of modified metabolic syndrome and the each of the metabolic syndrome-related disorders. For independent variables, a variable of four anthropometric categories based on high or normal waist circumference and 50th quartile of percent body fat were used in this test, adjusted by age, education, smoking, drinking habits, dietary factors, and physical activity status.

Table 3.1 List of variables

	Names	Types	Definitions
Dependent Variables	Triglycerides	Dichotomous Normal '0', high '1'	Normal: serum triglyceride <150 mg/dl High: ≥150 mg/dL
	HDL	Dichotomous Normal '0', high '1'	Normal ≥40 mg/dL for male, ≥50 mg/dl for female Low <40 mg/dl for male <50 mg/dl for female
	Blood pressure Systolic Diastolic	Dichotomous Normal '0', high '1'	Systolic blood pressure High ≥130 mm Hg, Normal <130 mm Hg Diastolic blood pressure High ≥85 mm Hg Normal <85 mm Hg
	Fasting blood glucose	Dichotomous Normal '0', high '1'	High: >110 mg/dl Normal ≤110 mg/dl
	Modified metabolic syndrome (MMS)	Dichotomous Without metabolic syndrome '0' With metabolic syndrome '1'	Has 2 or more of the following: Triglyceride concentration ≥150 mg/dL, HDL cholesterol concentration <40 mg/dL in men or <50 mg/dL in women, Blood pressure ≥130/85 mm Hg, Fasting glucose concentration ≥100 mg/dL
Independent variables	Waist circumference (WC)	a. Continuous b. Dichotomous Normal '0', high '1'	Normal: WC <102 cm in men, <88 cm in women High: WC ≥102 cm in men, ≥88 cm in women
	Percent bodyfat (%BF)	a. Continuous b. Dichotomous Normal '0', high '1'	Normal: WC <75th %tile High: WC ≥75th %tile
Independent variables	Types of body fat distribution	Categorical	LFNW: Normal WC; %BF <50th%tile LFHW: abnormal WC;%BF <50th%tile HFNW: normal WC;%BF >50th%tile HFHW: abnormal WC; %BF >50th%tile

Table 3.1(cont'd)

	Names	Types	Definitions
Covariates	Age	Continuous	From 20 to 74 years of age
	Gender	Categorical Male '1'; female '2'	
	Smoking	Categorical Current: ' 3', Past: '2', Non-smoker '1'	'current smokers': smoked at the time of the interview; 'previous smokers': not current smokers but had smoked ≥100 cigarettes, 20 cigars, or 20 pipes of tobacco in their entire life 'nonsmokers': smoked less than those amounts in lifetime.
	Drinking	Categorical heavy ' 3', moderate '2', Non-drinker '1'	Heavy drinkers: those who drank >15 alcoholic beverages (beer, wine, or hard liquor) during the past month. Moderate drinkers: those who drank an alcoholic beverage (i.e., beer, wine, or hard liquor) between 1 to 15 drinks during the past month. Non-drinkers: those who drank no beer, wine, or hard liquor during the past month.
	Education	Categorical 0-8 years of education '1' 9-12 years '2' more than 12 years '3'	For NHANES III divides into three categories: ≤8 years, 9 to 12 years, and more than 12 years of education. For NAHSIT, divides into three categories: ≤9 years, 10 to 12 years, and more than 12 years of education. The difference is due to a slight difference between the education systems. In Taiwan, middle school is from 7-9th grade and the high school is from 10 to 12th grades.
	Physical activity	Categorical Actives '3' Moderate '2' Light '1' Inactive '0'	Active: reported greater than 5 activities/week Moderate: reported 2-5 activities/week Light: reported less than one activity/week, Inactive: reported with no activity in a weekly period
	Dietary factors Carbohydrate Fat	Continuous	 Percent carbohydrate from total energy consumed per day Percent fat from total energy consumed per day

CHAPTER 4

RESULTS

In this section, descriptive statistics of the study sample are first presented. Next, each aim and hypothesis from the first chapter is repeated followed by the data to refute or support it. Finally, data are shown that are relevant to the study topic, but not directly pertinent to a hypothesis.

Demographics of the study subjects

Descriptive and metabolic characteristics are in **Table 4.1** for the entire sample of overweight (BMI 25-30) non-Hispanic White participants, ages from 20-74 years from the NHANES III. A total of 960 males and 674 females met the selection criteria and were included. Within this overweight group, females were about 4 years older than males. Males had a higher waist circumference (WC) than females, but a lower percent body fat (%BF). For blood lipids, males had higher triglycerides, systolic blood pressure and diastolic blood pressure; females had higher HDL cholesterol. There was no difference in fasting glucose between males and females.

Table 4.1. Descriptive characteristics and metabolic factors (mean±SE) in the total sample of overweight (BMI 25-30) non-Hispanic White participants ages 20-74 yr from the National Health and Nutrition Examination Survey III, weighted sample.

	Men (n= 960)	Women (n= 674)	P value
Descriptive characteristics			
Age (y)	44.2 ± 0.5	48.5 ± 0.8	<0.001
BMI (kg/m^2)	27.1 ± 0.1	27.1 ± 0.1	0.903
Waist circumferences (cm)	97.5 ± 0.6	91.7 ± 0.3	<0.001
% Bodyfat from BIA	24.9 ± 0.3	37.7 ± 0.3	<0.001
Metabolic variables			
Triglycerides (mg/dl)	170.1± 0.8	144.3 ±4.6	<0.001
HDL cholesterol (mg/dl)	43.4± 0.6	53.6 ± 0.6	<0.001
Fasting Glucose (mg/dl)	100.3± 1.4	98.2 ± 1.5	0.333
Systolic blood pressure (mm Hg)	124.0± 0.6	121.3 ± 0.9	0.006
Diastolic blood pressure (mm Hg)	77.4± 0.3	73.6 ± 0.4	<0.001

Table 4.2. Prevalence of metabolic risk factors in Non-Hispanic White men and women ages 20-74 yr with BMI 25-30 from NHANES III, weighted sample.

	Men	Women	P*
Risk factors	% (95% CI)	% (95% CI)	
High Waist circumference	26.1(23.2,29.2)	67.1 (61.9, 71.9)	<0.001
Low HDL	45.2 (40.9, 49.5)	44.9 (40.8, 49.2)	0.935
High TG	46.8 (41.1, 52.6)	32.3 (27.6, 37.3)	0.000
High blood pressure	43.7 (39.3, 48.3)	38.1 (33.9, 42.6)	0.070
High Fasting Glucose	31.6 (27.7, 35.7)	22.7 (19.0, 26.9)	0.006
Metabolic Syndrome	32.1 (27.9, 36.6)	36.1 (31.0, 41.5)	0.165
Modified Metabolic Syndrome[1]	54.2 (49.1, 59.3)	39.5 (33.6, 45.7)	<0.001

[1] Based on NCEP ATPIII Criteria but not including high WC, i.e. having 2 or more of following abnormalities: Triglycerides ≥150 mg/dL; HDL: Men <40 mg/dL Women <50 mg/dL; Blood pressure ≥130/≥85 mmHg; Fasting glucose ≥100 mg/dL.

* Cochran-Mantel-Haenszel Chi-square Test

Table 4.2 shows the prevalence of metabolic risk factors for Non-Hispanic white men and women ages 20-74 year with BMI=25<30. About two-thirds of females had high WC. The prevalence of high WC was more than twice as high in females compared to males. The twofold higher prevalence of elevated WC of women in the present study might be expected to affect the use of WC to predict the risk of MMS. In fact, when high WC was excluded as a criteria of MS, the prevalence of MMS was higher in men than women (54.5% to 39.5%, P<0.01). Males had a higher prevalence than did females of high serum triglycerides, high fasting glucose and modified metabolic syndrome (MMS). There were no significant differences between genders for the prevalence of low HDL or high blood pressure. When high WC was excluded as a criterion, men had a higher prevalence of MMS than women.

Aim 1. To determine whether percent body fat assessed by Bioelectrical Impedance Analysis added to the predictive power of WC in risk for MMS and/or each metabolic syndrome related disorder (MSRD) (elevated triglycerides, low HDL cholesterol, high blood pressure, impaired fasting blood glucose) in non-Hispanic white, overweight (BMI 25-29.9) men and women (NHANES III).

$H1._1$: Both WC and percent body fat predict risk for MMS and/or each MRSD (elevated triglycerides, low HDL cholesterol, high blood pressure, and impaired fasting glucose) in overweight non-Hispanic white men and women.

$H1._2$: Percent body fat adds to the predictive power of WC to detect risk for MMS and/or each MSRD in overweight non-Hispanic white men and women (NHANES III).

The correlations of BMI, WC and %BF to the modified metabolic disorders are shown in **Table 4.3.** For this group of overweight, but not obese (BMI 25<30), non-Hispanic men and women, BMI was significantly correlated to both WC (r=0.61, 0.44) and to %BF (r= 0.23, 0.47) respectively, with WC stronger for men and %BF stronger for women. For both men and women, WC was weakly to moderately associated to risk for most of the metabolic disorders. For men %BF was weakly correlated with serum triglycerides and fasting blood glucose, but only with HDL and blood pressure in women. WC was significantly and more strongly associated with all MSRD compared to %BF in both men and women, but no association exceeded r=0.38.

Table 4.3. Pearson's correlations of BMI, waist circumference and percent body fat to the metabolic disorders in Non-Hispanic White men and women ages 20-74 year with BMI 25-30 from NHANES III, weighted sample.

	Men (n=960)		Women (n=674)	
	WC	%BF	WC	%BF
Body Mass Index	0.61* (0.000)	0.23* (0.000)	0.44* (0.000)	0.47* (0.000)
Waist Circumference	1.00	0.39* (0.000)	1.00	0.36* (0.000)
Percent Body Fat (%BF)	0.39* (0.000)	1.00	0.36* (0.000)	1.00
Serum triglycerides (mg/dL)	0.22* (0.000)	0.10* (0.013)	0.22* (0.000)	0.06 (0.286)
Serum HDL (mg/dL)	-0.11* (0.004)	0.00 (0.888)	-0.03* (0.563)	-0.08* (0.023)
Systolic blood pressure (mm Hg)	0.23* (0.000)	0.07 (0.085)	0.38* (0.000)	0.10* (0.011)
Diastolicblood pressure (mm Hg)	0.15* (0.000)	0.05 (0.096)	0.17* (0.001)	0.11* (0.010)
Fasting plasma glucose (mg/dL)	0.17* (0.000)	0.09* (0.010)	0.23* (0.001)	0.06 (0.120)

*Correlation is significant at the 0.05 level (2-tailed).

** Correlation is significant at the 0.01 level (2-tailed).

Multiple regression models shown in **Table 4.4** tested whether the %BF and WC could predict risk for each MSRD (elevated triglycerides, low HDL cholesterol, high blood pressure, and impaired fasting glucose) in the study population, controlling for covariates. WC alone was a strong, positive predictor of metabolic disorders independent of gender, except for systolic blood pressure and fasting glucose in men and HDL in women. When %BF was added to the regression equation, it did not add predictive power to any of the metabolic disorders, except for serum triglycerides in men. In model 3, when both WC and %BF were included in the regression, WC remained a predictor of all of the metabolic disorders for both men and women, with the previous exceptions. For men, %BF did not add to the predictive ability of WC for any of the metabolic disorders of metabolic syndrome. For women, however, adding %BF to WC resulted in %BF becoming a significant predictor of both serum HDL and fasting blood glucose. For both men and women and for all the metabolic disorders, adding %BF to WC did not change the R^2 or increased it less than 1% when compared to WC alone (**Table 4.4**, model 1 vs. model 3). After controlling for percent body fat (%BF), the WC remained the most significant predictor for all of the metabolic risks in which the odds ratio of MMS increased 7% for every 1 cm increase in WC (data not shown).

Table 4.4. Regression models using waist circumference and/or percent body fat to predict the metabolic syndrome related disorders in Non-Hispanic men and women with BMI 25-30 from NHANES III using waist circumference and/or % body fat as independent covariables.

	model 0[1]		model 1[2]		model 2[3]		model 3[4]		
	n	R^2	R^2	WC ß coef (SE)	R^2	% body fat ß coef (SE)	R^2	WC ß coef (SE)	% body fat ß coef (SE)
Men									
Serum Triglycerides	899	0.06	0.09	2.47(0.52) [a]	0.07	1.55 (0.68) [a]	0.09	2.32(0.62) [a]	0.47(0.81)
HDL	921	0.13	0.14	-0.2 (0.07) [a]	0.13	0.02 (0.07)	0.14	-.24(0.08) [a]	0.14 (0.08)
Systolic blood pressure	937	0.18	0.18	0.08(0.07)	0.18	0.09(0.11)	0.18	0.08(0.08)	0.01(0.11)
Diastolic blood pressure	937	0.03	0.04	0.19(0.07) [a]	0.03	0.05(0.06)	0.04	0.21(0.08) [a]	-0.05(0.06)
Fasting blood glucose	920	0.12	0.12	0.18(0.09)	0.12	0.10(0.12)	0.12	0.17(0.10)	0.02(0.13)
Women									
Serum Triglycerides	632	0.19	0.22	1.73(0.34) [a]	0.19	-0.25(0.87)	0.22	2.02(0.42) [a]	-1.56(0.93)
HDL	637	0.16	0.17	-0.17(0.1)	0.16	0.22(0.12)	0.17	-0.23(0.11) [a]	0.37(0.14) [a]
Systolic blood pressure	649	0.40	0.41	0.25(0.09) [a]	0.4	0.07(0.18)	0.41	0.27(0.10) [a]	-0.10(0.19)
Diastolic blood pressure	649	0.05	0.05	0.12(0.06) [a]	0.05	0.19(0.1)	0.06	0.09(0.05)	0.14(0.10)
Fasting blood glucose	635	0.11	0.13	0.29(0.08) [a]	0.10	-0.06(0.11)	0.13	0.34(0.09) [a]	-0.27(0.13) [a]

1. Multiple regression with variable of age, exercise level, alcohol consumption, % of energy from carbohydrates and fat, smoking status.
2. Multiple regression with the independent variable of waist circumference controlling for covariates (age, exercise level, alcohol consumption, percent of energy from carbohydrates and fat, smoking status).
3. Multiple regression with the independent variable of percent body fat controlling for all covariates.
4. Multiple regression with the independent variable of percent body fat, waist circumference fat controlling for all covariates.

[a] $p < 0.05$ Wald test

Aim 2. To determine whether body fat distribution modifies the effect of percent body fat and WC on MMS and each MSRD differently in overweight non-Hispanic white men.

$H2_{.1}$: For each percent fat quartile, those with high WC will have higher risk than those with normal WC for MMS and each MSRD in overweight non-Hispanic white men and women.

Table 4.5. Prevalence of modified metabolic syndrome (MMS[1]) and metabolic related risks in different quartiles of percent body fat measured by Bio-electrical Impedance within the normal and high WC categories in Non-Hispanic white **men** with BMI=25<30, ages 20-74 yr, from NHANES III, weighted sample.

Metabolic risks		Normal WC				
		Quartile of % Bodyfat[2]				
	n	Total	Q1	Q2	Q3	Q4
		% (SE)	% (SE)	% (SE)	% (SE)	% (SE)
Have MMS	626	48.8±2.6[a]	45.3±4.1	52.5±4.1[a]	44.0±5.8[a]	57.8±6.3[a]
High triglycerides	635	42.4±3.3[a]	38.5±4.3	43.6±4.7[a]	47.2±5.5	42.4±7.4
Low HDL	626	41.9±3.0[a]	44.7±3.0	42.8±5.0	36.0±5.1[a]	41.1±4.2
High Blood Pressure	635	39.6±2.8[a]	39.0±3.7	42.1±4.3	35.1±4.9[a]	43.0±4.5
High Fasting Glucose	635	28.0±2.0[a]	25.6±3.2	28.0±3.0	25.4±5.6[a]	40.1±6.8
		High WC				
Have MMS	319	69.8±3.8[a]	58.6±11.0	69.8±6.0[a]	76.1±5.7[a]	70.5±4.2[a]
High triglycerides	325	59.4±4.4[a]	48.2±9.4	64.5±7.7[a]	61.8±6.6	59.4±4.4
Low HDL	319	54.5±3.3[a]	49.8±9.9	62.0±7.6	59.0±6.0[a]	49.1±4.2
High Blood Pressure	325	55.3±3.0[a]	43.8±9.0	54.5±6.8	64.1±5.9[a]	54.8±4.5
High Fasting Glucose	325	41.7±3.7[a]	25.9±8.9	38.3±7.7	50.1±5.6[a]	44.9±5.7[a]

[1] MMS: Modified metabolic syndrome, based on NCEP ATP III, 5 risk factors to diagnosis metabolic syndrome (MS) but not including high waist circumference.

[2] Measured by Bio-electrical Impedance

[a] Values with the same superscript denote a significant difference between normal and high WC groups by Wald test, P<0.05.

Table 4.6. Prevalence of modified metabolic syndrome and metabolic related risks in different quartiles of percent bodyfat measured by Bio-electrical Impedance within the normal and high WC categories in Non-Hispanic white **women** with BMI=25<30, ages 20-74 yr, from NHANES III, weighted sample.

Metabolic risks	Normal WC					
	Quartile of % Bodyfat[2]					
	n	Total	Q1	Q2	Q3	Q4
		% (SE)	% (SE)	% (SE)	% (SE)	% (SE)
Have MMS[1]	194	19.2±4.1[a]	18.9±5.3[ab]	23.7±6.8[ab]	20.1±8.0[ab]	9.4±6.3[ab]
High triglycerides	194	18.6±3.3[a]	18.6±5.3[ab]	22.1±4.8[ab]	25.3±6.4[ab]	4.9±3.3[ab]
Low HDL	194	43.1±4.3	49.9±5.6	42.0±7.1	40.4±10.7	28.3±9.7
High Blood Pressure	194	19.4±3.5[a]	17.5±4.6[ab]	24.4±7.7	19.7±6.1[a]	12.4±6.7[ab]
High Fasting Glucose	194	8.9±3.0[a]	5.3±2.8[a]	10.2±4.1[a]	11.4±5.1[a]	14.4±7.6[a]
				High WC		
Have MMS	470	49.8±3.0[a]	51.5±6.8[a]	48.3±6.3[a]	57.0±5.2[ab]	42.1±5.4[ab]
High triglycerides	480	38.9±2.7[a]	43.3±6.7[a]	35.4±5.3[ab]	44.3±5.2[ab]	33.0±5.6[ab]
Low HDL	470	45.8±2.3	45.9±4.9	54.1±5.0	45.8±4.1	38.1±4.6
High Blood Pressure	480	47.4±2.6[a]	53.9±5.4[a]	39.4±6.2	53.6±3.5[a]	43.2±4.7[a]
High Fasting Glucose	480	29.5±2.5[a]	35.9±4.4[ab]	26.6±5.4[a]	32.2±5.0[a]	24.2±4.3[b]

[1] MMS: Modified metabolic syndrome, based on NCEP ATP III, 5 risk factors to diagnosis metabolic syndrome (MS) but not including high waist circumference.

[2] Measured by Bio-electrical Impedance; The quartile cut points of percent body fat were 22.9, 25.8 and 28.7 for men and 35.5, 38.1 and 40.3 for women, respectively.

[a] Values with the same superscript denote a significant difference between normal and high WC groups by Wald t-test, P<0.05.

[b] Values with the same superscript denotes a significant difference between quartile groups in a row, by Wald t-test, P<0.05

When BF distribution was divided into high and normal WC and quartiles of %BF as shown in **Tables 4.5** and **4.6**, both men and women with high WC had higher risk for MMS. The quartile cut-points of percent body fat were 22.9, 25.8 and 28.7 for men and 35.5, 38.1 and 40.3 for women, respectively. Men with high WC also had higher risk for all metabolic risks compared to men with normal WC. Women with high WC had higher risk for high triglycerides, high blood pressure and high fasting glucose, but not for high HDL. In both men and women, the trends of having MMS and most of the MSRD were highest in the third quartile, but not in the 4^{th} quartile in both normal and high WC groups. **Figures 4.1** illustrate the pattern of risk response by %BF quartiles. For men, risk of MMS increased in a stepwise fashion until the fourth quartile, when the risk dropped. For men there were no significant differences in risks across quartile groups, but for women there were. Most interesting was the apparent increase in risk for high fasting glucose for women with normal WC, but a decline in risk for women with high WC.

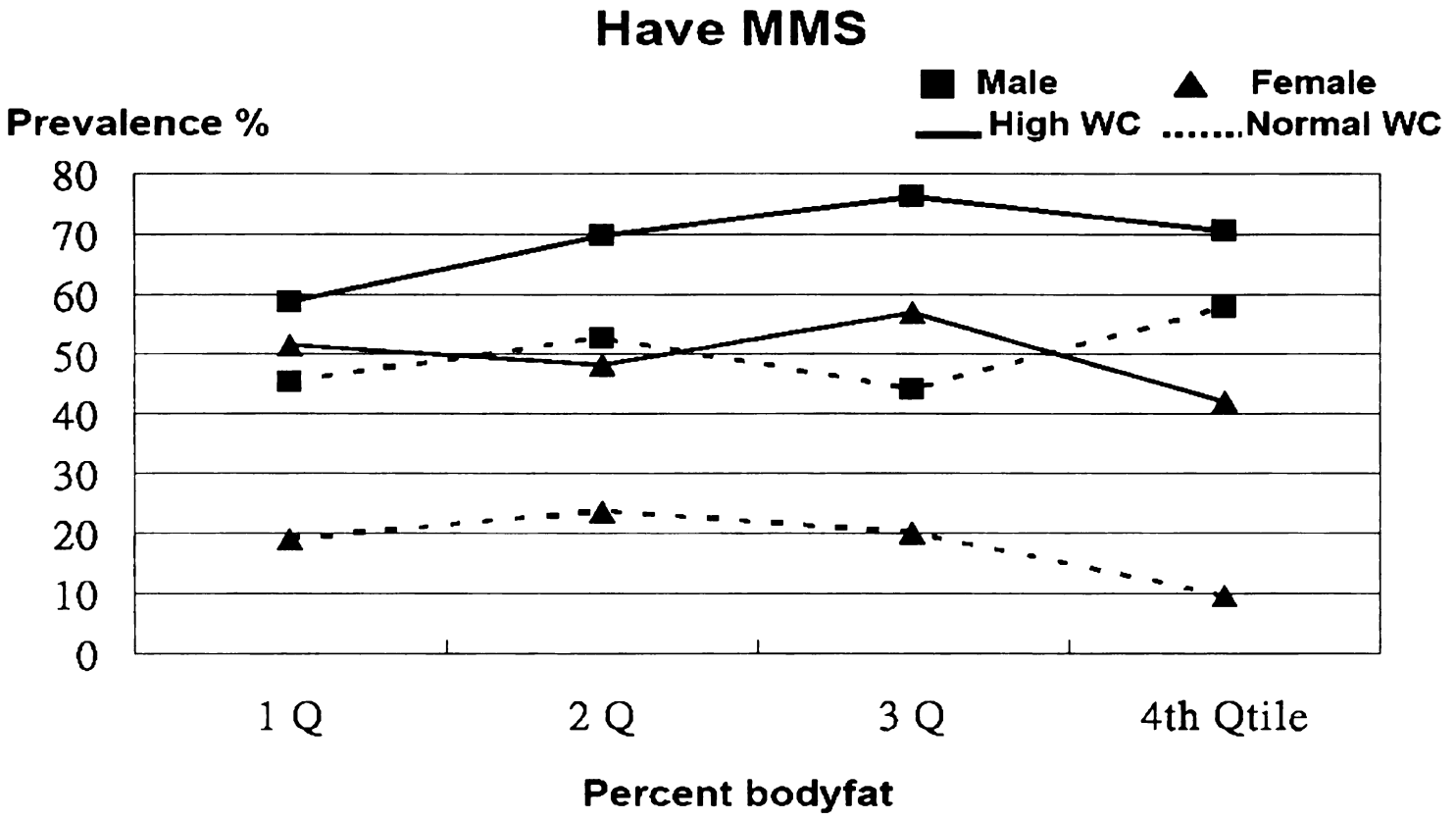


Figure 4.1 Prevalence of modified metabolic syndrome (MMS) in different quartiles of percent bodyfat between normal and high WC categories in Non-Hispanic women and men with BMI=25<30, ages 20-74 yr, from NHANES III, weighted sample.

H2.2: Those with high body fat (>50th %tile), and high waist circumference (HFHW) will have higher risk for MMS and each MSRD compared to those with low body fat (≤50th %tile) and high waist circumference (LFHWC), high body fat (>50th %tile) and normal waist circumference (HFNWC) and low body fat (≤50th %tile) and normal waist circumference (LFNWC) in overweight non-Hispanic white men and women.

Table 4.7 shows what happened when the quartiles were collapsed into two groups by a median split for %BF--high and low %BF. The risks for MMS and MSRD were higher in groups with high waist circumference when low body fat (≤50th %tile) and normal waist circumference (LFNWC) used as a reference group. For men this was only with high body fat (HFHWC). Men with HFHWC were about twice as likely to have MMS and high TG compared to those with LFNWC. Women with HFHWC were about twice as likely to have high blood pressure compared to those with LFNWC. The risk of high fasting glucose was about three times as high in both high WC groups (LFHWC, HFHWC) in women but not for men. In groups with normal waist circumference (LFNWC, HFLWC) the risks were not different regardless of their %BF. However, when comparing low fat (LFNWC, LFHWC) to high fat (HFNWC,HFHWC) groups in women, the risk for MMS and the most MSRD were both decreased in normal WC and high WC group except for high blood pressure but statistically non-significant.

Table 4.7. Odds ratio[1] of metabolic related risks[2] in low fat and normal waist circumference (LFNWC), low body fat and high waist circumference (LFHW), high body fat and normal waist circumference (HFNWC), and high body fat and high waist circumference (HFHWC) in Non-Hispanic whiter men and women with BMI=25<30, ages 20-74 yr, from NHANES III, weighted sample.

	Normal Waist			High Waist			
Metabolic risks	LFNWC[4]	HFNWC		LFHWC		HFHWC	
Men n=960							
Modified Metabolic Syndrome[3]	1.00	1.01	(0.64-1.60)	1.22	(0.62-2.40)	2.14	(1.44-3.16) *
Low HDL	1.00	0.77	(0.52-1.14)	1.36	(0.71-2.61)	1.34	(0.87-2.05)
High TG	1.00	1.20	(0.86-1.69)	1.57	(0.87-2.84)	1.82	(1.23-2.69) *
High blood pressure	1.00	0.82	(0.54-1.24)	0.97	(0.46-2.0)	1.27	(0.84-1.92)
High Fasting Glucose	1.00	1.29	(0.77-2.38)	0.87	(0.49-1.54)	1.43	(0.85- 2.38)
Women n=674							
Modified Metabolic Syndrome	1.00	0.58	(0.25 –1.35)	2.17	(1.27 – 3.70)*	1.64	(0.86-3.13)
Low HDL	1.00	0.58	(0.26-1.3)	1.49	(0.99-2.24)	0.85	(0.53-1.38)
High TG	1.00	0.71	(0.35-1.41)	1.81	(0.99-3.3)	1.55	(0.77- 3.1)
High blood pressure	1.00	0.72	(0.35-1.50)	1.76	(0.93-3.35)	1.95	(1.15-3.3) *
High Fasting Glucose	1.00	1.87	(0.86-4.08)	3.79	(1.55-9.26)*	3.35	(1.27-8.78) *

[1] Odds ratios adjusted for age, physical activity, smoking, alcohol intake, and % energy from carbohydrate and fat; confidence intervals in parentheses.

[2] Triglycerides ≥150 mg/dL; HDL: Men <40 mg/dL Women <50 mg/dL; Blood pressure ≥130/≥85 mmHg; Fasting glucose ≥100mg/dL

[3] Based on NCEP ATPIII Criteria but not including high WC, i.e. have any two or more of the above abnormalities in footnote [2]

[4] LFNWC: Low %Bodyfat normal waist circumference, Reference group , HFNWC: High %Bodyfat normal waist circumference LFHWC: Low %Bodyfat High waist circumference HFHWC: High %Bodyfat high waist circumference; The cut points of low percent body fat were 25.8% for men and 38.1% for women, The WC cut points were 102cm for men and 88 cm for women.

* Significantly different from LFNWC.

Aim 3. To examine the predictive power of WC and %BF to detect the risk for MMS and/or each MSRD in overweight Taiwanese men and women using data from the Nutrition and Health Survey in Taiwan 1993-1996 (NAHSIT).

A total of 291 males and 312 females were overweight, defined in Taiwan as having a BMI 24<27, and comprised the sample for Aim 3 of this study. Within this overweight group, females were about 4 years older than males. Males had a higher WC than females, but a lower %BF (**Table 4.8).** For blood lipid profiles, females had higher HDL cholesterol compared to males. There were no differences by gender in fasting glucose or blood pressure. There was a trend for men to have higher triglycerides, but the gender difference was not significant.

Table 4.8 Descriptive characteristics and metabolic related risks in the total sample of overweight (BMI 24-27) Taiwanese participants ages 20-74 yr from the Nutrition and Health Survey in Taiwan, weighted sample.

	Men (n=291)	Women (n= 312)	P value
Descriptive characteristics			
Age (y)	42.3±1.1	46.2±1.3	0.02
BMI (kg/m^2)	25.3±0.1	25.3±0.1	0.78
Waist circumferences (cm)	84.8±0.3	78.3±0.3	<0.001
% Bodyfat from BIA	22.9±1.0	30.8±0.5	<0.001
Metabolic variables			
Triglycerides (mg/dl)	135.8±9.1	109.0±6.9	0.053
HDL cholesterol (mg/dl)	46.3±2.0	55.8±1.4	<0.001
Fasting Glucose (mg/dl)	84.7±1.1	86.5±1.5	0.36
Systolic blood pressure (mm Hg)	125.7±1.2	124.5±2.1	0.71
Diastolic blood pressure (mm Hg)	82.7±0.8	78.8±1.4	0.07

Table 4.9 shows the prevalence of metabolic risk factors and MMS between overweight Taiwanese men and women. The prevalence of high WC was significantly higher in females compared to males (32.76% vs 14.05%), as was low HDL. Males tended to have a higher prevalence of high triglycerides compared to females. There were no significant differences in the prevalence of MMS and high blood pressure between genders.

Table 4.9. Prevalence of metabolic risk factors in overweight (BMI 24 to 27) Taiwanese men and women ages 20-74 yr from the Nutrition and Health Survey in Taiwan, weighted sample.

	Men		Women	
Risk factors	Percentage	95% CI	Percentage	95% CI
High Waist circumference	14.05[a]	(8.9, 21.6)	32.76[b]	(28.9, 36.9)
Low HDL	28.31	(13.6, 49.7)	44.53	(35.4, 56.5)
High TG	29.31	(19.7, 41.2)	22.63	(15.7, 31.5)
High blood pressure	53.24	(35.5, 70.2)	43.1	(36.1, 50.4)
High Fasting Glucose	7.17	(3.9, 13.0)	10.27	(5.9, 17.3)
Metabolic Syndrome	16.1	(9.2, 26.5)	18.7	(13.5, 25.3)
Modified Metabolic Syndrome[1]	35.6	(20.0, 55.0)	30.49	(25.8, 35.6)

[1] Based on NCEP ATPIII Criteria but not including high WC, i.e. having 2 or more of following abnormalities: Triglycerides ≥150 mg/dL; HDL: Men <40 mg/dL Women <50 mg/dL; Blood pressure ≥130/≥85 mmHg; Fasting glucose ≥100 mg/dL.

[ab] Different superscripts show significant differences between genders, P<0.01; Cochran-Mantel-Haenszel Chi-square Test

$H3._1$ Both %BF and WC predict risk for MMS and/or each MSRD (elevated triglycerides, low HDL cholesterol, high blood pressure, and impaired fasting blood glucose) in overweight Taiwanese men and women.

The correlations of WC and %BF to the modified metabolic disorders in Taiwanese overweight but not obese (BMI=24-27) men and women are shown in **Table 4.10.** In both men and women, BMI was significantly correlated to WC at (r=0.45, 0.29, respectively), but not to %BF. %BF was significantly correlated to WC only in men, but not in the women. WC was strongly associated for women with all of the metabolic disorders except for serum HDL. For men, WC only was significantly correlated with systolic blood pressure and fasting blood glucose. %BF was weakly correlated with all the metabolic risks in men. In women, only systolic and diastolic blood pressure were positively correlated with %BF. WC was significantly and more strongly associated with MSRD compared to %BF in both men and women, but no association exceeded r=0.37.

Table 4.10. Pearson's correlations of BMI, waist circumference and percent body fat to the metabolic disorders in Taiwanese men and women ages 20-74 year with BMI 24-27 from NAHSIT, weighted sample.

	Men		Women	
	WC	%BF	WC	%BF
Body Mass Index I)	0.45* (0.000)	0.05 (0.519)	0.29* (0.011)	0.07 (0.144)
Waist Circumference	1.00	0.38 (0.015)	1.00	0.09 (0.480)
Percent Body Fat	0.38* (0.015)	1.00	0.09 (0.480)	1.00
Serum triglycerides (mg/dL)	0.11 (0.214)	0.11 (0.326)	0.28* (0.016)	0.17 (0.076)
Serum HDL (mg/dL)	-0.02 (0.902)	-0.12 (0.428)	-0.09 (0.293)	-0.06 (0.552)
Systolic blood pressure (mm Hg)	0.37* (0.001)	0.12 (0.086)	0.23* (0.013)	0.21* (0.036)
Diastolic blood pressure (mm Hg)	0.23 (0.074)	0.05 (0.705)	0.11* (0.034)	0.18* (0.036)
Fasting plasma glucose (mg/dL)	0.20* (0.007)	0.02 (0.827)	0.37* (0.041)	0.05 (0.583)

*Correlation is significant at the 0.05 level (2-tailed).

Logistic regression models were developed to evaluate the relative contributions of WC versus %BF to risk for MSRD adjusted by age, physical activity, and alcohol intake. Percent energy intake from carbohydrates and fat were dropped from the equation here, due to too many missing values. Smoking status was also dropped from the regression equation in women, because only 2& of Taiwanese women smoked (**Table 4.11**). Although the overall model for each regression were significantly correlated to each of the MSRD, WC alone, %BF alone and combined WC and %BF together were not a significant predictor for most of the MSRD in both genders. Only %BF alone was a significant predictor for systolic blood pressure in women.

When using R^2 to determine the predictive power between WC and %BF, WC had better predictive power than did %BF for most MSRD in both men and women, but the differences were small. Percent body fat had slightly better predictive power for blood pressure in women. When both WC and %BF were combined in the equation model, the R^2 increased only slightly (1% to 3%) compared to WC alone (model 3 vs. model 1 in **Table 4.11**).

Table 4.11. Regression models using waist circumference and/or percent body fat to predict the metabolic syndrome related disorders in Taiwanese men and women age 20-74 with BMI 24 -27 from NAHSIT (n=603)· weighted sample using waist circumference and/or % body fat as independent covariables.

	model 0[1]		model 1[2]		model 2[3]		model 3[4]		
	n	R^2	R^2	WC ß coef (SE)	R^2	% body fat ß coef (SE)	R^2	WC ß coef (SE)	% body fat ß coef (SE)
Men									
Serum Triglycerides	283	0.10	0.11	1.13(1.80)	0.10	0.72 (1.31)	0.11	0.93(1.95)	0.55(1.37)
HDL	277	0.08	0.08	-0.07 (0.25)	0.08	-0.17 (0.23)	0.08	-0.02(0.21)	-0.17 (0.21)
Systolic blood pressure	287	0.28	0.29	0.37(0.28)	0.29	-0.08(0.19)	0.30	0.42(0.25)	-0.15(0.19)
Diastolic blood pressure	287	0.15	0.16	0.29(0.30)	0.15	-0.08(0.18)	0.16	0.34(0.28)	-0.13(0.14)
Fasting blood glucose	280	0.10	0.10	0.19(0.45)	0.11	-0.22(0.24)	0.11	0.29(0.42)	-0.27(0.20)
Women									
Serum Triglycerides	297	0.10	0.13	2.54(1.42)	0.11	1.77(1.36)	0.15	2.51(1.33)	1.72(1.16)
HDL	295	0.15	0.16	-0.34 (0.26)	0.15	0.23(0.37)	0.16	-0.34(0.27)	0.23(0.36)
Systolic blood pressure	310	0.28	0.28	0.12(0.26)	0.30	0.59(0.21)[a]	0.30	0.11(0.29)	0.59(0.21)[a]
Diastolic blood pressure	310	0.04	0.04	0.06(0.12)	0.07	0.37(0.19)	0.07	0.06(0.16)	0.37(0.19)
Fasting blood glucose	296	0.06	0.15	1.07(0.62)	0.07	-0.29(0.33)	0.16	1.07(0.60)	-0.28(0.31)

1. Multiple regression with variable of age, exercise level, alcohol consumption, smoking status.
2. Multiple regression with the independent variable of waist circumference controlling for covariates (age, exercise level, alcohol consumption, percent of energy from carbohydrates and fat , smoking status).
3. Multiple regression with the independent variable of percent body fat controlling for all covariates.
4. Multiple regression with the independent variable of percent body fat, waist circumference fat controlling for all covariates.

[a] $p < 0.05$ Wald test

H3.2 Those with high body fat (>50th %tile) and high waist circumference (HFHW) will have higher risk for MMS and each MSRD compared to those with low body fat (≤50th %tile) and high waist circumference (LFHW), high body fat (>50th %tile) and normal waist circumference (HFNW) and those with both low body fat (≤ 50th %tile) and normal waist circumference (LFNW) in overweight Taiwanese men and women

Although the sample was somewhat small for examination by gender, **Table 4.12** shows the prevalence of MMS and related metabolic risk factors for the sample divided into four groups of adults based on a median split by %BF. The 50th percentile cutpoints of %BF were 23.3% for men and 31.4% for women, respectively. In general, men and women with normal WC had lower prevalence of MSRD compare to high WC groups, with the possible exception of low HDL's being somewhat higher in normal WC groups. Women with higher WC had increased risk for high blood pressure and high fasting glucose compared to normal WC group.

In normal WC category, women had higher prevalence of MMS and metabolic related risks when %BF decreased. However, this phenomenon was not seen in high WC group except for high fasting glucose. In the high WC group, high percent bodyfat had higher risk for MMS and MSRD, the risk of having MMS was almost double in the high %BF group compared to the low %BF group (p=0.079).

Table 4.12. Prevalence of modified metabolic syndrome and related metabolic risk factors[1] in low and high percent bodyfat measure by Bio-electrical Impedance[2] with in the normal and high WC categories in overweight (BMI 24<27) Taiwanese adults, ages 20-74 yr from the Nutrition and Health Survey in Taiwan, weighted sample.

	Normal WC		High WC	
Metabolic risks	Low %BF	High %BF	Low %BF	High %BF
Men n=287	120	25	101	41
Modified Metabolic Syndrome[3]	33.58± 10.8	33.51± 12.5	44.00± 24.1	51.1± 9.0
Low HDL	30.07± 9.3	26.83± 9.13	20.69± 18.9	29.41± 13.9
High TG	25.18± 4.5[a]	29.58± 11.8	35.76± 18.1	46.73± 8.6[a]
High blood pressure	55.08± 8.7[b]	42.67± 11.4[ac]	84.19± 8.8[#ab]	72.66± 8.9[c]
High Fasting Glucose	6.3± 2.6	6.7± 1.9[#]	14.18± 9.6	10.06± 6.0
Women n=309	96	57	78	78
Modified Metabolic Syndrome	30.45±11.0	18.55 ±8.8[a]	26.49 ±5.2[b]	55.0 ±10.5[ab]
Low HDL	49.97± 10.7	33.17± 11.8	37.13±11.4	58.4± 11.2
High TG	20.83±7.7	17.35± 9.0	23.31± 6.6	35.3 ±5.3
High blood pressure	37.31± 6.5[b]	34.79± 6.0[c]	44.06± 8.7[#a]	69.72 ±6.5[abc]
High Fasting Glucose	6.5± 3.03[a]	1.34 ±1.1[#b]	24.17± 15.1	21.4± 4.6[ab]

[1] Triglycerides ≥150 mg/dL; HDL: Men <40 mg/d ıen <50 mg/dL; Blood pressure ≥130/≥85 mmHg; Fasting glucose ≥100 mg/dL

[2] The cut points of low and high percent body fat 3.3% for men and 31.4% for women, respectively.

[3] Based on NCEP ATPIII Criteria but not including high WC, i.e. have any two or more of the above abnormalities listed in footnote[1]

[#] Values with the same superscript denote a significant difference between males and female $p < 0.05$

[abc] Values with the same letter denotes a significant difference between quartile groups in a row, $p < 0.05$

CHAPTER 5
DISCUSSION

Aim 1. To determine whether percent body fat assessed by Bioelectrical Impedance Analysis adds to the predictive power of waist circumference (WC) in risk for modified metabolic syndrome (MMS) and/or each metabolic syndrome related disorder risk (elevated triglycerides, low HDL cholesterol, high blood pressure, impaired fasting blood glucose; MSRD) in non-Hispanic white, overweight (BMI 25-29.9) men and women (NHANES III).

This study was unique in limiting the examination of associations of anthropometric indicators for metabolic co-morbidities to a restricted range of BMI=25-30. The prevalence of modified metabolic syndrome, without high WC, was 54.2% in males and 39.5% in female, much higher than it was for the ATPIII definition for metabolic syndrome that includes WC. If using the modified ATP III definition in our study, the prevalence of metabolic are 32.1% in males and 36.1% in females which are still higher to the prevalence of metabolic syndrome in the same population in Park's study, since the prevalence reported used original NCEP ATP III definition which the fasting glucose was set as ≥ 110 mg (Park, Zhu et al., 2003).

The twofold higher prevalence of elevated WC of women in the present study might be reasonably expected to affect the use of WC to predict the risk of metabolic syndrome. In fact, when high WC was excluded as a criteria of metabolic syndrome, the prevalence of modified metabolic syndrome was higher in men than women (54.5% to 39.5%, $P<0.01$). The finding that MS was slightly

higher in women than men, using the ATPIII definition (32.1% in men and 36.1% in women respectively), suggests that WC makes a major contribution to MMS for women.

The rates of heart disease by gender also support the findings from the present study that show a decline in the gender gap in risk for CVD with advancing age (Barrett-Connor, 1997; Li, Engstrom et al., 2006). Estrogen and testosterone modulate glucose and lipid metabolism, such that a decline in estrogen or a relative increase in testosterone induces insulin resistance and a pro-atherogenic lipid profile (Regitz-Zagrosek, Lehmkuhl et al., 2006). Thus, it was not surprising to find in the present study that the prevalence of MS or MMS increased in women with advancing age. In the present study, the prevalence of MMS in women was only slightly increased to 39.5% compared to the prevalence by the ATPIII definition of 36.1%.

The main finding was that %BF provided no advantage over WC in screening for MSRD. Current evidence clearly supports that central obesity is a major contributor to metabolic syndrome (NCEP, 2001; Bergman, Kim et al., 2007). As others have found, women averaged higher %BF values than did men, supporting the necessity of using a sex-specific %BF range for predicting the risk of the MS (Jakicic, Wing et al., 1998; Zhu, Wang et al., 2003). That women have high %BF and men, high WC as found in the present study, has been well documented by others (Lemieux, Prud'homme et al., 1993).

The weak to moderate correlations of BMI to %BF, (r= 0.23, 0.47 for men versus women, respectively in the present study) is in contrast to other studies

that used wider spectrum of weights (r= 0.743 to 0.924) (Roubenoff, Dallal et al., 1995; Nagaya, Yoshida et al., 1999). The weak correlations of both BMI and %BF to metabolic risks in the present study were likely due to the narrowed BMI range, clearly demonstrating the varied body composition within the BMI range of 25-30. Weaker correlation in the present study may also reflect greater heterogeneity in factors other than adiposity that influenced lipid profiles.

In the present study, WC was more closely related to BMI than to %BF in both genders and closely associated with metabolic risks, except for HDL. This finding is in line with previous studies showing WC was the best predictor of metabolic risk that compared with other anthropometric indicators (Janssen I, 2002; Wang, 2003; Janssen, Katzmarzyk et al., 2004; Phillips, Jing et al., 2008).

For women in the present study, when both WC and %BF were in the prediction equation for MSRD, %BF related positively to HDL (higher %BF and higher HDL) and negatively to fasting blood glucose (higher BF and lower glucose). This observation is in line with some previous studies (Snijder, Dekker et al., 2004; Sakai, Ito et al., 2005; Bosy-Westphal, Geisler et al., 2006), but contrary to others (Nagaya, Yoshida et al., 1999; Deurenberg-Yap, Chew et al., 2002). In the Quebec Family Study, using a comparable number of adults, %BF added little additional information to BMI, as we also found with respect to cardiovascular disease risk factors in females (Tanaka, Togashi et al., 2002).

In the Australian Diabetes study investigators found a high hip circumference to be strongly associated with a reduced prevalence of undiagnosed diabetes and dyslipidemia up to age 75 (Snijder, Zimmet et al., 2004). Several mechanisms

could explain the inverse association of %BF to the metabolic disturbances in women after adjusting for WC. One possibility might be the effect of estrogen on CVD risk factors (Tanaka, Togashi et al., 2002), i.e., the protective effects of estrogen on plasma lipids might be stronger than the variability in adiposity within the narrow range of weights used in the present study. Another possibility is gender difference in the metabolism of lipids from the adipose depots on the thighs and hips versus the abdomen. Abe and Fukunaga (1994) found thigh adiposity in women associated with higher plasma HDL cholesterol levels and a lower incidence of diabetes (Abe and Fukunaga, 1994). Subcutaneous fat tissue from the hips and thighs has been suggested to play a protective role for MSRD, because subcutaneous adipose tissue is less sensitive to lipolytic stimuli compared to visceral fat (Busetto, 2001). Lipoprotein lipase (LPL) activity is lower in femoral subcutaneous adipose fat compared to visceral fat (Arner, 1995). This increased LPL activity in visceral region can lead to insulin resistance and beta cell dysfunction (Frayn, 2002; McCarty, 2003). Larger reserves of body fat on the buttocks and thighs of women versus marked accumulation of fat in the intra-abdominal visceral fat depots of men using computed tomography has been associated with more favorable levels of lipids and glucose in women (Williams, 2004; Tousignant, Faraj et al., 2008). Williams et al. (Williams, Hunter et al., 1997) found that trunk adiposity was associated with unfavorable serum lipids and lipoprotein levels and leg fatness was related to a favorable lipid profiles in women aged 17–77 years.

In the present study, although WC had an independent ability to predict most

of the metabolic risks, it explained a low to moderate percentage of the variability in the metabolic risks (total R^2 = 0.04 to 0.41in men and 0.06 to 0.41 in women respectively). A relatively narrowed BMI range in this study population might contribute to the low percentage of variability. Also, other factors such as genetic predisposition to chronic diseases must be important as well.

It might seem an odd finding that in women %BF was inversely associated with risk for MMS when adjusted for WC, but a similar finding has been reported elsewhere. Hunter et al. found that the relationship of visceral fat to metabolic complications was independent of concomitant variation in total body fat (Williams, Hunter et al., 1997; Seidell, Perusse et al., 2001). One reasonable explanation about the risk reduction when %BF was included in the equation in the present study is that when WC increases, not only visceral fat increases, but subcutaneous fat does as well. The ability of WC to predict abdominal subcutaneous and visceral fat in addition to total fat (Janssen, Heymsfield et al., 2002) should be considered as a potential mechanistic explanation for findings in the present study. Cross-sectional studies have shown that, once the amount of abdominal fat is taken into account, accumulation of fat and lean mass in the arms and legs seems to be protective against cardiovascular risk factors (Ferreira, Snijder et al., 2004; Snijder, Dekker et al., 2004). In most people, subcutaneous fat accounts for the largest component of total fat (Abate, Garg et al., 1997; Ross, Aru et al., 2002; Ross, Freeman et al., 2002), but for a given amount of total body fat, men have about twice the visceral fat as do pre-menopausal women (Lemieux, Prud'homme et al., 1993). The index of WC is comprised of both

subcutaneous fat and visceral fat in the abdominal region. It is the more metabolically active visceral fat accumulation is that contributes most to MS (Zierath, Livingston et al., 1998; Wong, Janssen et al., 2003; Hyun, Kim et al., 2008).

The findings from the present study clearly support that assessment of cardiovascular risk in overweight people solely from body weight or total body fatness can be quite misleading. Although the best methods for estimating the amount of visceral fat are imaging techniques, such as CT or magnetic resonance (Borkan, Gerzof et al., 1982; Leite, Wajchenberg et al., 2002), these are inappropriate for screening or routine clinical examinations due to high cost and/or radiation exposure. Thus, WC is a good choice for predicting visceral obesity in primary care and community-based studies.

Aim 2. To examine whether body fat distribution modifies the effect of percent body fat and waist circumference on modified metabolic syndrome and each metabolic syndrome related disorder differ in overweight non-Hispanic white men and women.

In this study, the prevalence of women with low %BF but high WC was similar to that from a previous report (St-Onge, Janssen et al., 2004), and consistent with other findings that people with less visceral obesity have more favorable metabolic profiles (Karelis, Faraj et al., 2005). Dvorak et al. (Dvorak, DeNino et al., 1999) analyzed a cohort of 71 healthy normal weight (NW) women (21–35

years old) and divided them into metabolically obese[3] and normal insulin sensitivity groups. Investigators found a higher %BF (32 ± 6 vs. 27 ± 6%, $P < 0.01$) and higher amounts of subcutaneous fat (213 ± 61 vs. 160 ± 78 cm^2, $P = 0.03$) and visceral adiposity (44 ± 16 vs. 35 ± 14 cm^2, $P < 0.05$) in the metabolically obese NW group versus the NW group, respectively.

In the present study, both genders with low %BF but high WC had a higher prevalence of MMS and related metabolic risks than those with high %BF but normal WC. This finding indicates that visceral obesity is a better predictor of the progression to CVD than is total %BF. Visceral fat is more sensitive to lipolytic activity, resulting in an increased release and accumulation of FFAs in multiple organs contributing to insulin resistance (Despres, 2006). Concomitant increases in adrenergic reactivity and blood pressure lead to vascular stiffness (Egan, Lu et al., 1999). However, the high prevalence of MMS in both men and women with normal WC indicates that WC cannot entirely be driving WC.

In this study, the metabolic risks increased with increasing %BF quartiles, but not in a linear fashion, further supporting that %BF was not as good as WC in predicting MMS and related metabolic disorders within this restricted BMI range. The finding that high %BF did not predict the highest metabolic risks with increasing %BF was consistent with the logistic regression that a protective effect of %BF to the metabolic syndrome and related metabolic risks. Analysis of the NHANES surveys found that, relative to the normal weight category, overweight

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[3] Metabolic ob ese NW women based on cut points for insulin sensitivity (normal = glucose disposal >8 mg / min x kg fat-free mass (FFM); impaired = glucose disposal <8 ml/min x kg FFM.

was associated with a statistically significant reduced number of deaths, after adjusting for sex, age, smoking, race-ethnic group, and alcohol consumption (Flegal, Graubard et al., 2005). Other researchers have observed a protective effect of peripheral obesity against cardiovascular disease. Tanko et al. reported that peripheral fat mass showed an independent negative correlation with both atherogenic metabolic risk factors and the most severe insulin resistance (2003). Dyslipidemic syndrome was found in women with high percentage central fat and low percentage peripheral fat (Tanko, Bagger et al., 2003).

Findings from present study support that WC may be a better predictor of modified metabolic syndrome and related metabolic risks than %BF. In women, higher levels of %BF were associated with reduced risk for high serum triglycerides, low HDL, high fasting glucose and modified metabolic syndrome when adjusted for WC.

Aim 3. To examine the predictive power of waist circumference and percent body fat to detect the risk for modified metabolic syndrome and/or each metabolic syndrome related disorder in overweight Taiwanese men and women using data from the Nutrition and Health Survey in Taiwan 1993-1996 (NAHSIT).

The prevalence rates of MS in the Taiwanese sample were about half that of the US white sample, but had rates that were similar by gender and increased with age (Park, Zhu et al., 2003). The contributions of the MSRD to the prevalence of MS and to MMS appear to differ by gender between these two samples. Dividing the prevalence of MS by that for MMS in the Taiwanese

sample, about 45% (16.1/35.6) of men and 61% (18.7/30.5) in women had high WC as one of the criteria. In contrast, in the non-Hispanic whites about 59% (32.1/54.2) of men and 91% (36.1/39.5) of women had high WC as one of the criteria. Thus, high WC contributed more strongly to the prevalence of MS in non-Hispanic whites. This shows that not only the prevalence of metabolic syndrome differed, but also the components of metabolic syndrome. About 55% and 40% of Taiwanese men and women who have MS do not have high WC, indicating factors other than abdominal adiposity play a major role in the etiology of MS in Taiwan.

Using the NCEP ATP III definition of MS, high blood pressure, high triglycerides and low HDL with or without high WC was most common for Taiwanese men, while the non-Hispanic white sample had a more evenly distributed pattern of prevalence of co-morbidities (Pan, 2002). Most Taiwanese women had a clustering of high WC, low HDL and high blood pressure, while most white women had a syndrome of high WC, low HDL and high triglycerides (Pan, 2002).

Differences in the prevalence of MSRD for MS between the Taiwanese and non Hispanic whites might have been due in part to differences in the protocol for measuring WC between NHANES III and the NAHSIT. In NAHSIT, the WC was measured midway between the iliac crest and the lowest rib, while in the NHANES III survey, WC was measured at the iliac crest. Thus, in women, but not in men, there can be a difference of up to 2 cm between a waist measurement taken immediately above the iliac crest and a measure taken midway between the

iliac crest and the lowest rib (Wang, Thornton et al., 2003). This difference in measurement location, cannot explain the difference entirely, because although the prevalence differed, the distribution patterns in WC were similar by gender. In NAHSIT, the prevalence of high WC was over twice as in women compared to men (32.8% vs. 14.1%), similar to that in non-Hispanic Whites (67% vs. 26%).

In the present study, the higher prevalence of hypertension in the Taiwanese versus non-Hispanic white adults revealed considerable underlying variation between these two groups. One mechanism by which body fat is thought to influence hypertension is increased insulin resistance especially from central adiposity. However, it has been known that after controlling for BMI, Asians have a higher prevalence of hypertension than do whites (Chandalia, Abate et al., 1999; Colin Bell, Adair et al., 2002; Pan, Flegal et al., 2004). One study demonstrated that Asian Indian men are more insulin resistant than Caucasian men independently of generalized or truncal adiposity (Chandalia, Abate et al., 1999), suggesting that some Asian populations have a higher prevalence of hypertension than Caucasians. It is likely that genetic and/or environmental factors such as high sodium intake contribute to the higher prevalence of hypertension in some Asians (Jones, 1995; Chandalia, Abate et al., 1999; Colin Bell, Adair et al., 2002; Pan, Flegal et al., 2004).

Analysis of the NAHSIT dataset from Taiwan resulted in very weak correlations between BMI and %BF for both men and women (r=0.05 and 0.07, respectively), a finding that differs from a study on Japanese adults. Using national survey data in Japan, Nagaya et al. examined 12,287 Japanese men and

6657 women to find BMI strongly correlated with %BF across the entire spectrum of BMI (r = 0.743 and 0.924, respectively) (Nagaya, Yoshida et al., 1999). Again, this difference was due to the range in BMI's, from 13.8 to 43.4 kg/m^2 in Nagaya's study to a range restricted to 24 to 27kg/m^2 in the present study. Such findings demonstrate a large inter-individual variation in %BF within a narrowed range of BMI. It also explains the small R^2 in the regression analysis of WC and %BF to the MS and metabolic related risks.

Similar to findings in NHANES III data, the logistic regressions for MMS or co-morbidities with the NAHSIT dataset provide compelling evidence that %BF coupled with WC does not predict an increase in MMS and metabolic related health risks better than does WC alone. One unexpected finding from the NAHSIT regressions, though, was that adding %BF to WC in the equation predicted high serum triglycerides and MMS in females (Table 4.12). Again, this finding suggests that factors other than %BF or WC are also contributing to the etiology of metabolic risks in Taiwanese overweight, but not obese, adults. Both the narrowed BMI range and smaller sample size in NAHSIT contribute to failure of obtaining precise estimates in the present study. In addition, the reference group for the prediction equations was normal WC and low %BF in overweight but not obese subjects instead of the normal weight group.

In the present study, same as the American population, WC remain a better predictor of modified metabolic syndrome and related metabolic risks than %BF in Taiwanese overweight but not obese population. Men and women with normal WC had lower prevalence of MSRD compare to high WC groups, with the

possible exception of low HDL's being somewhat higher in normal WC groups. Women with higher WC had increased risk for high blood pressure and high fasting glucose compared to normal WC group.

CHAPTER 6

CONCLUSION

The concluding chapter provides a summary of major findings, and the evaluation of the overall strengths and limitations of this research. The chapter concludes with implications for future research suggested by findings from this dissertation.

A. Summary of Findings

The aims of this research were as follows. 1) Determine whether %BF assessed by Bioelectrical Impedance Analysis (BIA) adds to the predictive power of WC in risk for MMS and/or each MSRD (elevated triglycerides, low HDL cholesterol, high blood pressure, impaired fasting blood glucose) by gender. 2) Examine whether BF distribution modifies the effect of %BF and WC on MMS and each MSRD differently in non-Hispanic whites and Taiwanese overweight, but not obese, men and women. Two national datasets NHANES III from the U.S. and NAHSIT from Taiwan were used to address these aims.

The main finding was that %BF measured by BIA provided no advantage over WC in screening for obesity-related metabolic risks. WC remained a strong positive predictor for MMS and MSRD and independent of gender, except for low HDL and high blood pressure in men. In this study, it was hypothesized that %BF as an indicator of total BF would have predictive power for MSRD. However, result s demonstrated that neither %BF alone nor %BF combined WC improved

the predictive power over WC alone for most of the MSRD. These findings confirmed that the MMS and co-morbidities are largely driven by central adiposity rather than total body adiposity. Another study also demonstrated that WC, and not BMI, explained obesity-related risks (Janssen, Katzmarzyk et al., 2004). In the present study, %BF was not superior to BMI in predicting MSRD for people classified as OW but not obese.

An important, and somewhat unexpected, finding of this study was that higher levels of %BF were associated with reduced risk for high serum triglycerides, low HDL, high fasting glucose and modified metabolic syndrome when adjusted for WC in women. One reasonable explanation for the risk reduction when %BF was included in the equation is that when WC increased, not only visceral fat increased but subcutaneous fat did as well. The WC index is a combination of both subcutaneous and intra-abdominal fat in the abdominal region. More and more studies support that intra abdominal fat (visceral fat) accumulation is the fundamental driver for MS (Kvist, Chowdhury et al., 1988; Abate, Garg et al., 1997; Wong, Janssen et al., 2003; Janssen, Katzmarzyk et al., 2004). Therefore, assessment of cardiovascular risk in overweight people solely from WC or total BF can be misleading, especially for women.

Using the current WC cut-point, more than two-thirds of over-weight but not obese white women had high WC, a rate twice that of white males in the same category. Comparing the prevalence of each component of the MMS between white men and women, all the metabolic risks were higher in men except for high WC. However, the prevalence of MS defined by NCEP-ATP III was slightly higher

in women than men suggesting that high WC in women makes a major contribution to MMS.

In examining BF distribution patterns and the prevalence of MS, MMS and MSRD, ethnic differences became apparent between the U.S. white and Taiwanese samples of over-weight adults. Both the WC and %BF were lower in the Taiwanese versus US white samples for both genders. The %BF was about 2% and 7% lower in Taiwanese men and women, respectively, compared to US non-Hispanic whites. The prevalence of high WC was also about half in the Taiwanese compared to non-Hispanic whites. In general, the prevalence rate of MS, MMS and each MSRD were all higher in non-Hispanic whites than in the Taiwanese for both genders, except for high blood pressure. Non-Hispanic white males had a higher prevalence of high serum triglycerides and high fasting glucose while non-Hispanic white females had high prevalence of high WC.

B. Strengths and Limitations

Given that the subject pools of NHANES III and NAHSIT were large and representative of the U.S. and Taiwanese populations, respectively, these are the best data sets which to test the hypotheses. Findings in this study are noteworthy, because for the first time differences among different body fat distribution patterns could be examined by high and low WC and %BF in over-weight but not obese people from two different populations. This is the first report that demonstrates an independent and opposite relationship of WC and

%BF with serum HDL and fasting blood glucose in non-Hispanic white women in both multiple regression analysis and in logistic regressions of this study.

This study has some limitations that warrant recognition. First, the cross-sectional nature of this study precludes causal inferences about the associations between WC, %BF, and MSRD. Ultimately, longitudinal data are necessary to establish whether the predictive models accurately characterize long-term risk for developing the MS. In addition, it would be desirable to control more covariates in the regression models for the Taiwanese to parallel what was done for the non-Hispanic whites. With hypertension so high in the Taiwanese sample, it might have been desirable to include sodium data as a covariate as well. Finally, there were some extreme cultural differences in the smoking covariate, where in 98% of Taiwanese women reported never smoking then this variable was dropped from the multiple regression analysis.

The %BF measured by BIA can be affected by factors that affect its validity such as cold temperatures, type of food and recency of eating, beverages, sweating, physical activity and other factors influencing conductivity and the body hydration status (Kyle, Bosaeus et al., 2004; Kyle, Bosaeus et al., 2004). In this study, Both BIA measurements in NHANES III and NAHSIT were carried out in the morning after an overnight fast, a standard procedure necessary for accurate measurements.

C. Implications

In this study, a narrowed range of BMI was used to test the hypotheses, providing some important implications for clinical practice and public health where it is desirable to target those over-weight, but not obese. The wide variation in BF distribution found within a limited BMI range can help to evaluate the effect of total BF and abdominal fat to metabolic risks more precisely than by using the entire range of BMI's. In both samples, at BMI$\geq$30, there were few subjects with either normal WC or %BF. However, a narrowed range of BMI also raised some difficulties for data analysis. A smaller sample size and a higher variation of %BF within this narrowed range of BMI. This contributed to a wide range of standard errors and confidence intervals. This high degree of variation means that was more difficult to detect some relationships between BF and MSRD, especially in the Taiwanese. Regardless, researchers and clinicians should be aware that for people with BMI=25<30, WC is a better indicator of risk for MMS than is %BF or even BMI. In order to screen high-risk individuals, health care professionals should measure WC at all clinical visits and not just measure weight.

Based on the NCEP-ATP III definition, the MS criteria includes three or more of following risk factors--high WC, high serum triglycerides, low HDL, high blood pressure and high fasting blood glucose. In the present study, almost 90% of OW but not obese non-Hispanic white women who had MS had high WC as one of the three components. This might over estimate the true MS in this group. i.e., for those who with high WC might only have had high subcutaneous abdominal adiposity instead of high intra-abdominal adiposity.

Findings from this study demonstrate that WC remained a strong positive predictor for MMS and most of the co-morbidities. However, the finding that high %BF did not predict the highest metabolic risks with increasing %BF percentiles was consistent with the logistic regression demonstrating a protective effect of %BF, especially in non-Hispanic white women. In that regard, future studies are needed to demonstrate that a combination of risk factors, and particularly a combination of insulin resistance syndrome features and indices of obesity, has greater clinical utility than WC.

D. Recommendations for Future Research

In this study, results demonstrate an independent and opposite relationship of WC and %BF with serum HDL and fasting blood glucose in non-Hispanic white women. It is not clear if this phenomenon would also hold true for obese people. That is to what extent is there *a protective effect* of total body adiposity to risk for MS? More studies need to address this question to elucidate the true relationship between BF distribution and the MS. Additionally, because neither WC nor %BF can distinguish between subcutaneous BF and intra abdominal adiposity, investigation of a new anthropometric screening tool might be useful for a way to remove the thickness of the abdominal skinfold from the WC to assess risk..

Racial and ethnic variation in metabolic risks complicates the determination of body adiposity and its association with metabolic risks. In the present study, the MS and co-morbidities were explained by WC and not by %BF. However, the

prevalence of high WC varied between non-Hispanic whites and Taiwanese suggesting that further studies might be necessary to examine the possibility of a differential disease/obesity relationship between Asians/Taiwanese and other ethnic groups. Such studies should focus on the role of %BF, WC, and subcutaneous versus intra abdominal fat in relation to risk for MS.

Appendix 1

Detailed laboratory procedures for metabolic risk and anthropometric variables in NHANES III and NAHSIT

Both NHANES and NAHSIT data have similar sampling designs, data collection procedures and analyses protocol. In this appendix, the NHANES data are first described for each measurement and analysis procedure for each variable that were used in this study. Then, any variables for which the analysis differed for the NAHSIT, were described in the NAHSIT section.

Laboratory analyses data

In NHANES III, serum TG was measured enzymatically in serum or plasma on a Hitachi 717 Analyzer (Hitachi, Tokyo, Japan) using commercial reagents (Triglycerides/GPO reagent system pack, Boehringer Mannheim Diagnostics). By using a series of coupled reactions in which triglycerides were hydrolyzed to produce glycerol, glycerol was then oxidized by using glycerol oxidase and H_2O_2. One of the reaction products, was measured quantitatively in a peroxidase-catalyzed reaction that produces a color similar to that for cholesterol and absorbancy is measured at 500 nm. The reaction sequence was as follows.

(1) Triglycerides $\xrightarrow{\text{lipase}}$ glycerol + fatty acids

(2) Glycerol + ATP $\xrightarrow{\text{glycerokinase}}$ glycerol-3-phosphate + ADP

High-density lipoprotein-cholesterol (HDL-C) was measured after precipitation of other lipoproteins with a polyanion/divalent cation mixture based on the following steps:

a. Add 100 µL of heparin sulfate-MnCl mixture to 1 mL of serum for each

sample. The reaction yields apo-B-containing lipoprotein, precipitate, and soluble HDL-cholesterol

b. Remove precipitate by centrifuging at 1500 x g for 30 min. Remove the clear supernatant and placing it into a 20-mL glass vial.

c. Place 500 µL of the supernatant and 50 µL sodium bicarbonate into an Eppendorf tube. Vortex intermittently. Let the tubes stand at 20-25 C for 10 minutes; then centrifuge at 10,000 x g for two minutes.

d. Measure HDL-cholesterol in clear supernatant.

Two quality control pools were used to monitor the analysis of and triglyceride and HDL. The precision of lipid and lipoprotein analyses was determined from duplicate analysis of each pool analyzed in each run. The triglyceride control pools (Q) and HDL-cholesterol control pools (MQ and AQ) were prepared by Centers for Disease Control (CDC). These pools were also analyzed in duplicate in every analytical run for a maximum of 50 runs. They were used to assess accuracy with respect to CDC reference methods and analytical precision.

Blood pressure was reported as the average of six readings, three taken during the household interview and three taken during the physical exam. At the household interview, an interviewer measured blood pressure three times with the participant resting quietly, sitting in a chair at home. A physician took three additional blood pressure measurements in the mobile examination center. In both venues, blood pressure was measured with a standard sphygmomanometer (W. A. Baum, Copiague, NY). One of four cuff sizes (pediatric, regular adult, large, or thigh) was chosen based on the circumference of the participant's arm,

as indicated by the manufacturer's guidelines.

Plasma glucose was measured by using a hexokinase enzymatic method. Venous whole blood was collected into a vacuum tube containing the glycolytic inhibitors potassium oxalate and sodium fluoride and was centrifuged immediately at 1500*g* for 10 minutes. The plasma was frozen at -70°C, shipped on dry ice to the University of Missouri Diabetes Diagnostic Laboratory, and stored at -70°C until analysis. Plasma glucose was measured using a modified hexokinase enzymatic method (Cobas Mira assay; Roche, Basel, Switzerland), both within assay and between-assay quality control procedures were used; the coefficient of variation of the method was 1.6–3.7% during the six years of the survey.

Anthropometric variables

In NHANES III, weight and height were measured using standardized techniques (DHHS 1997). Body weight was measured with an electronic load cell scale to the nearest 0.01 kg (Toledo 8136 Scale). Participants wore only personal undergarments and disposable paper shirts, pants and foam slippers were provided, but no adjustment was made in the analyses from the minimal clothing weight (0.18 kg).

Stature was measured using a fixed stadiometer (Holtain Height Stadiometer). Participants stood on the floor board of the stadiometer with his or her back to the vertical backboard of the stadiometer. The heels, buttocks, scapulae and head were against the upright surface of the stadiometer with the head positioned in the Frankfort horizontal plane. Hair ornaments, buns, braids,

etc. were removed to obtain an accurate measurement. Afterwards the examiner read the measurement and the assistant recorded it to the nearest 0.1 cm.

Waist circumference was measured in a standing position. The examiner marked a horizontal line at the high point of the iliac crest and then crossed the line to indicate the mid-axillary line of the body. The examiner then stood on the participant's right side and placed the measuring tape around the trunk in a horizontal plane at this level and marked on the right side of the trunk. The measurement was made at minimal respiration to the nearest 0.1 cm.

NHANES III used the following steps to ensure the quality of measurements: 1) one participant was selected by the computer to have body measurements replicated by another technician every other day; 2) tolerance levels/ranges were set for weight, height and waist circumference measurement to function as a quality control measure by minimizing possible measuring and recording errors; 3) anthropometric technicians were periodically observed by the body measurement consultant to ensure standardization. The consultant reviewed any deviations from the protocol with the technicians. There was no validation testing described in the NHANES III operation and reference manual (DHHS 1996).

A body composition analyzer for BIA (model 1990B; Valhalla Scientific, San Diego) was used for the measurement of whole body electrical resistance and impedance. During the BIA procedure, subjects lay supine on a nonconductive examination table without a pillow under their head. The

technician instructed the subject to remain motionless and relaxed with their arms and legs slightly apart and not touching any other part of the body. Participants had a single, tetrapolar BIA measurement of resistance (Res) and reactance at 50 kHz taken between the right wrist and ankle while in a supine position. The percent body fat estimates were derived from prediction equations for fat-free mass (FFM) that were validated and cross-validated for men and women separately and for blacks and whites between the ages of 12 and 94 y. The converted NHANES III, RJL resistance values were used to calculate the impedance index of stature in cm squared divided by resistance (S^2/Res)in the TBW and FFM prediction equations (Zhu, Wang et al. 2003). The equations for men and for women were as follows:

Males TBW =1.203 +0.176 weight +0.449 S^2/Res

Females TBW=3.747 + 0.113 weight + 0.45 S^2/Res

Males FFM =10.678 + 0:262 weight + 0.652 S^2/Res + 0.015 Res

Females FFM =9.529 + 0.168 weight + 0.696 S^2/Res + 0.016 Res

The National Institute of Standards and Technology independently certified measurement accuracy of the Valhalla impedance machines used in NHANES III after the survey. Detailed information on the BIA procedure is presented elsewhere (Kuczmarski 1996; NCHS. 1998). The percent body fat was calculated as follows:

Total body Fat = weight – Fat Free Mass and %BF = BF/weight.

NAHSIT

Laboratory, clinical and anthropometric measurements were identical for NHASIT with three exceptions: 1) fasting whole-blood glucose was measured with heparinized blood by the glucose oxidase method using a glucose analyzer (Model 23A, YSI, USA) immediately after blood drawing. The blood sample was not frozen as in NHANES and a different laboratory was used in the analysis. For NAHSIT, a Hitachi 747 analyzer (Hitachi 717 analyzer in NHANES III) was used to measure serum triglyceride, cholesterol, and HDL-C values in the central laboratory; 2) blood pressure was measured by standard sphygmomanometers at home after the participants rested at least five minutes. A cuff of appropriate size was used for each participant. Two, and not six, blood pressure measurements were made 30 seconds apart with the arm at the level of the heart. If the two measurements were more than 10 mmHg apart, a third measurement was made. The two closest blood pressure values were averaged to obtain the mean blood pressure; 3) The BIA machine used in NAHSIT was the SELCO SIF891 and the formula used to calculate percent body fat were based on healthy Japanese male and females.

Covariates.

The covariates in NAHSIT were continuous rather than categorical such as years of education and income. These were converted to ranked categories as similar as possible to the NHANES data. In NAHSIT, physical activity was assessed using both the frequency and average time spent on activities in the

preceding month, but in NHANESIII only frequency was asked. Occupation related activities were also included in the NAHSIT but not in NHANES III. For comparison purpose, only frequency of leisure time activities of NAHSIT data was used in this study and was converted to ranked categories use the same method as for NHANES III.

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