A PROPOSED SCORING SYSTEM FOR QUANTIFICATION OF METABOLIC SYNDROME SEVERITY

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ABSTRACT

Due to many limitations of the current metabolic syndrome (MetS) definition, several researchers have questioned the clinical utility of MetS. It has been suggested that MetS should be assessed on a continuum rather than dichotomously labeling MetS presence or absence. Additionally, it is unclear which risk factor(s) contribute the most to MetS presence. **PURPOSE:** The aims of the current study were: 1) to establish a scoring system for assessing presence and severity (number of traits) of MetS and 2) to determine the most influential contributor to incident MetS in women, men, and combined genders. **METHODS:** Overweight and sedentary subjects (N=208) were obtained from previous exercise intervention studies. Two MetS scoring systems were formulated: one including all 5 current MetS criteria (5score) and one including 5 additional measurements (10score). Additional variables included in 10score were: BMI, CRP, TNFα, % fat, and VO_2max. Individual traits were divided into quartiles with 0, 1, 3, and 5 points assigned according to worsening metabolic profile. Additionally, weighted multipliers were added to reflect relative risk of each trait. MetS score was defined as the summary score of all individual traits. Kernel smooth functions were used to determine the relationship between MetS score and probability of MetS. Additionally, linear regression was employed to test the relationship between MetS score MetS severity. Backward elimination and forward selection were used to determine the most influential contributors to MetS. **RESULTS:** 5score displayed a sigmoidal relationship with MetS probability whereas 10score was linearly related to MetS risk. Both 5score (r^2=0.74) and 10score (r^2=0.23) were significant predictors of MetS severity (both $p<0.0001$). Backward elimination and forward selection revealed traits contributed to MetS in the

following order: for women, HDL-C>FG>TG>SBP>WC, for men, TG>FG>WC>SBP>HDL-C, and combined TG>FG>HDL-C>SBP>WC. According to forward selection, HDL-C explained 21% ($p<0.0001$) of the null deviance in women and was the most influential factor for MetS incidence. This was significantly greater than the independent effects of SBP ($p<0.0001$) and WC ($p=0.0018$), but not FG ($p=0.0833$) or TG ($p=1.0000$). TG accounted for 34% ($p<0.0001$) of null deviance in men and was shown to be the primary factor contributing to MetS. This was significantly higher than the independent effects of WC ($p<0.0001$), FG ($p<0.0001$), HDL-C ($p=0.0239$), and SBP ($p<0.0001$). In combined, TG accounted for 27% ($p<0.0001$) of null deviance and was shown to be the primary contributor to MetS. This was significantly higher than the independent effects of WC ($p<0.0001$), FG ($p<0.0001$), and SBP ($p<0.0001$), but not HDL-C ($p=0.1797$). **CONCLUSIONS:** 5score and 10score are significant predictors of MetS presence and severity. Inclusion of redundant markers for obesity and inflammation in 10score may have weakened its relationship to MetS. Future research is needed to determine whether 5score and 10score are significant predictors of CVD, T2D, and mortality. Individual MetS traits do not display a linear relationship to incident MetS. Additionally, MetS traits behave differently between genders. HDL-C appears to be the most significant contributor to incident MetS in women. In men and combined, TG appears to be the most significant contributor to MetS.

INTRODUCTION

Metabolic syndrome (MetS) constitutes a clustering of metabolic risk factors for the development of type 2 diabetes (T2D), cardiovascular disease (CVD), and mortality. Previous research has confirmed that MetS is a significant risk factor for both CVD (4, 33, 74, 90, 100, 104, 119, 122, 129, 164) and T2D (33, 63, 89, 98, 122). Current estimates show that nearly 25% of US adults are classified as having MetS (44, 104, 113). However, several researchers have argued against the use of MetS in a clinical setting (4, 79, 122, 143). Several arguments against MetS have been proposed: 1) discrepancy between MetS definitions, 2) lack of improved predictive power compared to other tools, 3) need for additional diagnostic criteria, 4) dichotomously labeling the presence of MetS, and 5) equal weights assigned to all MetS traits. Additionally, physical fitness is not currently considered when diagnosing MetS. Development of a new MetS scoring tool grading severity of individual components and including non-traditional risk factors may improve the utility of MetS in clinical and research settings.

METS AS A RISK FACTOR

MetS has consistently proven to be a significant risk factor for the development of CVD (4, 33, 74, 90, 100, 104, 119, 122, 129, 164), T2D (33, 63, 89, 98, 122), and mortality (72, 74, 90, 100). One study demonstrated that MetS accounts for 21% of the variance associated with incident coronary heart disease (CHD) (90). Another study by Dekker et al (33) found that individuals with MetS had 2 fold higher CVD incidence in 10 years. Several studies have demonstrated increased mortality rates in MetS, primarily due to CVD (33, 74, 90, 100). Malik et al (100) showed that mortality was increased 40% in MetS and that CVD mortality was increased 200%. Additionally, MetS has been

shown to be a risk factor for T2D. In fact, over 85% of individuals with T2D also are classified as having MetS (4). Wilson et al (164) demonstrated that risk of T2D increase 5 fold in individuals with 1-2 MetS traits and nearly 25 fold in those with ≥3 traits.

METS PREVALENCE

MetS has been shown to be a highly prevalent condition affecting over 15% of Europeans (72) and approximately 25% of US adults (44, 104, 113). Different populations have been shown to have different rates of MetS with rates being lower among African Americans and higher among Hispanic Americans (44, 113). However, MetS rates appear to be similar between men and women (72). MetS prevalence has also been shown to increase with increasing weight (54, 83, 113) and age (4, 44). Park et al (113) demonstrated that MetS prevalence was 4.6%, 22.4%, and 59.6% for normal-weight, overweight, and obese men, respectively. Another study by Ford et al showed that MetS prevalence increased from 6.7% in persons aged 20-29 to 43.5% in those aged 60-69.

DISCREPANCY BETWEEN DEFINITIONS

Several organizations have proposed definitions for MetS (34, 59) . The most established definitions come from the World Health Organization (WHO), European Group for the Study of Insulin Resistance (EGIR), American Association of Clinical Endocrinologists (AACE), International Diabetes Foundation (IDF), and the National Cholesterol Education Program's Adult Treatment Panel III (ATP III). These definitions are very similar with respect to the criteria used to define MetS. However, there are significant discrepancies with regard to threshold cut-off points and methods used to assess risk factors. Additionally, some organizations require the presence of insulin

resistance (IR) or abdominal obesity prior to diagnosis of MetS. WHO has been shown to be superior to ATP III with respect to prediction of T2D, but not CVD (65, 89). Despite differences in definitions, MetS prevalence appears to be similar between WHO and ATP III when examining different definitions (65, 104).

These findings indicate the need for a unified MetS definition for prediction of morbidity and mortality. Currently, ATP III appears to be the most commonly used MetS definition (34, 36). According to this definition, individuals are considered to have MetS if they meet 3 or more of the following criteria: waist circumference (WC) ≥102cm for men and ≥88cm for women, fasting triglycerides (TG) ≥150mg/dl, high-density lipoprotein cholesterol (HDL-C) <40mg/dl for men and <50 mg/dl for women, blood pressure (BP) ≥130/85 (or on anti-hypertensive medication), and fasting glucose (FG) ≥100mg/dl (or on glucose lowering medication) (59).

METS PREDICTIVE POWER

Due to the inclusion of multiple risk factors, MetS presence is a significant predictor of morbidity and mortality. However, it has previously been shown that MetS is inferior to Framingham Risk Score (FRS) and Diabetes Predicting Model (DPM) for the prediction of CVD and T2D, respectively (143). Due to the lack of improved predictive ability, some authors have questioned the utility of MetS diagnosis (4, 79, 122, 143). Some research studies have found that MetS presence does not improve disease prediction beyond assessment of each risk factor independently (4, 65, 122, 129). This suggests that MetS is no greater than the sum of its individual components. This has left some authors to question the existence of a "true" metabolic syndrome (79). Some of the

lack of improved predictive ability can be attributed to the need for additional criteria, dichotomous assessment of MetS, and equally weighted risk factors.

ADDITIONAL CRITERIA

Recently, several additional MetS criteria have been proposed. Several studies have indicated that body composition (6, 17, 18, 133), physical fitness (24, 38, 48, 78, 88, 92, 111), and chronic inflammation (31, 70, 166) may significantly contribute to MetS. Previous research has shown that MetS increases with increasing Body Mass Index (BMI) (46, 75, 97, 142, 155, 168). Furthermore, many researchers have demonstrated that metabolic perturbations are primarily due to adipose tissue rather than weight, per se (6, 17, 18, 133). Therefore, inclusion of BMI and percent body fat may improve the predictive ability of MetS. Additionally, physical fitness may offer protection against the detrimental effects of MetS. Jurca et al (78) showed that muscular strength is inversely related to MetS. Numerous studies have indicated an inverse relationship between aerobic capacity and CVD (22, 28, 96, 107), T2D (158), and mortality (27, 28, 96, 107, 109, 144, 157). Furthermore, aerobic capacity is inversely related to incident MetS (9, 22, 24, 38, 48, 88, 92, 111). These data further support the addition of aerobic capacity in MetS assessment. Chronic inflammation has also recently been shown to be directly related to MetS presence and severity (31, 70, 166). Inflammation is now recognized as a metabolic risk factor for the development of MetS (59). Inclusion of C-reactive protein (CRP) has been shown to improve the predictive ability of MetS with respect to CVD (123, 125, 131). Some authors (140) have proposed that it is necessary to examine several markers of inflammation in order to appreciate risk associated with a pro-

inflammatory state. Therefore, inclusion of other inflammatory cytokines may improve the predictive ability of MetS.

DICHOTOMOUS ASSESSMENT

The dichotomous label of MetS may compromise essential information about metabolic processes and limit its utility in predicting disease. Several studies have confirmed that CVD and mortality risks are significantly elevated in individuals displaying 1-2 MetS traits (33, 100, 164), indicating that risk is elevated prior to development of overt MetS. According to current MetS definitions, individuals with <3 traits have no increase in risk of morbidity and mortality. Likewise, individuals with ≥3 traits have increased risk regardless of the number or severity of traits present. Furthermore, disease risk associated with worsening or improving metabolic profile is not reflected by current MetS definitions unless a clinical threshold is reached. Taken together, these results indicate the need for a revised MetS definition reflecting risk associated with mild or severe MetS. Graded risk may improve the predictive ability and utility of MetS.

EQUAL WEIGHTS

Current MetS definitions contribute equal weight to all MetS traits. Baseline MetS traits appear to contribute differently to MetS incidence (112) suggesting that individual risk factors carry different risk of morbidity and mortality. Many authors have attempted to determine which risk factors contribute the most to MetS incidence and severity. These studies have primarily employed factor analysis, a statistical method for assessing highly intercorrelated variables. Results from these studies have consistently demonstrated heavy loadings for both obesity and IR (63, 65, 92, 119), suggesting these

two traits may contribute significantly higher risk to the development of MetS. Accordingly, these variables are considered underlying risk factors for MetS (59). These findings suggest that MetS traits may not carry equal health consequences. Additionally, non-traditional risk factors such as aerobic capacity may carry higher health consequences (positive or negative). Factor analysis has shown aerobic capacity to load more heavily than other MetS traits such as FG, systolic blood pressure, and triglycerides (92). Together, these findings indicate the need to assess severity of individual components in order to more accurately reflect risk associated with MetS.

PREVIOUS ATTEMPTS TO QUANTIFY METS

Due to the limitations of the current definitions, some researchers have proposed different schemes to quantify severity of MetS. The simplest approach to date is to assess number of MetS traits present. Several groups have shown increasing disease risk with increasing number of MetS traits even with only 1-2 traits present (33, 131, 164). Furthermore, number of MetS traits is closely related to CAD severity, cerebrovascular disease, and T2D (137). In addition, non-traditional risk factors such as uric acid, HOMA, and apolipoproteins A1 and B increase with increasing number of MetS traits. These findings indicate that number of traits may serve as a surrogate marker of MetS severity.

Another previously employed method of quantifying MetS severity is development of z-scores (48, 77, 162). According to this method, values for each trait are standardized and assessed through regression analysis. Wijndaele et al (162) demonstrated that individuals with ≥3 MetS traits displayed a higher z-score. Furthermore, these authors found increasing MetS z-score to be directly related to

number of MetS traits, suggesting trait number may also be an effective indicator of MetS severity. However, due to the complexity of statistical methods, this scoring system has not proven to be practical in a clinical setting.

Previous work from this lab has established a more clinically relevant scoring system. According to this system, risk factors are divided into quartiles with point values assigned based on severity of individual MetS traits. The sum of all quartile scores is indicative of risk associated with MetS. However, like other systems, this method assigns equal weight to all MetS traits. Additionally, quartile cut-off points did not appear to be based on previously established recommendations. This makes implementation into a clinical setting more difficult as it requires practitioners to remember additional and somewhat arbitrary cut-off point.

STUDY OBJECTIVES

The current research project aimed to accomplish the following goals:

- Design a clinically relevant scoring system for assessing presence and severity (number of traits) of MetS. In order to establish this scoring system, MetS traits were divided into quartiles based on previous research and current recommendations. Additionally, weighted multipliers were added to each risk factor to reflect its contribution to incident MetS, CVD, T2D, and mortality. Given the contribution of body composition, physical fitness, and chronic inflammation to MetS, the present study included the following risk factors in addition to previously established MetS criteria: BMI, percent body fat, aerobic capacity (VO_2max), CRP and tumor necrosis factor α (TNFα).
- Determine which MetS trait is the most significant predictor of MetS presence.

METHODS

Subjects. Data included in the present study are from subjects (N=208) previously screened for participation in exercise intervention studies at the University of Missouri (n=180) and the University of Kansas (n=28). The data set contains data both from men (n=86) and women (n=122). Data from the University of Kansas was included to address the disproportionate number of females in the data set. Subjects were recruited primarily due to the presence of overweight or obesity. The previous studies were approved by the Institutional Review Boards of the respective universities. Informed consent was obtained from subjects during screening for participation in the original research studies.

MetS traits measured in the current study included: waist circumference (WC), blood pressure (BP), triglycerides (TG), high density lipoprotein-cholesterol (HDL-C), fasting glucose (FG), body mass index (BMI), percent body fat (% fat), C-reactive protein (CRP), tumor necrosis factor α (TNFα), and aerobic capacity (VO_2max). Data for the 5 current components of MetS (WC, BP, TG, HDL-C, and FG) were available for all 208 subjects in the current study. Five additional measures (BMI, % fat, CRP, TNFα, and VO_2max) were obtained for a subset of subjects in order to test their relationship with MetS and to develop a new MetS definition including 10 variables. This additional data was obtained primarily from subjects who qualified for participation in the exercise intervention studies. These subjects were required to meet criterion values for at least 2 MetS traits and thus may have more severe MetS than individuals who did not qualify. Complete data sets for all 10 variables were available for 78 subjects (31 male, 47 female).

MetS. MetS criteria were defined according to the National Cholesterol Education Program Adult Treatment Panel III (ATP III) definition (58): waist circumference (WC) ≥102cm for men and ≥88cm for women, fasting triglycerides (TG) ≥150mg/dl, high-density lipoprotein cholesterol (HDL-C) <40mg/dl for men and <50 mg/dl for women, blood pressure (BP) ≥130/85 (or on anti-hypertensive medication), and fasting glucose (FG) ≥100mg/dl (or on glucose lowering medication).

Anthropometry. Body weight was measured to the nearest 0.05kg and height to the nearest 0.5cm and used to calculate BMI (kg/m^2). Three site skinfold measurements were performed according to the formula by Jackson and Pollack. Sites used were chest, abdomen, and thigh for males; triceps, suprailiac, and thigh for females. Mean values from 2 of 3 measurements within 1mm at each site were used to calculate body density and percent body fat. WC was determined by measuring the circumference at the narrowest point between the costal margin and the iliac crest.

Blood Pressure. BP was obtained with patients in a seated position following a five minute rest. Two measurements were obtained for each participant and the average of the two values was used as the reported resting BP values.

Aerobic Capacity. Maximal aerobic capacity was assessed via a maximal treadmill test using the Bruce protocol until volitional fatigue. The highest VO_2 value obtained was recorded as the subject's VO_2max

Blood Collection. Blood samples used for analysis were obtained from an antecubital vein following a 12 hour overnight fast. Subjects refrained from exercise for at least 48 hours prior to blood collection. Samples were collected into 10 ml EDTA, sodium heparin, or serum separator vacutainer tubes. Samples were allowed to clot and

serum and plasma were separated by centrifugation at 4ºC for 15 min at 2000g in a Marathon 21000R centrifuge (Fisher Scientific, Pittsburgh, PA). Serum and plasma samples were then frozen at -80ºC until analyzed.

Biochemial Analysis.

Fasting Glucose. Fasting plasma glucose concentrations were determined by an automated analyzer (pHOx Plus L, Nova Biomedical, Waltham, MA) using the glucose oxidase method. Intra-assay coefficient of variance (CV) for glucose in this lab has been shown to be 1.8%.

Triglycerides. TG were measured in plasma using a colorimetric diagnostic kit (Thermo, Arlington, TX). Absorbance was determined using a Beckman DU 530 spectrophotometer (Beckman Instruments Inc., Fullerton, CA) and known standards used to construct a standard curve. Intra-assay CV for TG from this lab has been reported to be 1.7%.

HDL-C. HDL was separated from LDL using an ultracentrugation procedure, and isolated from plasma by single spin density gradient ultracentrugation. Samples were adjusted to a density of 1.30 g/ml by the addition of solid KBr (0.4946 g/ml plasma) and overlaid with normal saline (0.15 M NaCl-0.01% EDTA, pH 7.4). HDL was separated in the density range ρ=1.063-1.256 kg/L by ultracentrugation for 150 min at 65,000 rpm using a Sorvall Discovery 100SE ultracentrifuge and a T-890 rotor. Plasma HDL-C concentration was determined using a modified heparin-$MnCl_2$-dextran sulfate method. Plasma samples were mixed with the heparin-$MnCl_2$-dextran sulfate, vortexed, incubated at 37ºC, and centrifuged at 1500g for 20 min. Samples were analyzed for cholesterol

content using a spectrophotometer at 500nm. Intra-assay CV for HDL-C from this lab has been shown to be1.0%.

CRP. Plasma CRP was analyzed using a high-sensitivity CRP (hsCRP) chemiluminscence technique (Immulite 1000, Diagnostic Products Corporation, Los Angeles, CA). Intra-assay CV for CRP in this lab has been shown to be 2.0%.

TNFα. TNFα was measured using a commercially available enzyme-linked immunosorbant assay (ELISA) (R&D Systems, Inc., Minneapolis, MN). The intra-assay CV for this assay was found to be 6.6%.

Formulation of Scoring Systems.

In order to more accurately reflect morbidity and mortality risk associated with MetS, 2 scoring systems were created. The first system (5score) included only the 5 current criteria for diagnosis of MetS (WC, BP, TG, HDL-C, and FG). The second system (10score) included the 5 current MetS criteria as well as 5 additional variables (BMI, % body fat, VO_2max, CRP, and TNFα) previously shown to be related to MetS. These variables were included based primarily on previous literature supporting a role for these markers in: MetS incidence, CVD and/or T2D incidence, all-cause mortality, and ease of measurement in a clinical or research setting.

In both scoring systems, each criterion measurement was divided into quartile rankings with point values assigned according to severity of each trait. Quartile ranks were assigned point values of 0, 1, 3, and 5 for quartiles 1, 2, 3, and 4, respectively. Therefore, higher MetS scores reflect increased risk. In order to make MetS score more easily incorporated into clinical use, quartile rankings used current recommendations when available. Current MetS threshold values were used as the minimum value for

quartile 3. This accounts for increased risk associated with values that are elevated, but do not reach current MetS threshold values. Additionally, inclusion of a fourth quartile above current MetS thresholds accounts for increased risk associated with more extreme values not currently assessed by MetS.

In addition to point values based on quartile rank, weighted multipliers were added to variables to reflect their contribution to deleterious health effects. The following criteria were considered when assigning weighted multipliers: contribution to incident MetS, CVD, T2D, and mortality. Weighted multipliers for 5score developed primarily by an extensive literature review. Traits closely related to incident MetS, CVD, T2D, and mortality were assigned higher weighted values. Additionally, weighted multipliers loosely corresponded to a report by Palaniappan et al (112). According to these authors, odds ratio of incident MetS based on baseline components were 2.0, 1.6, 1.6, 1.6, and 1.1 for WC, FG, HDL-C, TG, and BP, respectively. However, these authors did not assess risk of CVD, T2D, or mortality. Table 1 shows a comparison of ATP III MetS definition with 5score and 10score.

Waist Circumference. According to the ATP III definition of MetS, enlarged WC is an underlying cause of MetS (59). Furthermore, WC correlates highly with visceral adipose tissue (VAT) (25, 126) which contributes greatly to incident MetS (9, 23, 46, 55, 146, 168). Therefore, WC may play a central role in development and progression of MetS. For the basis of this report, WC cut-off points were based on a report by Lean et al (95). According to these researchers, WC values of ≥94cm in men and ≥80cm in women correspond well with elevated BMI (25-29.9) and WHR (0.95). Therefore, in the present study, WC quartile cut-off points were defined as: <95, 95-101,

102-115, and >115cm for men and <80, 80-87, 88-102, and >102cm for women. The health consequences of WC are highlighted by the fact that 10% increase in WC corresponds to a 30% increase in mortality risk (18). For the present study, WC was assigned a multiplier of 2.0.

Blood Pressure. Blood pressure has been proven to be a significant risk factor for CVD (2, 26, 91, 134, 153, 154) and mortality (53, 151). Relative risk of CVD increases approximately 2 fold for every 20mmHg increase in systolic or10mmHg increase in diastolic blood pressure (26). However, decreasing BP below approximately 130/80mmHg does not appear to offer additional protection against CVD (66). In accordance with current guidelines (26), this study established the following cut-off points for BP: <120/80, 120-129/80-84, 130-139/85-89, and ≥140/90mmHg. When subject's systolic and diastolic quartiles differed, the higher quartile value was used in calculating MetS score. Of all current MetS criteria, elevated BP appears to contribute the least to incident MetS (112). Additionally, some studies have failed to implicate isolated hypertension as a risk factor for CVD (5, 69). However, elevated BP combined with other risk factors such as impaired FG is a significant risk factor (69). Therefore, BP was assigned a weighted value of 1.0 for the present study.

Fasting Glucose. In addition to abdominal obesity, IR has been proposed as an underlying cause of MetS (59). Factor analysis studies have consistently demonstrated heavy loadings for markers of IR (63, 65, 119), suggesting this risk factor may contribute significantly to the development of MetS. Deleterious health consequences of IR are usually contributed to the resultant hyperglycemia rather than IR per se (8). Bjornholt et al (19) demonstrated that individuals with FG >85mg/dl had a 40% increase risk of all

cause mortality compared to those with FG ≤85mg/dl. Based on this data, the current project used the following cut-off points for FG quartiles: <85, 85-99, 100-114, and ≥115 mg/dl. FG has been shown to be similarly effective as impaired glucose tolerance for predicting CVD (103, 132) and T2D (32). Elevated FG has been shown to be a highly significant predictor of mortality even after adjustment for confounding variables such as hypercholesterolemia and hypertension (15, 19, 29, 42, 108). Considering the health risks associated with elevated FG, this risk factor was assigned a multiplier of 2.0.

HDL-C. HDL-C is inversely related to CVD (13, 57, 139, 160) and all-cause mortality (163). Evidence from the Framingham Heart Study has shown that CVD risk is increased at concentrations well above the current clinical threshold for MetS diagnosis (163). Men with HDL-C 47-54mg/dl had a relative risk of 2.77 for CHD. Similarly, women with HDL 59-69mg/dl had a relative risk of 2.60 for CHD. This evidence suggests that the current MetS diagnostic criterion is too low to reflect risk associated with mildly lowered HDL-C. The Framingham study (163) divided subjects in the following quintiles: ≤34, 35-40, 41-46, 47-54 and ≥55mg/dl for men and ≤44, 45-51, 52-58, 59-69, and ≥70mg/dl for women. The present study approximated these values when determining HDL-C quartile cut-off points. For the present study, HDL quartiles were defined as: <40, 40-49, 50-59, and ≥60mg/dl for men and <50, 50-59, 60-69, and ≥70mg/dl for women. Palaniappan et al (112) determined HDL-C was second only to WC in predicting development of MetS. Therefore, HDL-C was assigned a multiplier of 1.5 in the current score system.

Triglycerides. Miller et al (105) demonstrated that risk of coronary artery disease is significantly elevated at TG ≥100mg/dl, the median value for US adults. Data

from the Prospective Cardiovascular Münster Study (PROCAM) paralleled this finding (10). Quartile cut-off points for the present study were taken from the PROCAM (10) scoring system: <100, 100-149, 150-199, and ≥200mg/dl. The current project used these same cut-off values to assess risk associated with fasting TG. While fasting TG has been shown to be an independent risk factor, risk associated with TG is attenuated after adjusting for HDL-C (12, 21, 62, 76), suggesting TG is not as significant as other MetS traits. Miller et al (105) found that both diabetes mellitus and low HDL-C were better predictors of incident coronary artery disease than TG. The PROCAM study (10) identified the following risk factors in order of decreasing significance in predicting acute coronary events: age, LDL-C, smoking, low HDL-C, SBP, family history, diabetes mellitus, and TG. Based on these findings, the current project assigned fasting TG a weight value of 1.0.

BMI. BMI has previously been associated with MetS (99, 141, 155, 168), CVD (86, 87, 138, 152), and mortality (1, 6, 16, 43, 68). A recent study demonstrated that men with BMI values of 23-24.9 had a 5 fold higher odds ratio of MetS than men with BMI of 18.5-20.9 (141). Women in this range had a 7.5 fold higher MetS odds ratio. This data suggests that moderate increases in weight may carry significant metabolic and health risks. Factor analysis has implicated BMI as a central feature of MetS (99). Liese et al (97) found that individuals with worsening MetS profile over three years tended to gain weight, suggesting weight gain mediates metabolic perturbations. Accordingly, Maison et al (99) found that changes in BMI were highly correlated to changes in BP, FG, TG, and HDL-C. The present study employed current BMI classification guidelines (6): <25,

25-29.9, 30-34.9, and ≥35 kg/m^2 as quartile cut-off points. Given the health consequences of obesity, the current study assigned BMI a weight value of 2.0.

Percent Body Fat. Body composition has been proposed as a potential mediator of health risk associated with body mass (6, 17, 18, 133). High levels of skeletal muscle strength are associated with significant improvements in metabolic profile (78). Furthermore, lean individuals with high BMI have similar metabolic profile as lean, normal-weight individuals (133). Zhu et al (170) demonstrated that men with body fat percentages of 12, 21, 29, and 36 had similar MetS prevalence as men with BMI of 18.5, 25, 30, and 35, respectively. For women, these values were: 24, 31, 37, and 43%. The present study used similar cut-off points of: <15, 15-22, 23-30, and >30% for men and <25, 25-32, 33-40, and >40% for women. Due to a lack of epidemiological data implicating body composition as a risk factor, percent body fat was assigned a weighted value of 1.0.

CRP. CRP has previously been shown to be an independent risk factor for both CVD (114, 123-125, 128) and T2D (41, 49, 125). Furthermore, modified MetS definitions including CRP have been shown to enhance MetS predictive ability (41, 49, 123, 125, 131). CRP concentrations have been closely tied to obesity (39, 40, 45, 52, 80, 145, 147)and IR (39, 40, 101, 117, 118). Adipose tissue appears to be the major source of CRP (45, 80, 147) and adjustment for obesity weakens the association between CRP and health risk (41). This study used current guidelines from the Center for Disease Control and Prevention and the American Heart Association (114) to determined quartile cut-offs. Quartiles were as follows: <1, 1-2.9, 3-4.9, and ≥5mg/L. Given the attenuated risk after adjustment for confounding risk factors, CRP was assigned a multiplier of 1.0.

TNFα. TNFα is highly related to several MetS traits including obesity (71, 84, 171), TG (71, 166), low HDL-C (166), and IR (51, 116, 127, 140, 169). Recent evidence has shown TNFα to induce IR through several mechanisms including inhibition of IRS-1 (116, 127), activation of JNK (116) and activation of Iκκβ (169). Additionally, it has previously been suggested that multiple inflammatory markers should be measured to accurately reflect risk associated with inflammation (140). Due to the lack of established guidelines for TNFα, the present quartiles were formulated by dividing the data set into quartiles. For the current study, TNFα quartiles were defined as: <1, 1-1.9, 2-2.9, and ≥3pg/ml. While TNFα has been closely linked to IR, evidence linking TNFα to MetS is lacking. Therefore, TNFα was assigned a weighted multiplier of 1.0.

VO_2max. Substantial data has shown that high aerobic capacity offers protection against CVD (28, 96), T2D (158), and mortality (27, 28, 96, 107, 109, 144, 157). Numerous studies have determined aerobic capacity is inversely related to MetS (22, 24, 38, 78, 88, 92, 111). Furthermore, factor analysis studies have shown VO_2max weighs more heavily than current MetS criteria and may therefore contribute more to incident MetS (92). For the present study, quartile cut-offs were based loosely on sex-specific VO_2max norms for individuals aged 40-49 years (7). For men, the quartiles were: <30, 30-39.9, 40-49.9, and ≥50ml/kg/min. For women the quartiles were: <25, 25-34.9, 35-44.9, and ≥45ml/kg/min. These quartiles correspond roughly to the ≤10, 10-49, 50-89, and ≥90th percentile (7). Given the close association between VO_2max and CVD, T2D, and mortality, aerobic capacity was assigned a weighted multiplier of 2.0.

Statistics. Statistics for the present study were performed using R 2.7.0 statistical package for windows. Given the differences in data distribution and quartile cut-off

points between sexes, all analyses were performed individually for women, men, and combined data. In order to determine the relationships of individual MetS traits to probability of MetS, generalized additive models (GAM) were used. The model accounting for the most deviance was considered the best fit model. Deviance is defined as -2 times the logarithmic likelihood ratio of the reduced model compared to the full model. Deviance is a method for generalizing variation associated with a model and is not constrained to normally distributed data as is variance. Since dichotomous assessment of MetS violates the rule of normal distribution, deviance rather than variance was used in the present analysis. Additionally, Akaike's Information Criterion (AIC) was employed to compare the parsimoniousness between models. In order to determine the most influential contributor(s) to incident MetS, backward elimination and forward selection were employed. Backward elimination and forward selection calculations included only the 5 current MetS criteria. Backward elimination included all 5 components in the initial equation and eliminated the trait contributing the least deviance. This process was repeated with only the remaining traits included. The last trait included was considered the most significant contributor. Conversely, forward selection started with only the null deviance and added individual traits. The trait accounting for the greatest deviance was considered the most influential and was added to the equation first. This process was repeated including the remaining traits. The last trait added was considered the least significant contributor.

In order to validate the scoring systems, relationships between score and MetS presence and severity were calculated. This method is similar to that used by Wijndaele et al (132). These authors validated their scoring system against MetS presence and

number of traits. Relationships between scoring systems and MetS presence were calculated using a kernel smooth function with bandwidths of 15 and 20 for 5score and 10score, respectively. This method averages all data points within the bandwidth window to determine probability at a given data point. Increasing bandwidth minimizes noise associated with this technique and is therefore particularly useful when dealing with smaller sample sizes. Additionally, linear regression was employed to calculate the relationship between scoring systems and number of MetS traits present (according to ATP III definition), a surrogate marker of MetS severity.

Table 1. Comparison of MetS criteria between ATP III and proposed MetS score system.

	ATP III		MetS Score			
Trait	Men	Women	Men	Women	Points	Multiplier
WC (cm)	≥102cm	≥88cm	<95	<80	0	
			95-101	80-87	1	2.0
			102-115	88-102	3	
			>115	>102	5	
FG (mg/dl)	≥100	≥100	<85	<85	0	
			85-99	85-99	1	2.0
			100-114	100-114	3	
			≥115	≥115	5	
TG (mg/dl)	≥150	≥150	<100	<100	0	
			100-149	100-149	1	1.0
			150-199	150-199	3	
			>200	>200	5	
HDL-C (mg/dl)	<40	<50	≥60	≥70	0	
			50-59	60-69	1	1.5
			40-49	50-59	3	
			<40	<50	5	
	Systolic	Diastolic	Systolic	Diastolic		
BP (mmHg)	≥130	≥85	<120	<80	0	
			120-129	80-84	1	1.0
			130-139	85-89	3	
			≥140	≥90	5	
BMI (kg/m2)	N/A	N/A	<25	<25	0	
			25-29.9	25-29.9	1	2.0
			30-34.9	30-34.9	3	
			35-39.9	35-39.9	5	
CRP (mg/L)	N/A	N/A	<1	<1	0	
			1-2.9	1-2.9	1	1.0
			3-4.9	3-4.9	3	
			5-9.9	5-9.9	5	
TNFα (pg/ml)	N/A	N/A	<1	<1	0	
			1-1.99	1-1.99	1	1.0
			2.0-2.99	2.0-2.99	3	
			≥3	≥3	5	
% Fat	N/A	N/A	<15	<25	0	
			15-22	25-32	1	1.0
			23-30	32-40	3	
			>30	>40	5	
VO_2max (ml/kg/min)	N/A	N/A	>50	>45	0	
			40-49.9	35-44.9	1	2.0
			30-39.9	25-34.9	3	
			<30	<25	5	

WC=waist circumference, TG=triglycerides, FG=fasting glucose, HDL-C=high density lipoprotein cholesterol, BP=blood pressure, BMI=body mass index, CRP=C-reactive protein, TNFα=tumor necrosis factor-α, VO_2max=maximal aerobic capacity.

RESULTS

Subject Characteristics. Subject characteristics for all 208 subjects can be found in Table 2. Subjects were 18-58 years of age (mean 36±1 years) and displayed 2 MetS traits (range 0-5). Mean 5score was found to be 18.8±0.4 (range 5-35.5). Mean 10score was found to be 42.6±1.0 (range 20.5-59.5). The most common MetS trait was elevated WC (n=187) followed by low HDL-C (n=82), elevated FG (n=78), elevated TG (n=72), and high blood pressure (n=44). Table 3 shows subject characteristics for the subset of subjects with all 10 traits measured.

Table 2. Subject characteristics.

Trait	Male	Female	Combined
Number	86	122	208
Age	37±1	37±1	37±1
WC (cm)	109.3±1.0	104.8±1.0	106.7±0.7
TG (mg/dl)	168.3±11.0	132.0±4.6	147.0±5.4
HDL-C (mg/dl)	42.9±1.0	53.9±1.1	49.3±0.9
FG (mg/dl)	102.6±1.6	95.0±1.2	98.1±1.0
SBP (mmHG)	125±1	117±1	121±1
DBP (mmHG)	81±1	75±1	78±1
5score	20.0±0.7	18.0±0.5	18.8±0.4

Abbreviations same as previously. SBP=systolic blood pressure, DBP=diastolic blood pressure

Table 3. Subject characteristics for subjects with 10 traits measured.

Trait	Male	Female	Combined
Number	31	47	78
Age	40±2	39±1	39±1
WC (cm)	111.9±1.6	108.7±1.5	110.0±1.1
TG (mg/dl)	199.2±22.7	137.9±7.3	162.3±10.4
HDL-C (mg/dl)	40.9±1.9	50.2±1.6	46.5±1.3
FG (mg/dl)	101.3±2.3	97.6±1.9	99.1±1.4
SBP (mmHg)	125±2	119±2	122±1
DBP (mmHg)	82±1	77±1	79±1
BMI (kg/m2)	32.6±0.6	33.4±0.6	33.1±0.5
CRP (mg/L)	1.8±0.4	4.0±1.2	3.1±0.8
TNFα (pg/ml)	2.64±0.42	2.73±0.37	2.66±0.28
% Fat	28±1	39±1	35±1
VO_2max (ml/kg/min)	32.2±0.6	24.3±0.5	27.3±0.6
10score	41.9±1.5	43.0±1.3	42.6±1.0

Abbreviations same as previously.

5score as a Predictor of MetS. Figure 1 shows the relationship between 5score and MetS presence. Due to the dichotomous nature of MetS, all data points are considered either 0 (MetS not present) or 1 (MetS present). This figure indicates a sigmoidal relationship between 5score and MetS. According to this figure, 5score values of <10 are associated with low likelihood of MetS. Values between 10 and 30 are associated with a sharp, nearly linear increase in probability of MetS. 5score values >30 demonstrate a slower increasing probability of MetS. Graphs calculated individually for men and women revealed similar relationships although the sigmoidal nature of the relationship was slightly more apparent in women (data not shown). Therefore, the data were combined to determine the relationship between 5score and probability of MetS. As shown in Figure 1, 5score values of 10, 20, and 30 roughly corresponded to 15, 50, and 85% probability of MetS, respectively.

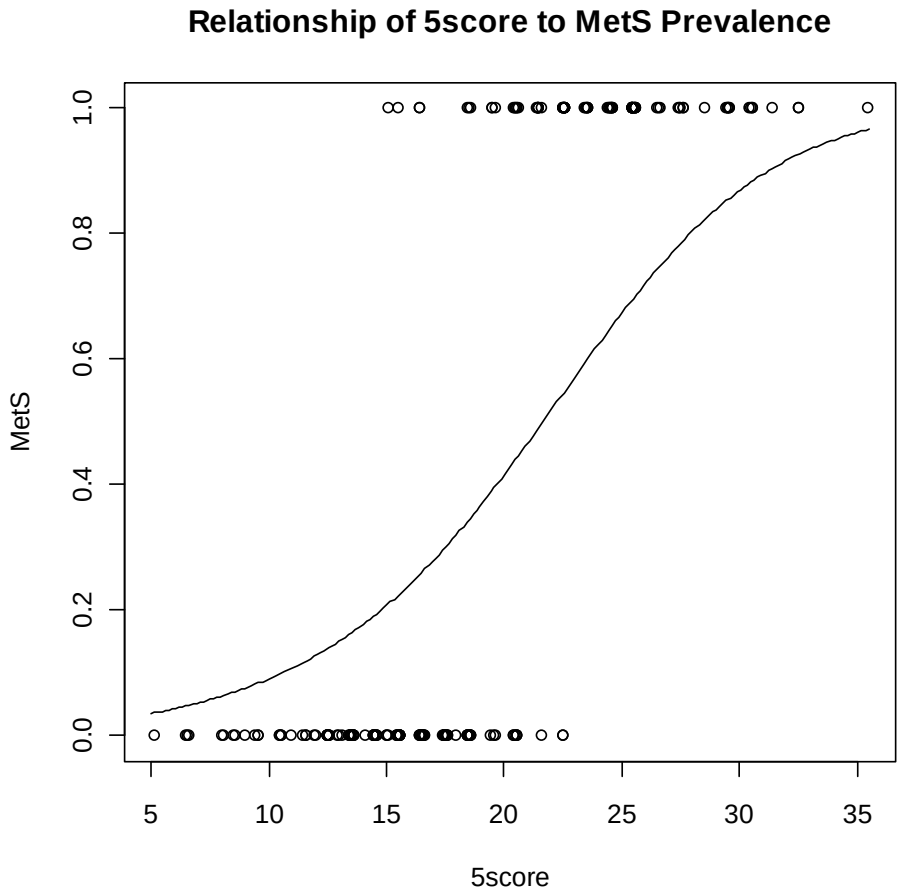

Figure 1. 5score as a predictor of MetS presence. A sigmoidal relationship exists between 5score and MetS presence. MetS probability is low at low 5score values, but increases sharply at 5score values ~10 and plateaus at values ~30. x-axis indicates 5score values observed in the present study. y-axis indicates MetS probability (0=no, 1=yes). Open circles indicate observed data points from the present study (n=208). Relationship was calculated by averaging all data points with a bandwidth window of 15 (±7.5).

10score as a Predictor of MetS. Figure 2 shows the relationship between 10score and MetS presence. This relationship appears much more linear than that of 5score. Individual analysis of men and women revealed 10score to be a stronger predictor of MetS in men than women. However, the relatively small sample size of men (n=31) and women (n=47) likely influenced this discrepancy. Therefore, data was combined to eliminate the effect of small sample size. 10score values of 30, 40, and 50 roughly corresponded to 30, 50, and 70% probability of MetS, respectively.

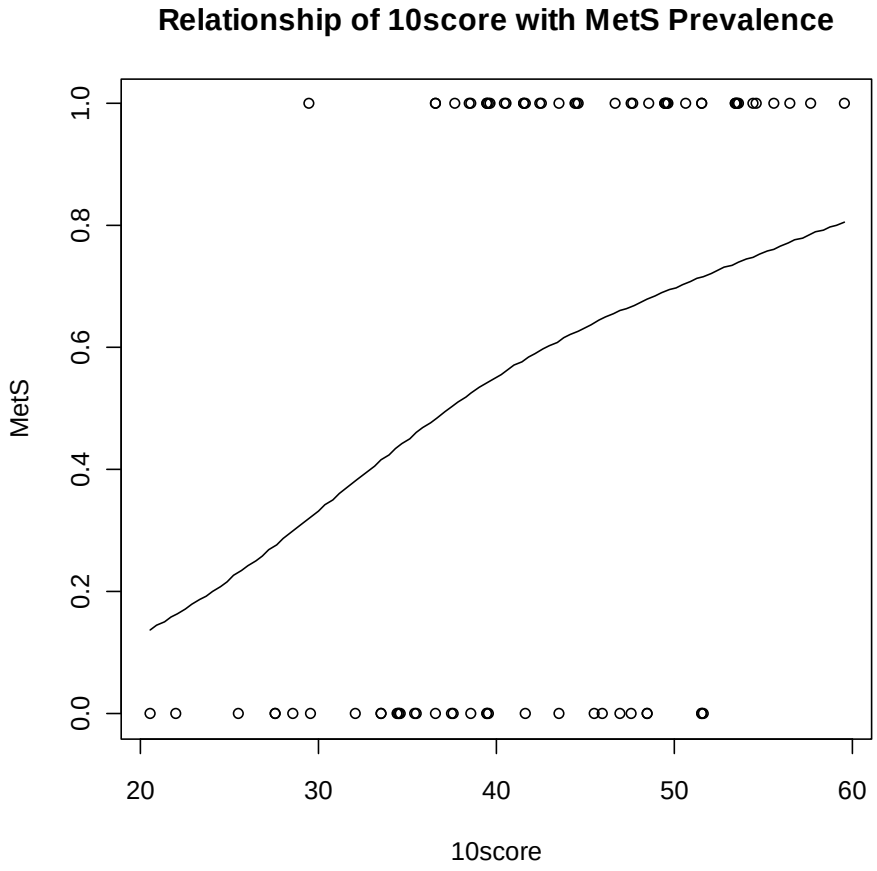

Figure 2. 10score as a predictor of MetS presence. A nearly linear relationship exists between 10score and MetS presence. x-axis indicates 10score values observed in the present study. y-axis indicates MetS probability (0=no, 1=yes). Open circles indicate observed data points from the present study (n=78). Relationship was calculated by averaging all data points with a bandwidth window of 20 (±10).

Relationship of 5score to MetS Severity. Number of MetS traits has been shown to be an indicator of MetS severity (137). Therefore, in order to assess the relationship between scoring systems and MetS severity, number of MetS traits was used as an indicator of MetS severity. As shown in Figure 3, a direct relationship exists between 5score and number of MetS traits present. Linear regression analysis revealed this equation to be: $y=8.6543+4.4703x$ ($r^2=0.7394$, $p<0.0001$). For combined data, 0, 1, 2, 3, 4, and 5 traits corresponded to 5score values of 8.65, 13.12, 17.59, 22.07, 26.54, and 31.01, respectively. Separate analysis of men and women revealed similar relationships between sexes. The calculated regression line was: $y=8.7395+4.3509x$ ($r^2=.7028$,

p<0.0001) for men and y=8.4495+4.6455x (r^2=0.7603, p<0.0001) for women (data not shown).

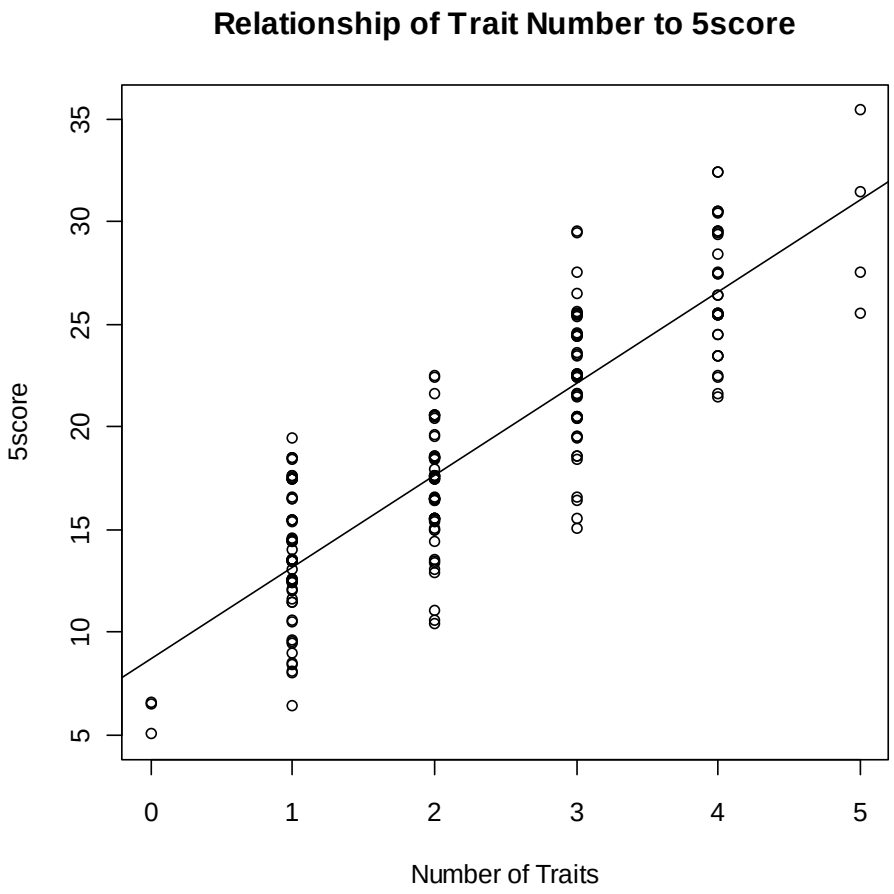

Figure 3. Relationship of MetS severity to 5score. 5score is directly related to severity of MetS. Solid lines indicate the linear relationship between 5score and MetS severity. Open circles indicate observed cases (n=208). y=8.6543+4.4703x (r^2=0.7394, p<0.0001). Similar findings were observed for both men and women.

Relationship of 10score to MetS Severity. As shown in Figure 4, 10score was found to be directly related to number of MetS traits present. Linear regression analysis revealed this equation to be: y=30.4196+4.4426x (r^2=0.234, p<0.0001). The slope of this equation was slightly less than that of 5score. Additionally, r^2 of this relationship was significantly less than that of 5 score (0.234 and 0.7394, respectively). This finding suggests 5score is a better predictor of MetS severity than 10score. All individuals

analyzed for 10score had at least 1 MetS trait. For combined data, 1, 2, 3, 4, and 5 MetS traits corresponded to 10score values of 34.86, 39.30, 43.75, 48.19, and 52.63, respectively. Separate analysis of men and women revealed similar results between sexes. The calculated regression line was: $y=29.979+4.073x$ ($r^2=0.1929$, $p=0.0135$) for men and $y=29.816+5.063x$ ($r^2=0.2938$, $p<0.0001$) for women (data not shown). Given the relatively small sample sizes of men and women, data was pooled to analyze the relationship between 10score and MetS severity.

Figure 4. Relationship of MetS severity to 10score. 10score is directly related to severity of MetS. Solid lines indicate the linear relationship between 10score and MetS severity. Open circles indicate observed cases (n=78). $y=30.4196+4.4426x$ ($r^2=0.234$, $p<0.0001$). Similar findings were observed for both men and women.

Individual Traits and MetS Probability. Relationships between individual MetS traits and probability of MetS can be found in Figures 5 and 6 for women and men, respectively. Lines portraying the relationship between individual traits and MetS probability were calculated using a kernel smooth function with bandwidths of 20, 30, 20, 75, 30, and 30 for WC, FG, HDL-C, TG, SBP, and DBP, respectively. These figures should be interpreted with caution due to biased end effects of this method.

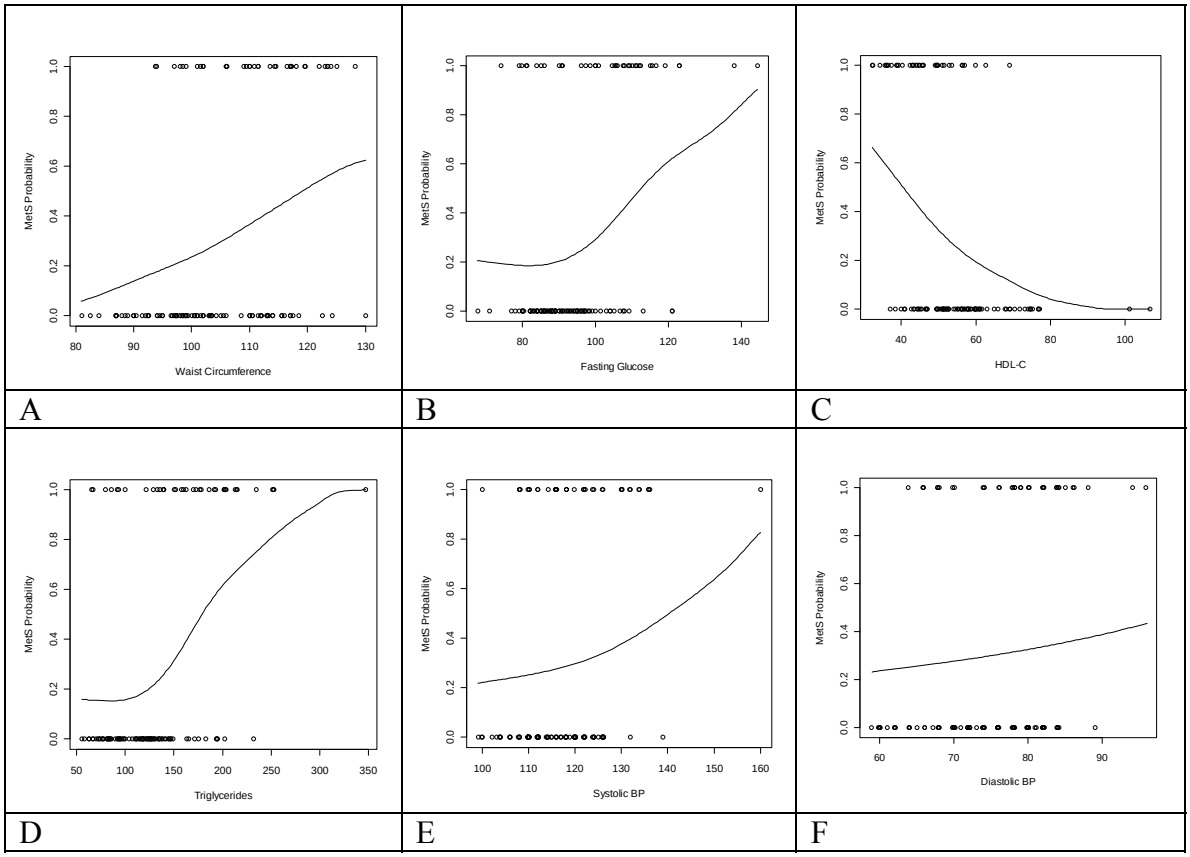

Figure 5. Relationship of individual traits to MetS probability in women. Solid lines indicate likelihood of MetS. Open circles indicate observed cases. X-axis shows observed values for each trait and y-axis indicates probability of MetS. Open circles indicate observed data points. A=WC, bandwidth 20, B=FG, bandwidth 30, C=HDL-C, bandwidth 20, D=TG, bandwidth 75, E=SBP, bandwidth 30, F=DBP, bandwidth 30.

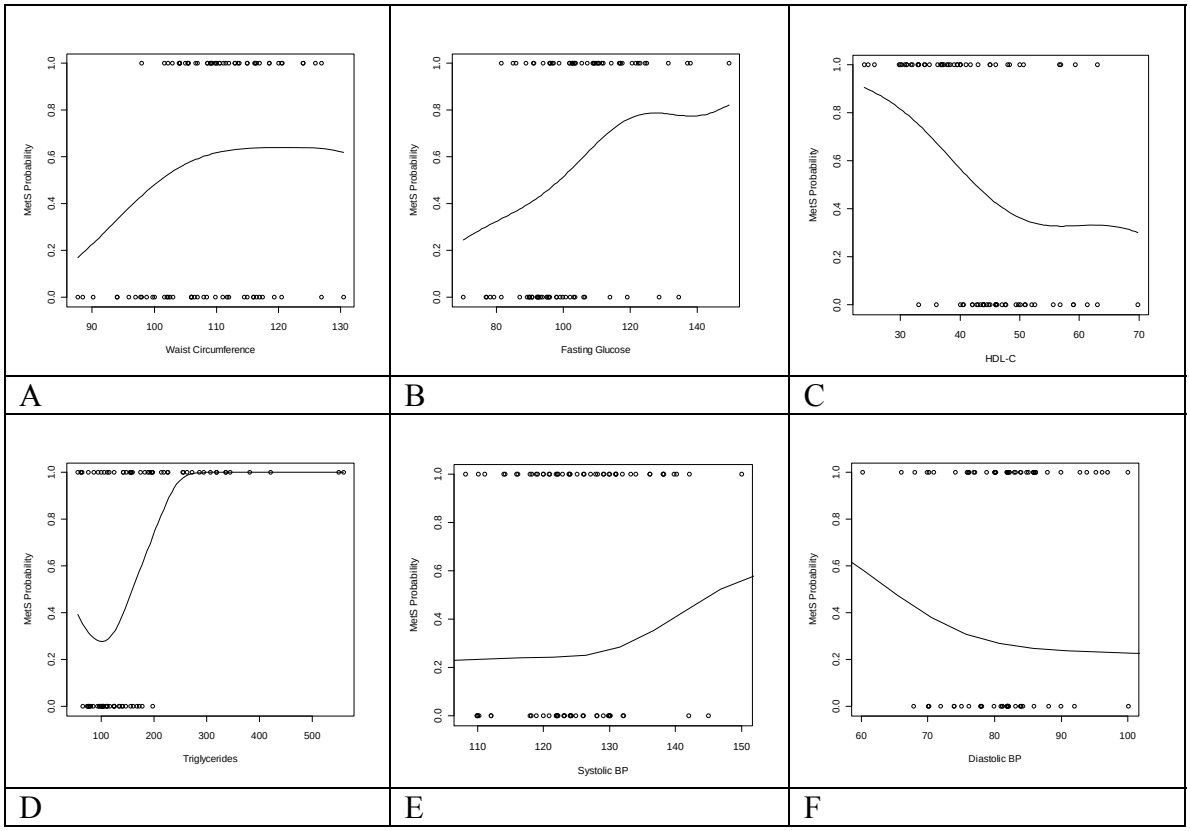

Figure 6. Relationship of individual traits to MetS probability in men. Solid lines indicate likelihood of MetS. Open circles indicate observed cases. X-axis shows observed values for each trait and y-axis indicates probability of MetS. Open circles indicate observed data points. A=WC, bandwidth 20, B=FG, bandwidth 30, C=HDL-C, bandwidth 20, D=TG, bandwidth 75, E=SBP, bandwidth 30, F=DBP, bandwidth 30.

As shown in these figures, MetS traits contribute very differently to the probability of developing MetS between men and women. The differences between men and women were most prominent when examining WC, FG, and DBP. In women, WC is linearly related to MetS probability with risk increasing from approximately 0.05 at WC 80cm to approximately 0.6 at WC 130cm. In men, MetS probability increases linearly from approximately 0.2 at WC 90 to approximately 0.6 at WC 110cm. Beyond this point, WC contributes little to MetS probability. FG is exponentially related to MetS probability in women, with approximately 0.2 probability at FG 70-90mg/dl. Beyond this point, MetS probability increases dramatically reaching approximately 0.9 at FG 140. In men, however, FG appears to be hyperbolically related to MetS probability. Risk increases sharply from approximately 0.2 at FG 70mg/dl to approximately 0.8 at FG 120mg/dl. Beyond this point, FG appears to contribute little to the probability of MetS. DBP appears to be only weakly related to MetS in women. Risk increases from approximately 0.2 at DBP 60mmHg to approximately 0.4 at DBP 100. However, in men, there appears to be an inverse relationship between DBP and MetS probability. However, this finding is likely due to an end effect of the data. A single subject was found to have MetS with DBP 60mmHg but positive for MetS. This case likely influenced the strong inverse relationship between DBP and MetS probability observed in men. Based on these studies, in the present study, SBP appears more strongly related to MetS probability than DBP. In women, SBP 100-120mmHg was associated with approximately 0.2 probability of MetS. Beyond this point, MetS probability increased dramatically to a value of approximately 0.8 at SBP 160mmHg. In men, blood pressure 100-130mmHg is associated with MetS probability of approximately 0.2. However, this

probability increases to approximately 0.6 at SBP 160mmHg. In both men and women, the sharp increase in MetS probability appears to be attributable to an end effect of the data. Therefore, it appears that BP is not as significant a risk factor as other MetS characteristics. TG also appears to be exponentially related to MetS probability. In both men and women, MetS probability appears to increase dramatically at TG>100mg/dl. In contrast to other MetS traits, HDL-C appears to be inversely exponentially related to MetS probability. In women, HDL-C 40mg/dl was associated with approximately 0.5 probability of MetS. This probability is reduced to approximately 0.1 at HDL-C 70mg/dl. In men, HDL-C 30mg/dl was associated with approximately 0.8 MetS probability. This was decreased to approximately 0.3 at HDL-C 50mg/dl. Further increases in HDL-C did not appear to reduce MetS probability.

As indicated in Figures 5 and 6, MetS traits are not linearly related to incident MetS. Therefore, we were unable to use linear regression to determine the relationships between individual traits and MetS. Due to this limitation, we chose to use a logistic generalized additive model (GAM) to model relationships between individual traits and MetS. This model attempts to account for the relationship between individual traits and MetS. Additionally, due the different relationships between individual MetS traits and MetS probability between sexes, these relationships were examined in sex-specific analysis. Furthermore, different MetS criteria for WC and HDL-C between sexes could bias the results of this analysis.

Regression analysis revealed GAM to be the best model for prediction of MetS. Of all models tested, GAM1 proved to be the best fit. This model included all 5 MetS traits with 3 degrees of freedom each. This model explained 87, 96, and 70% of the null

deviance in women, men, and combined data, respectively. Additionally, this model provided the most parsimonious explanation of the deviance. AIC values of 51.9, 36.8, and 115.1 were observed for women, men, and combined, respectively. Results of regression models calculated for women and men in the present analysis can be found in Table 4. A graphical representation of GAM1 can be found in Figures 7a, b, and c for women, men, and combined, respectively. In these graphs, a y-axis value of 0 corresponds to a 50% probability of MetS according to the ATP III definition.

In order to determine the most influential contributor(s) to MetS, backward elimination and forward selection were employed. Application of backward elimination and forward selection to the GAM1 model resulted in similar results for women, men, and combined data. In women, the most influential factor was determined to be HDL-C followed by FG, TG, SBP, and WC.

Table 4. Comparison of regression models for predicting MetS.

	Model	Deviance	AIC
Women			
	Null	151.3	52.6
	GAM1 [wc(3df)+fg(3df)+hdl(3df)+tg(3df)+sbp(3df)]	19.9	51.9
	GAM2 [wc(3df)+fg(3df)+hdl+tg+sbp]	33.6	53.6
	GAM3 [wc(2df)+fg(2df)+hdl+tg+sbp]	38.6	54.5
	GLM (wc+fg+hdl+tg+sbp)	42.7	54.7
Men			
	Null	118.5	109.4
	GAM1 [wc(3df)+fg(3df)+hdl(3df)+tg(3df)+sbp(3df)]	4.8	36.8
	GAM2 [wc(3df)+fg(3df)+hdl+tg+sbp]	29.9	49.9
	GAM3 [wc(2df)+fg(2df)+hdl+tg+sbp]	37.7	53.7
	GLM (wc+fg+hdl-c+tg+sbp)	54.7	66.7

GAM=generalized additive model, GLM=generalized linear model, AIC= Akaike's information criterion. Numbers in parentheses represent number of degrees of freedom for each variable. Model with the least deviance was considered the best fit. Model with the lowest AIC were considered the most parsimonious.

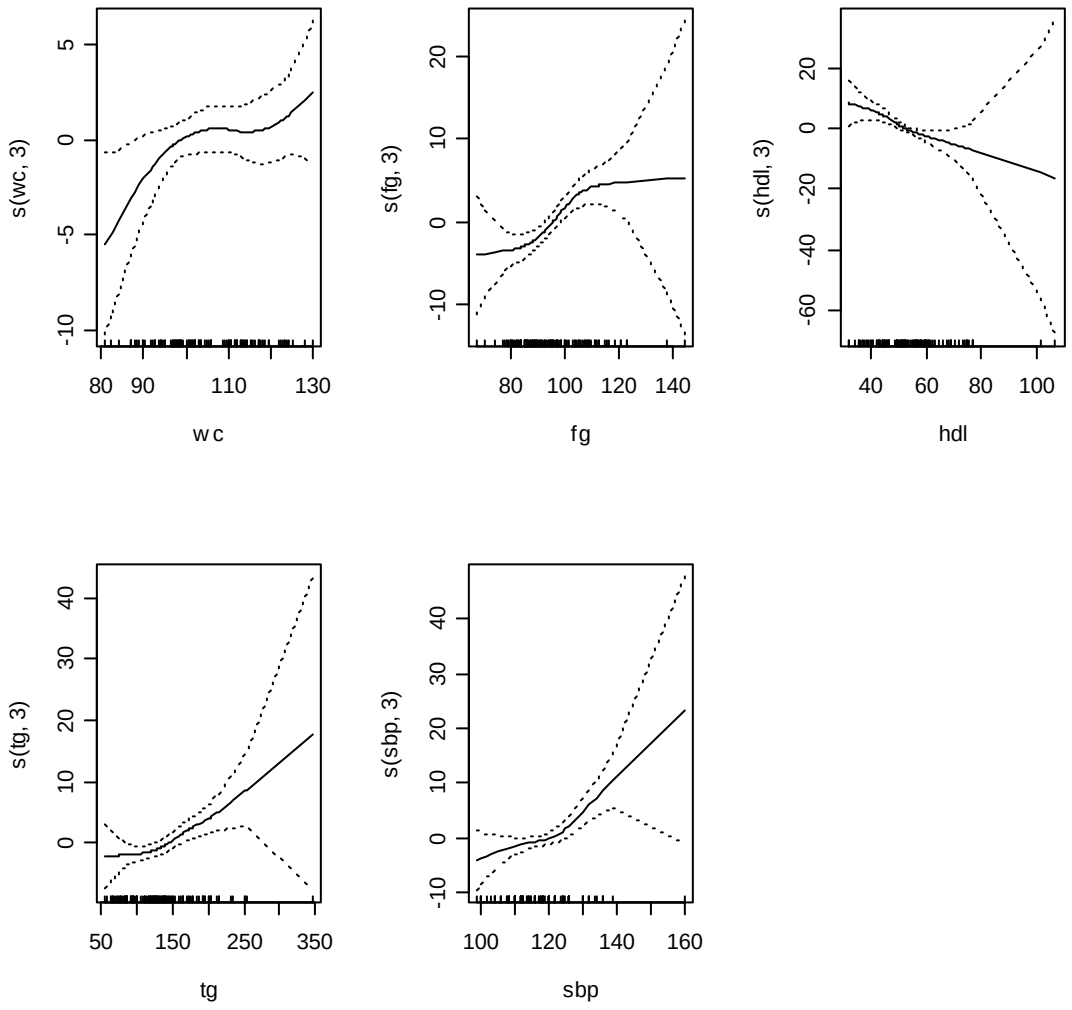

Figure 7a. Logistic generalized additive model of relationships of individual traits to MetS probability in women. Graphical representation of GAM1. Solid lines indicate relationship between traits and MetS probabliltiy. Dotted lines indicate SEM. X-axis indicates value for individual traits. Tick marks indicate observed cases. Y-axis indicates log odds of ATP III defined MetS. By definition, y-value of 0 correponds to a 50% probability of MetS.

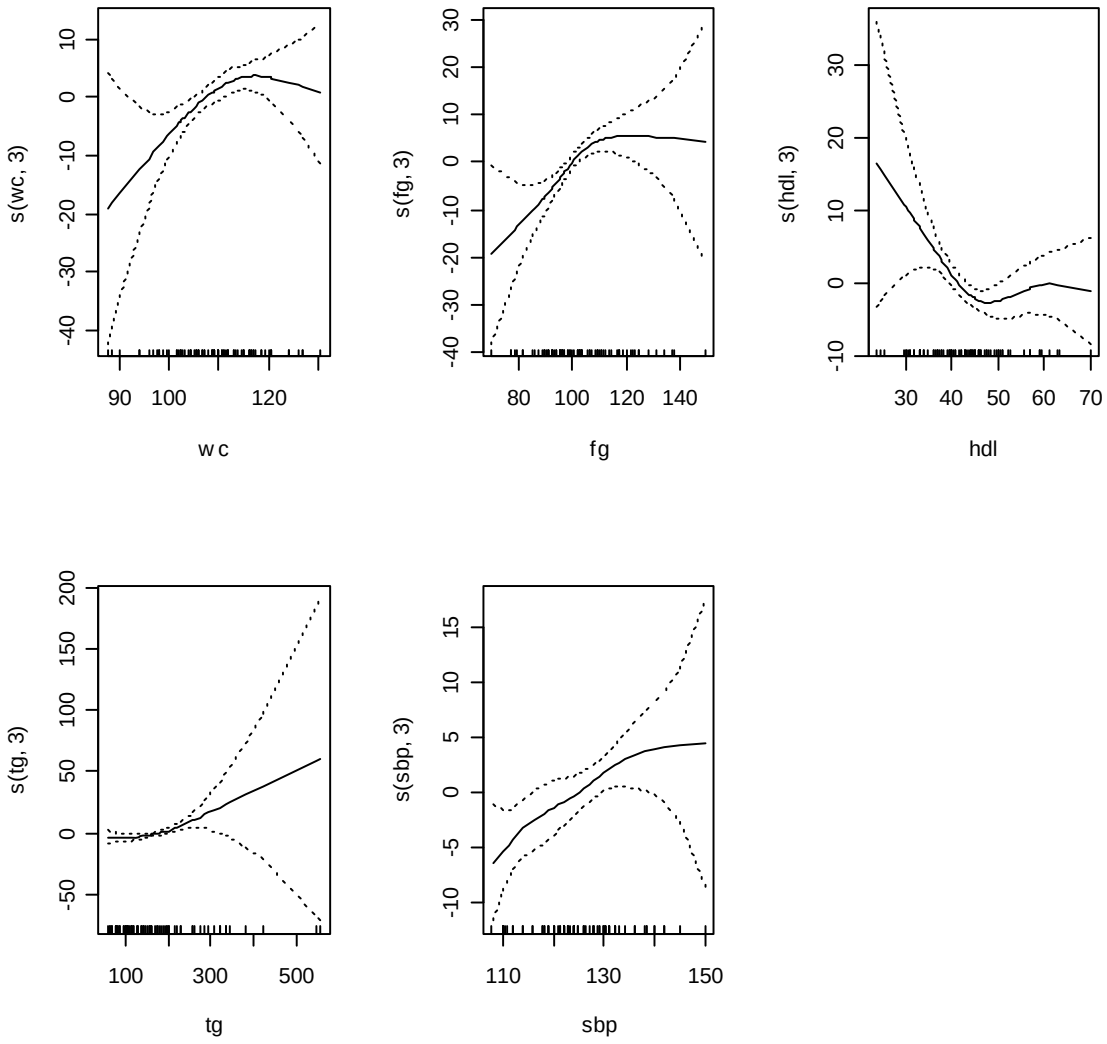

Figure 7b. Logistic generalized additive model of relationship of traits to MetS probability in men. Graphical representation of GAM1. Solid lines indicate relationship between traits and MetS probabliltiy. Dotted lines indicate SEM. X-axis indicates value for individual traits. Tick marks indicate observed cases. Y-axis indicates log odds of ATP III defined MetS. By definition, y-value of 0 correponds to a 50% probability of MetS.

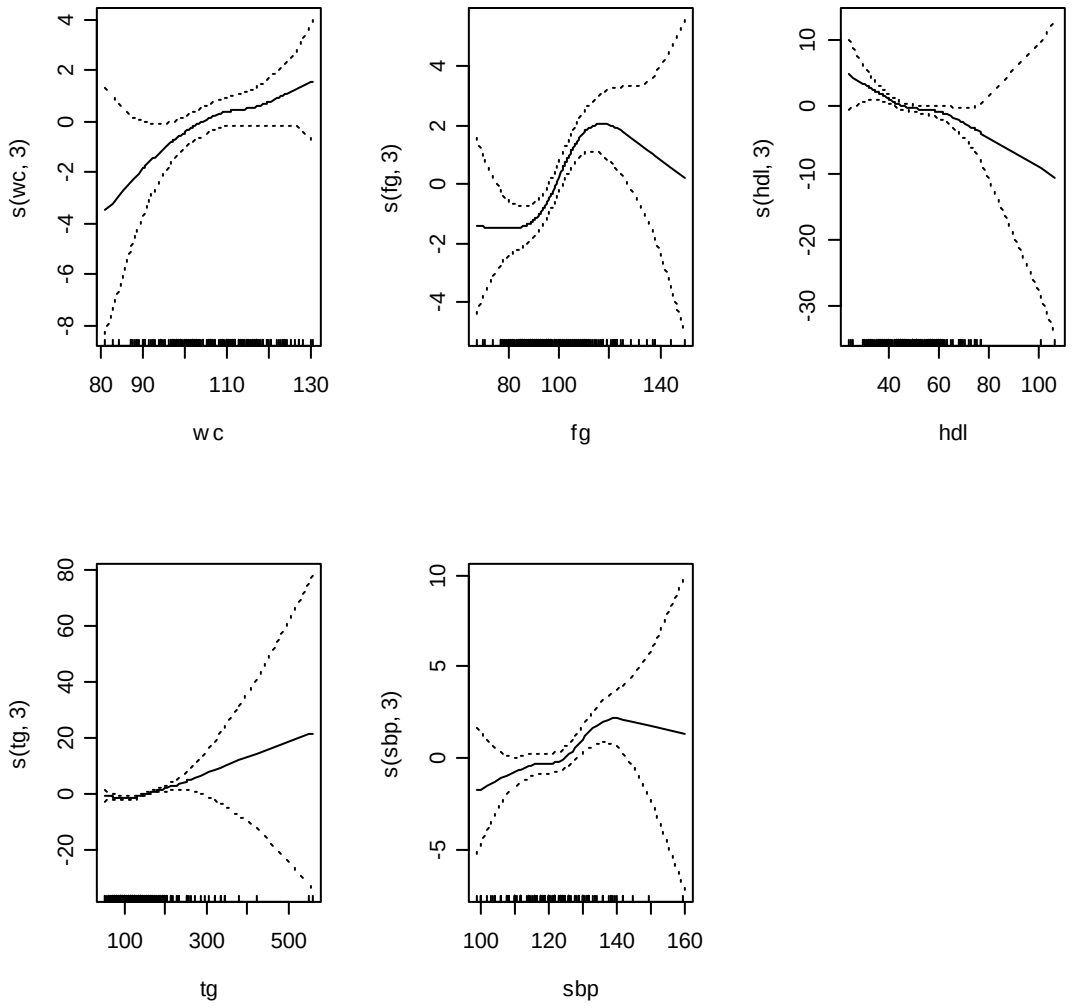

Figure 7c. Logistic generalized additive model of relationship of traits to MetS probability in combined genders. Graphical representation of GAM1. Solid lines indicate relationship between traits and MetS probabliltiy. Dotted lines indicate SEM. X-axis indicates value for individual traits. Tick marks indicate observed cases. Y-axis indicates log odds of ATP III defined MetS. By definition, y-value of 0 correponds to a 50% probability of MetS

Figure 8 shows results from forward selection in women. As shown in this figure, HDL-C accounted for 21% of the null deviance. HDL-C explained significantly more deviance than WC or SBP (both $p<0.0001$), but not TG or FG (0.0833 and 1.0000, respectively). HDL-C explained a greater absolute difference in deviance than TG and was therefore considered the most influential factor. Therefore, HDL-C was retained in the model and the forward selection process was repeated using the remaining variables. This process revealed FG to be the next most influential trait. HDL-C+FG accounted for 45% of the null deviance. This was significantly higher than HDL-C+WC or HDL-C+SBP ($p<0.0001$ and $p=0.0003$, respectively), but not HDL-C+TG ($p=0.0886$). HDL-C+FG+TG accounted for 65% of the null deviance. This was significantly higher than HDL-C+FG+WC and HDL-C+FG+SBP ($p<0.0001$ and $=0.0091$, respectively). HDL-C+FG+TG+SBP accounted for 82% of the null deviance and was significantly higher than HDL-C+FG+TG+WC ($p<0.0001$). Inclusion of all MetS traits accounted for 86% of the null deviance. Therefore, according to forward selection, MetS traits contribute to incident MetS in the following order: HDL-C>FG>TG>SBP>WC in women.

Figure 9 shows the results of forward selection in men. For men, the most influential factor was TG followed by FG, WC, SBP, and HDL-C. TG was shown to be the most influential trait, accounting for 34% of the null deviance. This was significantly higher than any other MetS trait ($p<0.0001$ for all except HDL-C, $p=0.0239$). TG was therefore retained in the model and the forward selection process repeated with the remaining variables. This process revealed FG to be the next most influential trait. TG+FG accounted for 56% of the null deviance. This was significantly higher than TG+WC, TG+SBP, and TG+HDL-C ($p<0.0001$, <0.0001, and $=0.0003$, respectively).

TG+FG+WC accounted for70% of the null deviance. This was significantly higher than TG+FG+HDL-C and TG+FG+SBP (p=0.0285 and 0.0044, respectively). Both TG+FG+WC+SBP and TG+FG+WC+HDL-C accounted for 80% of the null deviance. However, the difference between these combinations was not significant (p=0.5834). TG+FG+WC+SBP accounted for a greater absolute difference in deviance and therefore SBP was considered a more influential contributor than HDL-C. Inclusion of all MetS traits accounted for 96% of the null deviance. According to these results, MetS traits contribute to incident MetS in the following order: TG>FG>WC>SBP>HDL-C in men.

Figure 10 shows the results of forward selection for combined data. Analysis of combined data found the most influential factor was TG followed by FG, HDL-C, SBP, and WC. TG was found to be the most influential factor, accounting for 27% of the null deviance. This was significantly higher than any other MetS trait (p<0.0001). TG was retained in the model and the forward selection process was repeated including the remaining variables. This process revealed FG to be the second most influential trait. TG+FG accounted for 45% of the null deviance and was significantly higher than TG+WC, TG+HDL-C, and TG+SBP (p<0.0001, =0.0359, and <0.0001, respectively). TG+FG+HDL-C accounted for 60% of the null deviance. This was significantly higher than TG+FG+WC and TG+FG+SBP (p=0.0002 and <0.0001, respectively). TG+FG+HDL-C+SBP accounted for 67% of the null deviance and was significantly different than TG+FG+HDL-C+WC (p=0.0027). Inclusion of all MetS traits accounted for 70% of the null deviance. In combined data, MetS traits contribute to incident MetS in the following order: TG>FG>HDL-C>SBP>WC.

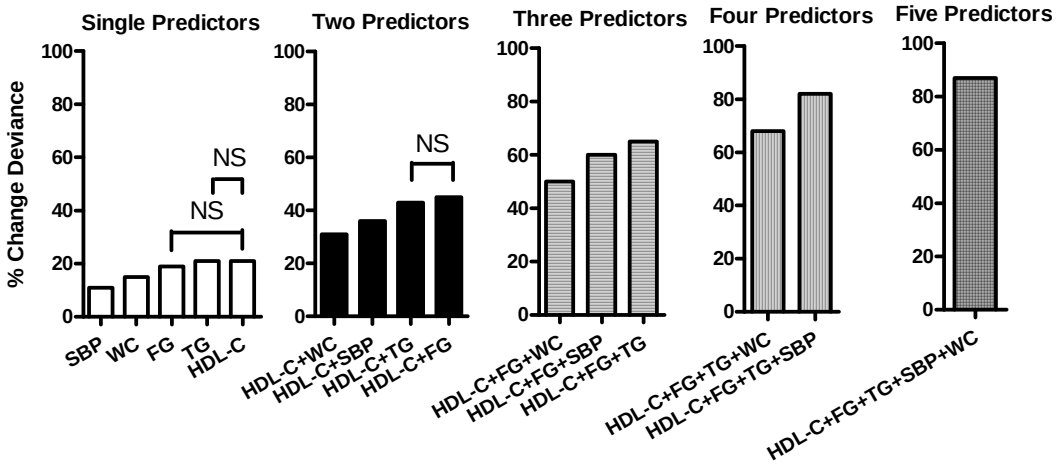

Figure 8. MetS traits as predictor of MetS presence according to forward selection in women. Traits were added individually to the logistic generalized additive model. The trait explaining the greatest absolute deviance was considered the most significant and retained in the equation. This process was repeated with the remaining traits until all 5 were included in the model. The final combination explains the greatest deviance and represents the order of contribution to MetS. Each trait or combination is significantly ($p<0.05$) greater than previous except those indicated by NS. NS denotes nonsignificant difference.

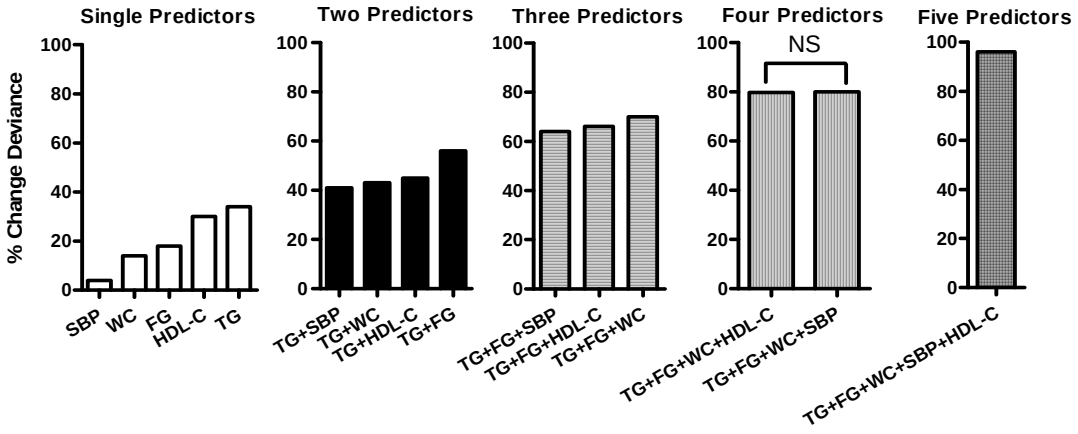

Figure 9. MetS traits as predictor of MetS presence according to forward selection in men. Traits were added individually to the logistic generalized additive model. The trait explaining the greatest absolute deviance was considered the most significant and retained in the equation. This process was repeated with the remaining traits until all 5 were included in the model. The final combination explains the greatest deviance and represents the order of contribution to MetS. Each trait or combination is significantly ($p<0.05$) greater than previous except those indicated by NS. NS denotes nonsignificant difference.

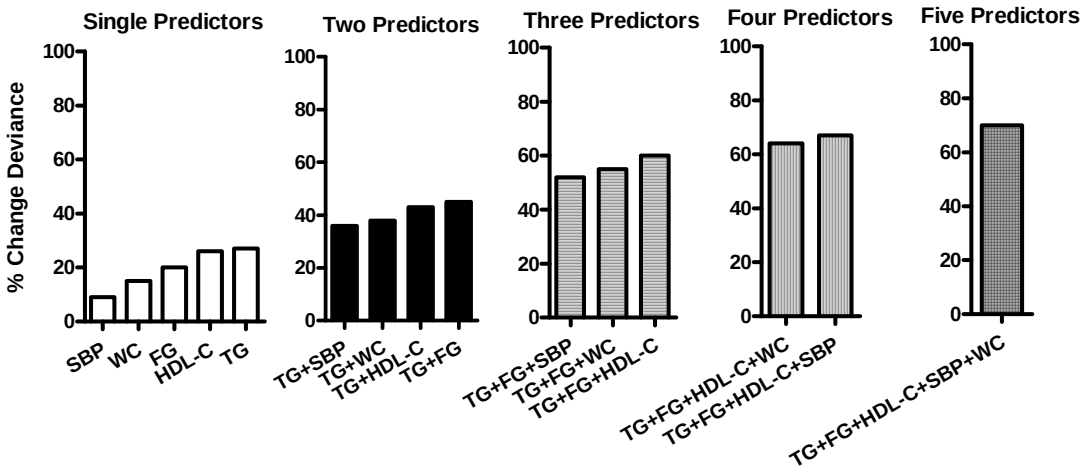

Figure 10. MetS traits as predictors of MetS presence according to forward selection in combined. Traits were added individually to the logistic generalized additive model. The trait explaining the greatest absolute deviance was considered the most significant and retained in the equation. This process was repeated with the remaining traits until all 5 were included in the model. The final combination explains the greatest deviance and represents the order of contribution to MetS. Each trait or combination is significantly ($p<0.05$) greater than previous except those indicated by NS. NS denotes nonsignificant difference.

DISCUSSION

Effectiveness of Scoring Systems. Results from the present study indicate that the proposed scoring systems (5score and 10score) are effective predictors of MetS presence and a means to assess severity (number of traits) of MetS. As shown in Figure 1, the sigmoidal shape of the relationship between 5score and MetS presence indicates that it may serve as a more sensitive tool than 10score. It is likely that risk of MetS is not appreciably altered with small changes in MetS score at low and high MetS risk. Individuals with moderately impaired metabolic processes are likely to be highly affected by even minor changes (positive or negative) in metabolic profile. This relationship is reflected by the sigmoidal shape of the relationship between 5score and MetS probability. The discrepancy between scoring systems may be due to redundant measurements included in the formulation of 10score. Multiple measures of obesity (WC, BMI, and percent fat) and inflammation (CRP and TNFα) may result in a bias toward these measurements and limit the utility of this tool. However, several authors have shown that addition of non-traditional risk factors such as CRP enhance the predictive ability of MetS (123-125, 145). Additionally, aerobic capacity has been shown to be highly related to MetS (24, 38, 83, 88, 92, 93, 161) and may in fact be a more significant risk factor than other MetS criteria such as TG, FG, HDL-C, and BP (92). Therefore, it could be hypothesized that it may be beneficial to include additional MetS criteria. However, assessment of multiple indicators of the same risk factor may limit the predictive ability of this tool. Previous MetS score systems developed by this lab (149) have shown significant correlations between MetS score and WC (r=0.84), % fat (r=0.38), TG

(r=0.38). FG (r=0.57), CRP (r=0.51), BP (r=0.35) and VO2max (r=-0.71). These results suggest that additional MetS criteria may enhance the predictive ability of MetS.

Additionally, linear regression revealed 5score and 10score predict MetS severity in a linear manner. 0, 1, 2, 3, 4, and 5 MetS traits corresponded to 5score values of 8.65, 13.12, 17.59, 22.07, 26.54, and 31.01, respectively and 10score values of 30.42, 34.86, 39.30, 43.75, 48.19, and 52.63, respectively. Solymoss et al (137) determined that number of MetS traits is a significant predictor of CAD severity, cerebrovascular disease, and T2D. Therefore, the proposed scoring systems may prove to be significant predictors of various health conditions or even mortality. Current MetS definitions do not account for increased risk of morbidity and mortality until a threshold value is reached for 3 of 5 risk factors. Several authors have noted increased risk of CVD (33, 100, 137, 164) and T2D (87, 137, 164) with only 1-2 MetS traits present. The proposed scoring systems in the present study reflects this increased risk associated with mild metabolic perturbations. Comparing the effectiveness of scoring systems revealed 5score (r^2=0.74) explained a greater amount of the variance than 10score (r^2=0.23). This suggests that 5score may be a more significant predictor of risk than 10score. This again may be due to redundant markers of obesity and inflammation included in 10score.

The current data set did not include sufficient follow-up to determine whether 5score and 10score are significant predictors of CVD, T2D, and mortality. Application of the proposed scoring systems to large-scale epidemiological data with significant follow-up is necessary to confirm the predictability of the proposed scoring systems. Additionally, the current data does not allow for comparison of the proposed scoring system to current MetS definitions with respect to morbidity and mortality prediction.

Future research should be conducted to determine whether the proposed scoring system is superior to ATP III MetS in predicting CVD, T2D, and mortality.

Without morbidity and mortality, we chose to validate the scoring system by examining its relationship to ATP III defined MetS and number of traits present. This technique is similar to those used by Wijndaele et al (132). These authors used MetS presence and number of traits to validate a MetS z-score. According to these authors, z-score accounts for 61% of the variance associated with incident MetS. In the present study, 5score accounted for nearly 75% of the variance associated with increasing number of traits. This finding suggests that 5score may serve as a better predictor of risk than continuous MetS z-score. This is likely due to the inclusion of weighted multipliers in 5score. Serious methodological inconsistencies prevent direct comparison of these studies. Most notably, Wijndaele et al (162) used the IDF definition of MetS whereas the present study used ATP III guidelines. The present study may be the first attempt to develop and test a scoring system for the severity of MetS. Future projects comparing 5score and 10score to z-score are necessary to determine which system more accurately reflects risk associated with MetS.

As shown in Figure 1, the relationship between 5score and MetS probability revealed a significant sigmoidal shape. Changes in the slope of the graph occurred at 5score values of ~10 and ~30. These values correspond to MetS probability of approximately 15 and 85%, respectively. Additionally, MetS probability of 50% occurred at 5score value of ~20. 0, 1, 2, 3, 4, and 5 MetS traits corresponded to 5score values of 8.65, 13.12, 17.59, 22.07, 26.54, and 31.01, respectively. Considering these results, the following quartiles are recommended for 5score with respect to MetS

incidence and severity: <10=low risk, 10-19=moderate risk, 20-29=high risk, and ≥30=very high risk. Figure 2 shows a nearly linear relationship between 10score and MetS probability. 10score values of 30, 40, and 50 correspond to MetS probability of ~30, ~50, and ~70%, respectively. Additionally, 0, 1, 2, 3, 4, and 5 MetS traits corresponded to 10score values of 30.42, 34.86, 39.30, 43.75, 48.19, and 52.63, respectively. According to these results, recommended 10score quartiles are: <30=low risk, 30-39=moderate risk, 40-49=high risk, and ≥50=very high risk.

Contribution of Individual Traits to MetS. As shown in Figures 5 and 6, MetS traits do not contribute equally to the development of MetS. These graphs demonstrate the complexity of the interaction of MetS traits. To our knowledge, this is the first study to demonstrate the relationship between individual traits and MetS probability. In men, risk of MetS appears to plateau at high values of WC and FG. This is likely due to the fact that individuals with extremely high abdominal obesity (9, 23, 46, 168) and insulin resistance (115, 122, 129, 130) express multiple additional MetS traits. Therefore the influence of these risk factors on MetS at high values may be attenuated by the contribution of other MetS traits. It is also possible that elevated WC and FG may develop prior to the expression of other MetS traits. Both abdominal adiposity and insulin resistance are considered underlying causes of MetS (59) and have been shown to contribute significantly to MetS development and progression (63, 65, 92, 99). These risk factors may develop prior to the expression of other metabolic perturbations such as elevated TG, hypertension, and lowered HDL-C. Subjects in the present study were relatively young (mean age=37 years). Therefore, it is possible that individuals in the

current study did not have sufficiently prolonged exposure to develop additional metabolic complications.

As shown in Figure 6a, probability of MetS was 0.2 for men with WC≥90cm and 0.5 for individuals with WC≥102. This suggests that metabolic perturbations occur at values well below current MetS criteria. Lean et al (95) demonstrated that WC≥94cm corresponds closely to elevated BMI and waist-to-hip ratio (WHR), suggesting elevated risk with this level of WC. Increasing WC from 102 to 130 cm results in only modest increases in MetS probability (0.5 and 0.6, respectively). This suggests that the primary risk associated with increasing adiposity occurs at relatively minor perturbations in WC.

Due to the lack of women with WC<88cm, the present study was unable to assess the relationship of low WC and MetS in women. Unlike men, WC appears linearly related to MetS in women. MetS risk increases from ~0.1 at WC 80 to ~0.6 at WC 130cm. The difference in MetS risk associated with WC between genders may be due to distribution of adipose tissue. The current study did not assess WHR. It is therefore possible that women in the present study displayed a more advantageous WHR than men and were protected from MetS incidence associated with abdominal obesity.

Other MetS traits such as TG, SBP, and FG (in women) appear to be exponentially related to MetS. MetS risk does not appear to increase until a threshold value is reached. After this point, risk of MetS increases sharply. In both men and women, FG 70 mg/dl corresponded to a 0.2 probability of MetS. However, the shape of the graphs was different between women and men (Figures 5b and 6b, respectively). While women showed an exponential increase in MetS probability, men demonstrated a hyperbolic relationship. This is the first study to demonstrate differential associations of

FG with MetS between men and women. The difference in the association between FG and MetS probability is likely due to differences in data distribution. Only 5 men in the present study had FG≤85 mg/dl. However, 27 females met this criterion. It is likely that with a larger male sample size, the relationship would be similar. In both men and women, MetS risk appears to increase at approximately 100 mg/dl. Beyond this point, risk of MetS increases in a nearly linear fashion. SBP and DBP appeared to contribute very differently to MetS probability in the present study. In both women and men, SBP was positively related to MetS in an exponential fashion. In men, DBP appeared to be inversely related to MetS. However, this is due primarily to a single case with DBP 60 and MetS positive. The discrepancy between the figures can be primarily explained by procedural methods. Individuals meeting either SBP or DBP criterion are considered to have MetS. In the present study, SBP appears to be more strongly related MetS than DBP. This is in agreement with a study by Sesso et al (134) demonstrating SBP is a better predictor of CVD than DBP.

As shown in Figures 5c and 6c, HDL-C was inversely exponentially related to MetS probability in both women and men. In men, the threshold value for increased MetS risk appeared to be approximately 50 mg/dl. In women, the threshold value for increased risk appeared to occur at approximately 80 mg/dl. These values are significantly higher than the current MetS criteria of 40 mg/dl and 50 mg/dl, respectively. This finding is in agreement with that of Wilson et al (163). These authors demonstrated that CVD risk was increased at HDL-C ~54 mg/dl in men and 70 mg/dl in women. However, at high HDL-C, risk of MetS does not appear to be further reduced. Additionally, DBP does not appear to contribute to risk of MetS.

Figures 5 and 6 appear to be in agreement with previous reports showing WC and FG are more strongly related to MetS than other risk factors such as TG and BP (63, 65, 92, 99). The strong inverse relationship between HDL-C and MetS is a somewhat novel finding of the present study. Several reports have shown an inverse relationship between HDL-C and MetS (33, 63, 164), but the strength of the relationship has yielded conflicting results (63, 65). Palaniappan et al (112) demonstrated that HDL-C was second only to WC in prediction of future MetS incidence. According to these authors, HDL-C was equal to FG in contribution to incidence MetS with a relative risk of 1.6. The strong inverse relationship in the present study appears to agree with this finding.

Predictors of MetS. Figures 5 and 6 demonstrate the relationship of individual MetS traits with probability of MetS. However, these figures do not offer any quantitative analysis demonstrating the most influential trait(s). These figures were created using kernel smooth functions which are somewhat biased toward end effects. This method averages all data points within the specified bandwidth. Extreme data points (low or high) are therefore given additional influence due to smaller bandwidths and fewer data points included. The current study employed a generalized additive model (GAM) to assess contribution of individual traits to MetS probability (Figure 7a-c). Additionally, both backward elimination and forward selection were employed to determine the most influential determinants of MetS. According to this analysis, predictor of MetS are different between men, women, and combined. However, within each group, backward elimination and forward selection resulted in similar results. This may be the first study to employ backward elimination and forward selection to assess risk factor contribution to MetS.

According to forward selection, HDL-C accounted for 21% of the null deviance in women, suggesting this is the most influential factor. These results are shown in Figure 8. While HDL-C explained the greatest absolute deviance, it was not significantly greater than FG ($p=0.0832$) or TG ($p=1.0000$). This finding is similar to those of Palaniappan et al (112). These authors demonstrated that FG, TG, and HDL-C all carried a 1.6 odds ratio for development of MetS. Backward elimination and forward selection selected traits in the following order for women: HDL-C>FG>TG>SBP>WC. Addition of subsequent traits significantly increased the amount of deviance explained compared to the previous model (all $p<0.05$). Inclusion of HDL-C+FG+TG accounted for 65% of the deviance. Therefore, measurement of these three traits accounts for the majority of risk associated with MetS.

In men forward selection determined TG accounted for the greatest amount of deviance (34%). These results are shown in Figure 9. This was significantly greater than any other trait (all $p<0.05$). This finding conflicts with findings from Assmann et al (10) who demonstrated TG contributes significantly less to CAD than other risk factors. This finding could be due to outliers within the dataset. In men alone, 3 cases were observed with TG>400mg/dl. Backward elimination and forward selection selected traits in the following order for men: TG>FG>WC>SBP>HDL-C. Addition of subsequent traits significantly increased the amount of deviance explained compared to the previous model (all $p<0.01$). TG+FG accounted for 56% of the null deviance in men. TG+FG+WC accounted for 70% of the deviance. This data suggests that these three variables account for the majority of risk associated with MetS.

Forward selection determined TG to be the most influential factor in combined, accounting for 27% of the deviance. These results are presented in Figure 10. This was significantly greater than WC, FG, and SBP (all $p<0.0001$), but not HDL-C ($p=0.1797$). Backward elimination and forward selection selected traits in the following order for combined data: TG>FG>HDL-C>SBP>WC. Addition of subsequent traits significantly increased the amount of deviance explained compared to the previous model (all $p<0.01$). TG+FG+HDL-C accounted for 60% of the null deviance, suggesting these variables account for the majority of risk associated with MetS.

According to this data, assessment of 3 MetS traits may provide a reasonable estimation of risk associated with MetS. However, it is necessary to assess different MetS traits for women and men. In women, HDL-C, FG, and TG account for the majority of risk and should be used to estimate MetS risk. In men, TG, FG, and WC account for the majority of risk. This data suggests that low HDL-C may contribute significantly higher risk in women and elevated TG may prove to be riskier in men.

Several studies (63, 65, 92, 99, 119) have been employed factor analysis, a statistical method for evaluating highly intercorrelated variables to determine the most significant contributors to MetS. These studies have consistently shown high loadings for WC and FG. According to ATP III, these risk factors are considered the underlying cause of MetS (59). The results of backward elimination and forward selection in the present study conflict with these previous reports. This study may be the first to employ backward elimination and forward selection to determine the most influential MetS criteria. In the present study, WC was shown to be the least influential contributor in women and third most influential contributor in men. The discrepancy between this and

other studies is likely due to sampling bias of the current study. Subjects in the present study were obtained from exercise intervention studies targeting overweight and obese individuals. The current study attempted to resolve this discrepancy by including data from all screening participants. Elevated WC was a common feature with nearly 90% of subjects meeting the sex-specific criteria for MetS. A limited WC range may mask the influence of WC on MetS, especially at low values.

Additionally, other authors have suggested TG to be only a minor contributor to morbidity compared to other MetS traits (10, 142). Assmann et al (10) determined that high LDL-C, low HDL-C, hypertension, and diabetes all contributed significantly more to CAD development than high TG. The present study showed TG to be the most influential factor in both men and combined data. In women, TG was shown to be the third most influential factor. The close relationship between TG and MetS in the present study may be the effect of a few outliers. Removal of these points may impact the relationship between TG and MetS. Additionally, this weakened relationship may more accurately reflect risk associated with elevated TG. The present study did not attempt to remove these outliers due to the relatively small sample size of men.

As mentioned previously, most analyses of MetS contribution has employed factor analysis to assess risk. These studies often use multiple markers of obesity, insulin resistance, lipoprotein metabolism, and blood pressure (63, 65, 92, 99, 119). The current study employed backward elimination and forward selection to determine which traits are more influential on MetS risk. Additionally, the present study limited analysis to the 5 criteria currently used for MetS diagnosis. This method eliminates or adds variables individually to assess the additive effects risk factor combinations. This may be the first

study to employ this statistical method for analysis of MetS. While backward elimination and forward selection are significantly more simple statistical approaches, they are subject to statistical limitations. Backward elimination initially included all 5 MetS traits and progressively eliminated the trait contributing the least explained deviance. According to this method, significant error is introduced into the equation with the elimination of multiple traits. Conversely, forward selection started with the null deviance and added traits according to increasing deviance explained. According to this method, significant error is present in the initial equation, but is reduced as traits are added to the equation. Due to these limitations, the current study employed both backward elimination and forward selection. These methods produced similar results within groups with regards to the order of influence of MetS traits. Agreement between backward elimination and forward selection gives confidence to the results of the present analysis.

Conclusions. The present study provides a potential scoring system for quantifying risk associated with MetS. This scoring system has been shown to be a significant predictor of MetS presence and severity (number of traits). Inclusion of redundant markers of obesity weakened the relationship between 10score and MetS presence and severity. Future research is necessary to determine whether the proposed scoring system is a significant predictor of morbidity and mortality. Additionally, the present study demonstrated that MetS traits contribute differently to MetS risk between genders. In women, HDL-C is the most significant contributor. In men and combined genders, TG is the most significant contributor.

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APPENDIX A

EXTENDED LITERATURE REVIEW

METS CONTROVERSIES

The concept of the metabolic syndrome (MetS) has gained significant attention since its inception. MetS refers to a clustering of risk factors associated with the development of cardiovascular disease (CVD) and type 2 diabetes (T2D). Numerous organizations have adopted the concept and developed functional definitions and criteria for diagnosis of MetS (34). Perhaps the most widely accepted definition in clinical practice is that of the National Cholesterol Education Program Adult Treatment Panel III (ATP III) (36). Current estimates show nearly 25% of Americans are classified as having MetS according to this definition (44, 104, 113). Despite, the popularity and utility of MetS, some authors have recently questioned its utility or even the existence of a true metabolic syndrome (65, 79, 122, 129, 143). In a recent review article, Kahn et al (79) present several conflicts facing the current definition of MetS. These arguments included: 1) the lack of improved predictive power compared to other tools, 2) the need for additional diagnostic criteria, 3) dichotomously labeling the presence of MetS, and 4) equal weights assigned to all MetS traits. Additionally, physical fitness is not currently considered when diagnosing MetS. High aerobic capacity or lean body mass may be protective against the detrimental effects of MetS (22, 38, 78, 83, 93, 111, 161). Due to the limitations associated with the current definition of MetS, it is necessary to re-evaluate the implementation of MetS. Few attempts have been made to assess the severity of risk associated with differing degrees of MetS (48, 87, 149).

METS AS RISK FACTOR

MetS has consistently proven to be a significant risk factor for the development of CVD (4, 33, 74, 90, 100, 104, 119, 129, 164), T2D (33, 63, 89, 98, 122), and mortality

(72, 74, 90, 100). One study demonstrated that MetS accounts for 21% of the variance associated with incident coronary heart disease (CHD) (90). Another study by Dekker et al (33) found that individuals with MetS had 2 fold higher CVD incidence in 10 years. Several studies have demonstrated increased mortality rates in MetS, primarily due to CVD (33, 74, 90, 100). Isomaa et al (74) showed that all-cause mortality is increased 10% in MetS in as little as 7 years. Another study by Malik et al (100) showed that mortality was increased 40% in MetS and that CVD mortality was increased 200%. Additionally, MetS has been shown to be a risk factor for T2D (33, 64, 122, 164). In fact, over 85% of individuals with T2D also are classified as having MetS (4). Wilson et al (164) demonstrated that risk of T2D increase 5 fold in individuals with 1-2 MetS traits and nearly 25 fold in those with ≥3 traits. Furthermore, these authors demonstrated that MetS accounts for 30% of incident CVD and 50% of incident T2D (164).

Due to its inclusion of multiple risk factors, MetS would be expected to be a better predictor of lifestyle related diseases than previously established tools. However, in the San Antonio Heart Study and the Mexico City Diabetes Study, MetS displayed lower sensitivity and higher false positive rate than the Framingham Risk Score (FRS) and the Diabetes Predicting Model (DPM) for predicting CVD and T2D, respectively (143). Additionally, combining MetS and FRS or DPM did not add any predictive information. Dekker et al (33) found that adjustment for FRS significantly attenuated CVD hazard ratio associated with MetS. It has previously been suggested that dichotomously labeling individuals according to MetS may compromise essential information about metabolic processes and prediction of disease risk (79, 129, 143). Without grading severity of individual risk factors or assessing which factors are present,

MetS contributes equal disease prediction to all traits based on a single clinical threshold. Additionally, the lack of improved predictability can be partly attributed to the fact that MetS includes only previously established, traditional risk factors (79, 129). Many non-traditional risk factors have been proposed as additional diagnostic criteria for MetS. Two possible candidates are C-reactive protein (CRP) and tumor necrosis factor-α (TNFα). Alternative markers of obesity and body composition have also been suggested as new MetS criteria. Additionally, recent evidence suggests that aerobic capacity (38, 78, 83, 93, 161) and physical activity (20, 24, 37, 48, 77, 121) may be considered negative MetS risk factors.

PREVIOUSLY ESTABLISHED METS CRITERIA

Waist Circumference. Waist Circumference (WC) has been identified as a criterion measure for MetS. Factor analysis of MetS has found that central obesity is the primary contributor to MetS incidence (99). In accordance with this, ATP III criteria has established central obesity as an underlying risk factor for MetS (59). Current MetS guidelines consider WC ≥102 and ≥88 cm for men and women, respectively to be abdominally obese (58). However, these values have been challenged by some authors (14, 95). Lean et al (95) found that WC ≥94 cm for men and ≥80 cm for women identified individuals with elevated BMI and waist-to-hip ratio (WHR). In accordance with this, Baik et al (14) found mortality was increased in men with WC ≥96 cm. This data suggests that risk of abdominal obesity may be increased at values lower than the current MetS threshold.

Studies employing magnetic resonance imaging (MRI) have shown WC is highly correlated to total adiposity (r=0.94) (126) as well as visceral adipose tissue (VAT)

(r=0.669) (25). VAT is more metabolically active and a greater source of inflammatory cytokines compared to subcutaneous adipose tissue (SAT) (146). It has previously been demonstrated that VAT area correlates much more highly with MetS features than total body fat and increases prediction of MetS severity (168). Several studies have indicated that WC is more highly correlated to VAT than other anthropometric measurements (25, 60, 75, 135). Therefore, assessment of VAT through simple methods such as WC is preferred to total body fat percentage in diagnosis of MetS.

WC has consistently been shown to be a significant predictor of MetS prevalence and severity with a 1cm increase in WC corresponding to a 6% increase in risk of developing MetS (75). Given the role of abdominal obesity in MetS development, some organizations require the presence of enlarged WC prior to MetS diagnosis (34). Measures of central adiposity including WC (75, 110, 152), VAT area (23, 46, 54, 168), and subscapular and triceps skinfold measurements (167) have been shown to be more highly related to MetS, CVD, and T2D than indicators of total body obesity such as BMI and percent body fat. In one study, individuals with similar WC had similar rates of MetS regardless of BMI classification (75). These authors proposed that WC be measured in a graded fashion to more accurately reflect risk associated with abdominal obesity. In support of this, Okosun et al (110) found that WC was significantly correlated to number of MetS traits. This study demonstrated that elevated WC increased risk of having 2, 3, or ≥4 MetS traits by 6, 7, and 9 fold, respectively. Furthermore, WC has been shown to be a significant predictor of all-cause mortality with a 10% increase in WC corresponding to a 30% increase risk of all-cause mortality (18).

Fasting Glucose. Insulin resistance (IR) is considered to be an underlying cause of MetS by ATP III definition (59). MetS definitions from other organizations such as the World Health Organization (WHO) and the American Association of Clinical Endocrinologists (AACE) require the presence of IR prior to diagnosis of MetS (34). In accordance with this, numerous factor analysis studies have shown that an IR factor contributes heavily to the prevalence of MetS (63, 65, 90, 119). In several cases, the IR factor loads more heavily than others, implicating IR as the primary or central feature of MetS.

Fasting glucose (FG) ≥100mg/dl is currently considered a criterion for MetS diagnosis (58). This value was recently lowered from 110mg/dl to reflect an increased risk of chronic disease and mortality at lower values of FG. Kim et al (85) found that compared to FG <100, MetS odds ratio was increased 2 fold with FG of 100-109mg/dl. Furthermore, MetS odds ratio was increased 4 fold in those with FG ≥ 110 mg/dl. These findings support the role of IR in the development of MetS.

The link between impaired fasting glucose (IFG) and T2D has been well established. A recent study by de Vegt et al (32) demonstrated that IFG is predicts T2D as well as impaired glucose tolerance (IGT). Additional evidence has supported a role for IFG in both CVD (3, 15, 19, 29, 42, 103, 120, 132) and all-cause mortality (15, 42, 108). All-cause mortality risk is increased with FG >85mg/dl (19) and increases even more sharply with FG ≥110 mg/dl (29). Individuals with this level of IFG have a 3.5 fold higher risk of mortality (108). This suggests that IFG is a significant risk factor even with only mildly elevated FG. One study found a 21mg/dl increase in FG corresponded to a 10% increase in mortality risk (132). IFG has proven to be a significant predictor of

mortality in as little as 3 years of follow-up (108), suggesting that hyperglycemia may have a potent effect on mortality. Despite the relationship between IFG and mortality, some authors have found no increase in risk unless other risk factors such as hypertension are present (3, 69). Indeed, Alexander et al (3) found that increasing CHD prevalence in individuals with IFG was largely attributable to the presence of other risk factors. These authors concluded that MetS, not hyperglycemia per se, increases mortality risk.

Harris et al (67) found that IFG prevalence increased from 6.5% in the period of 1976-1980 to 9.7% in 1988-1994. Interestingly, these authors noted that prevalence of CVD risk factors such as hypertension and hypercholesterolemia were unchanged during this period. In 2003, the American Diabetes Association (ADA) lowered the threshold for IFG to 100 mg/dl. As a result, current estimates show nearly 35% of the US population is considered to have IFG (85). Sharp increases in IFG prevalence combined with relatively stable prevalence of other risk factors suggests that IFG may contribute more to incident CVD and thus may be a more significant risk factor in current times.

In addition to IFG, numerous reports have demonstrated increased T2D (32), CVD (15, 103), and mortality (15, 103, 120) with impaired glucose tolerance (IGT). This suggests that postprandial hyperglycemia may increase risk of chronic disease or death even if FG values fall within the normal range. However, it is rare that individuals with IGT have normal FG (103). Comparison of IGT and IFG has shown IGT to be a better predictor of all-cause and CVD mortality, suggesting IGT may be more influential than IFG in risk of mortality (15, 103, 120). Previous reports have shown a high correlation ($r=0.90$) between IFG and IGT (132). Furthermore, IGT does not appear to add any predictive value beyond that of current CVD risk factors combined with IFG (103).

Together, this data indicates that IFG may be a simpler, and similarly effective tool for estimating mortality risk associated with IR than IGT.

Increased mortality risk associated with IFG appears to be primarily due to increased CVD mortality (15, 103, 120, 132). However, mechanistic actions remain elusive. Most authors contribute the increased risk to direct atherogenic effects of hyperglycemia rather than IR. It has been proposed that hyperglycemia results in glycosylation and altered function of proteins and lipids (8). Specifically, hyperglycemia results in glycosylation of low density lipoprotein (LDL). Glycosylated LDL is more susceptible to oxidative modification and uptake by scavenger receptors, contributing to early atherosclerosis. Additionally, glycosylated proteins are recognized by specific receptors resulting in secretion of inflammatory cytokines such as TNFα (8). In addition to these mechanisms, it is possible that IR and chronic hyperglycemia exerts its effects through other risk factors (3, 69).

Blood Pressure. Blood pressure (BP) has been shown to be a significant risk factor for CVD (2, 26, 91, 134, 153, 154) and mortality (53, 151). Sesso et al (134) demonstrated that relative risk of CVD was increased 2 fold in men with systolic blood pressure (SBP) ≥130mmHg or diastolic blood pressure (DBP) ≥81mmHg. Furthermore, these authors demonstrated that CVD risk was increased by approximately 30% and 45% for every 10mmHg increase in SBP and DBP, respectively. This is in agreement with the most recent report from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) (26). This report indicated that CVD risk doubles for every 20/10mmHg increase above 115/75mmHg. A study by van den Hoogen et al (151) reported a somewhat weaker association between BP and

CHD mortality. These authors found CHD mortality increased 17% for every 10mmHg increase in SBP and 13% for every 5mmHg increase in DBP. Interestingly, absolute risk associated with elevated blood pressure appears to vary greatly among different populations (151). However, relative risk of increased BP increases similarly across all populations. This evidence suggests that BP may be a more influential risk factor for some populations. However, hypertension is associated with increased CVD and morality in all populations.

BP may be an important risk factor for IR and T2D as well as CVD. BP has been associated with both elevated FG and IGT independent of other risk factors (130). Furthermore, it has recently been shown that genes encoding for BP response such as AGT (angiotensinogen), NOS3 (nitric oxide synthase 3) and SCNN1A (sodium channel, nonvoltage-gated 1 alpha) are also associated with insulin sensitivity and IR (61). For some genes (AGT and NOS3) this effect appears to be mediated by body mass, further supporting a role for MetS in contributing to both CVD and T2D through the interaction of multiple risk factors.

Some authors have suggested that hypertension enhances the negative effects of these other risk factors and that isolated hypertension is not a serious risk factor (5). This hypothesis claims that increased pressure against artery walls allows greater impact of other risk factors such as hyperglycemia to negatively impact endothelial function. Certainly, hypertension negatively influences cardiovascular health through this mechanism. However, additional evidence has shown elevated BP to be a significant predictor of CVD independent of other risk factors (2, 91, 134). Alexander (5) reviewed the mechanistic action of BP on CVD. In addition to pressure-induced endothelial

dysfunction, elevated BP may result in increased monocyte and lymphocyte adhesion, increased macrophage accumulation, smooth muscle cell proliferation, and increased oxidative stress. Additionally, this review proposed that hypertension results in smooth muscle cell proliferation and increased thickness of the artery wall and therefore increased diffusion distance of oxygen. Increased diffusion distance may increase oxidative stress, further contributing to atherosclerosis development. This hypothesis is supported by a four year follow-up study by Lakka et al (91) demonstrating that elevated BP accelerates the rate of intima-medial thickening in men. Therefore, elevated BP may precede development of atherosclerotic lesions. Interestingly, this study noted significant progression of atherosclerosis in men with mildly elevated BP. This suggests that BP may be a significant risk factor at "prehypertensive" ranges.

HDL-C. HDL-C has consistently been shown to be inversely related to CVD (57, 160) and mortality (163). A meta-analysis of four prospective studies revealed that increasing HDL-C by 1mg/dl reduces CHD risk by 2-3% (57). Results from the Framingham Heart study show that low levels of HDL-C (≤44mg/dl for women and ≤34mg/dl for men) increases all-cause mortality risk by 50% and 90%, respectively (163). This effect was primarily due to increased risk of CVD and CHD mortality which was approximately 300% higher in those with low HDL-C. One recent study found HDL-C, but not LDL-C or total cholesterol, was associated with a significant 2 fold increase in CVD and CHD mortality in elderly patients (160). This data suggests that low HDL-C may be a more influential risk factor than either total cholesterol or high LDL-C in determining CHD risk. In addition to CHD, HDL-C has been shown to be an independent risk factor for CVD and MetS. In the Insulin Resistance Atherosclerosis

Study (IRAS), HDL-C was second only to WC in predicting incident MetS (112). This study found that MetS risk increased 60% for every 15mg/dl decrement in HDL-C.

Previous research has shown that HDL infusion can prevent and even reverse the formation of atherosclerotic lesions. Badimon et al (13) fed rabbits a high cholesterol diet for 90 days in order to induce atherosclerosis. Rabbits receiving HDL infusion during the last 30 days showed significantly less aortic occlusion (17.8% vs. 38.8%) than those without HDL infusion. Additionally, this study found significant reductions in total and esterified cholesterol and phospholipids accumulation within the aortic wall. This evidence strongly supports the hypothesis that HDL offers cardiovascular protection through a reverse cholesterol transport mechanism. In addition to reduced lesion size, recent evidence has shown that HDL-C protects against atherosclerosis through other mechanisms such as enhanced endothelial function. Spieker et al (139) demonstrated that HDL infusion restored acetylcholine-induced vasodilation in hypercholesterolemic men. Therefore, it appears that HDL-C not only reverses lipid accumulation within the arterial wall, but may also help prevent the earliest stage of atherosclerosis.

TG. Previous research has found TG concentrations to be highly correlated to other features of MetS, particularly HDL-C (62, 76, 148). Due to the complex interactions of lipoproteins during metabolism, the role of TG as a CVD risk factor has been debated. It has been hypothesized that risk associated with hypertryglyceridemia is due to indirect, rather than direct effects. A review by Brewer (21) proposes that hypertriglyceridemia increases CVD risk through 3 independent mechanisms: increased cholesterol-rich remnants, increased atherogenic small, dense LDL, and decreased HDL-C. This review proposes that alterations in apolipoproteins may be the underlying cause

of hypertriglyceridemia-induced atherogenic profile. Specifically, apoproteins A-II, C-I, and C-III are thought to be elevated in hypertriglyceridemia. Together, this altered apoprotein profile results in increased TG production and decreased TG hydrolysis.

Despite controversy over the role of TG as a CVD risk factor, recent evidence indicates hypertriglyceridemia is an independent risk factor for CVD mortality (11, 30, 62, 76, 105). Several reports have demonstrated a stepwise increase incident CVD (62, 76, 105) and CVD mortality (11, 142) with increasing fasting and postprandial TG. Adjustment for HDL-C weakens this relationship (12, 62, 76), but TG remains a significant predictor of CVD and mortality. Bezafibrate, a common treatment for hypertriglyceridemia, significantly reduces relative risk for total (0.71) and non-fatal (0.67) myocardial infarction (148). Together, this data suggests that hypertriglyceridemia is an independent risk factor for CVD and mortality.

Miller et al (105) demonstrated that risk of coronary artery disease is significantly elevated at TG ≥100mg/dl, much lower than the current MetS definition. This finding was confirmed in both the Copenhagen Male Study (76) and the Prospective Cardiovascular Münster Study (PROCAM) (10). Additionally, it has been determined that other risk factors including diabetes (2.1) and low HDL-C (1.5) confer higher, or at least equal relative CVD risk than fasting TG (1.5) (105). This finding was confirmed by Assmann et al (10) who determined that LDL-C, low HDL-C, hypertension, and diabetes contributed significantly more to CVD development than hypertriglyceridemia.

INFLAMMATION AND METS

Nearly all components of MetS are associated with an inflammatory state. A review by Das proposes that MetS is a low-grade inflammatory condition (31). The American Heart Association (AHA) and the National Heart, Lung, and Blood Institute (NHLBI) recently identified a proinflammatory state as a metabolic risk factor along with atherogenic dyslipidemia and IR for MetS (59). Inclusion of inflammatory markers may add predictive power to MetS (123-125, 145). Factor analysis has shown inflammation is second only to IR (and weighs heavier than dyslipidemia) in predicting the development of MetS (63). In this analysis, CRP loaded heavily (.66) on the inflammation factor, offering evidence that CRP could potentially be used as a new diagnostic criterion for MetS. The interaction of inflammatory cytokines is a complex process. Therefore, it may be necessary to examine multiple inflammatory markers to appreciate risk associated with inflammation. Spranger et al (140) demonstrated that combined effects of inflammatory cytokines TNFα and interleukin-1β (IL-1β), but not individual cytokines modify risk of developing T2D. Therefore, it may be necessary to examine multiple inflammatory markers to appreciate the impact of inflammation on health and MetS. Furthermore, it has been suggested that TNFα may induce secretion of CRP and may therefore be viewed as an upstream indicator of inflammation (40). This could potentially implicate TNFα as a MetS risk factor.

Several studies have indicated high correlations between obesity and inflammation (39, 40, 45, 52, 71, 80, 145, 147, 171). Furthermore, weight loss has been shown to reduce circulating CRP (147) and TNFα (84, 171), suggesting obesity may contribute to a pro-inflammatory state. It has been hypothesized that adipose tissue,

particularly VAT, directly secretes pro-inflammatory cytokines into the circulation (40, 45, 71, 84, 147, 171). Reviews by Hotamisligil (70) and Wellen (159) discuss the link between obesity, metabolism, and inflammation in detail. These authors note several similarities between adipose tissue and immune cells including production and activation of inflammatory cytokines, pathogen sensing, and phagocytic properties. Furthermore, it is hypothesized that adipose tissue differentiated from immune cells, but retains several key features of immune cells such as secretion of inflammatory cytokines. It is now well accepted that adipose tissue is not inert, but contributes significantly to the secretion of cytokines, including CRP and TNFα. Hostamigil (70) proposed two mechanistic links between obesity and inflammation: 1) inflammatory markers secreted by adipose tissue may act to induce IR and therefore block anabolic processes to protect the body during times of caloric insufficiency 2) expansion of adipose tissue triggers catabolic inflammatory pathways to prevent further expansion and maintain an acceptable body weight and size.

CRP. CRP is an acute phase protein that serves as a marker of subclinical inflammation. Compared to other inflammatory markers such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNFα), CRP does not typically display diurnal variation, making it a more consistent marker for measuring inflammatory response (102). In clinical practice, CRP <1mg/L is considered normal and >3mg/L is considered high (114).

CRP has previously been established as an independent risk factor for the development of both CVD (114, 123-125, 128) and T2D (41, 49, 125). In fact, CRP has previously been shown to be a stronger predictor of CVD than LDL-C) (124). The minimal correlation between CRP and LDL-C suggests that CRP may identify a different

high-risk group than dyslipidemia, and thus add to the predictive power of MetS. While CRP is not considered a causative agent for the development of MetS (150), it may serve as a marker for inflammation induced by other risk factors that are already present and thus indicate severity of MetS. Cross sectional studies show CRP increases with increasing number and severity of individual MetS traits (40, 52, 80, 128, 131, 145). Additionally, CRP has been correlated to all features of MetS, particularly obesity (VAT) (39, 40, 45, 52, 80, 145, 147) and IR (39, 40, 101, 117, 118). It has been suggested that CRP is stimulated by other cytokines such as IL-6 and TNFα that are released by visceral adipocytes (40). Additionally, CRP has been shown to induce secretion of other inflammatory cytokines such as PAI-1 (35).

Modified MetS definitions including CRP as a criterion have been shown to increase MetS ability to predict CVD (123, 125, 131) and T2D (131). In the West of Scotland Coronary Prevention Study, the combination of MetS and high CRP resulted in increased incidence of CVD and T2D in as little as 5 years of follow-up (131). Ridker et al (123) found a similar increase in CVD incidence in 8 years of follow-up. These findings, however, have not been replicated in all studies (64, 128). In addition to CVD, CRP has also been implicated in incident T2D (41, 49, 117). CRP is positively correlated to both fasting (118) and day-long (101) insulin levels. Additionally, insulin resistant individuals display elevated CRP (39). Most strikingly, Freeman et al (49) found that individuals in the highest CRP quintile had a 3 fold higher risk of T2D after 5 years than those in the lowest quintile. Festa et al (41) demonstrated similar findings although this relationship was weakened after adjustment for body fat and insulin sensitivity. Taken

together, these data indicate that CRP may be involved in the development of both CVD and T2D.

TNFα. Another proinflammatory marker, TNFα, may also contribute to the deleterious effects of MetS. TNFα has been correlated with several features of MetS including obesity (71, 84, 166, 171), TG (71, 166), HDL-C (166) and IR (50, 71, 166). Furthermore, TNFα concentrations have been shown to be higher in individuals with MetS than those without and TNFα appears to increase with increasing number of MetS traits (166). It is therefore possible that TNFα could potentially serve as a new MetS criterion. Although few researchers have examined the role of TNFα as a criterion for MetS, it appears to play a crucial role in the inflammatory process by inducing secretion of other inflammatory agents such as interleukin-6 (IL-6) (116). Similar to CRP, the major source of TNFα appears to be adipose tissue (71, 84, 171). Previous research has shown that both TNFα mRNA (71) and protein (171) expression is significantly elevated in obese individuals and secretion increases with increasing obesity (71). Kern et al (84) demonstrated that adipocytes express much higher levels of TNFα mRNA than other tissues such as skeletal muscle. Furthermore, these authors showed that TNFα mRNA is reduced following weight loss, suggesting that adipose tissue is the primary site of TNFα transcription. Hotamisligil et al (71) also showed TNFα to be positively correlated to BMI but not WHR. This suggests that TNFα secretion is not specific to central obesity. However, some authors have found correlations between TNFα and markers of central adiposity (171). Together, these data indicate that adipose tissue and obesity are major sources of TNFα.

In addition to obesity, TNFα is closely associated with IR (50, 71, 166). Infusion of TNFα has been shown to result in decreased glucose disposal (116, 169), primarily due to decreased insulin signaling. Several researchers have noted that TNFα directly phosphorylates serine residues on insulin receptor substrate-1 (IRS-1) (116, 127) and inhibits tyrosine phosphorylation (169). It is well established that tyrosine phosphorylation of the insulin receptor and IRS-1 is essential for insulin signaling and that serine phosphorylation inhibits this process. In addition to direct inhibition of insulin signaling, TNFα may induce IR by acting on the JNK pathway. TNFα has been shown to phosphorylate c-Jun NH2 terminal kinase (JNK) (116). JNK in turn phosphorylates Akt substrate 160 (AS160), preventing GLUT4 translocation and thus decreased insulin-stimulated glucose uptake. Therefore, TNFα could potentially be viewed as an upstream inhibitor of insulin signaling. IR induced by TNFα may also be mediated through the Ικκβ pathway. TNFα has been shown to activate the Ικκ complex (169). Activation of Ικκβ stimulates NF-κβ transcription which in turn increases transcription of pro-inflammatory markers such as TNFα. Furthermore, a positive feedback appears to exist between inflammation and Ικκβ pathway. This data suggests that inflammation, particularly TNFα, may play a significant role in development of IR and MetS.

BODY COMPOSITION AND METS

Recently, some authors have questioned the health risks associated with overweight and mild obesity (16, 43, 86). Some researchers have shown no increased risk and even possibly decreased risk for chronic disease and mortality associated with overweight and moderate obesity. In a 14 year follow-up of overweight and obese men and women, Bender et al (16) showed that moderately obese (BMI 32-36) had no

elevated mortality risk over those with BMI 25-32. However, there was a significant 50% increase in mortality risk in individuals with BMI 36-40 and a 200% increase for those with BMI >40. A more recent study by Flegal et al (43) paralleled these findings. These researchers found no increase in all-cause mortality associated with overweight (BMI 25-30) or moderate obesity (BMI 30-35). However, individuals with BM I >35 had a significant increase in all-cause mortality. Therefore, while these studies failed to show increased risk for individuals with moderate overweight and obesity, morbid obesity remains a significant risk factor for all-cause mortality. Despite the apparent paradox between overweight and health risk, several studies have shown overweight to be a significant predictor of long-term mortality (1, 14, 68, 73, 138, 167). Some authors have noted that overweight and obesity increase mortality risk in a little as 4 (14) years while others have shown no increase in mortality until at least 15 (138, 167) years of follow-up.

Several authors have suggested that, in addition to IR, obesity may be considered a central feature of MetS (97, 99, 141, 155). Numerous studies show that MetS prevalence and severity increase with increasing degree of obesity (75, 97, 152, 155, 168). A recent longitudinal study by Maison et al (99) demonstrated that obesity may be the central feature of MetS. In this study, 3 primary features of MetS were determined: obesity, central obesity, and IR. After 4.5 years of follow-up, changes in obesity were highly correlated with changes in other metabolic parameters, suggesting changes in body weight may influence additional metabolic processes.

BMI. Body mass index (BMI) is a commonly used tool for assessing obesity in population-wide studies. Several epidemiological studies have employed modified

definitions of MetS to include BMI rather than WC as a marker of obesity (46, 75, 97, 141, 155, 168). These studies have consistently demonstrated that MetS prevalence and severity increase with increasing BMI. It has previously been shown that BMI predicts MetS similar to WC (141). This study found no difference in odds ratio for MetS prevalence when using a modified MetS definition including BMI rather than WC as a marker of obesity. Furthermore, Vanhala et al (152) noted increased MetS prevalence in individuals with a combination of elevated WHR and elevated BMI (66%) compared to those with either elevated WHR (40%) or elevated BMI (47%) alone. These findings suggest that BMI predicts MetS similarly to WC. Additionally, combining BMI and WC may predict MetS more accurately than either measure alone.

Overweight and obese individuals have been shown to have elevated rates of MetS (54, 75, 97, 152, 155, 168), CVD (73, 133, 138, 167), and mortality (1, 6, 17, 18, 68, 81, 135) compared to their lean counterparts. Given the clustering of metabolic abnormalities associated with obesity, it has been suggested that excess weight per se may not be responsible for the deleterious metabolic profile (86). However, it has previously been shown that increasing BMI even within the "normal" category confers increased metabolic risk. St-Ogne (141), et al found that men with high-normal BMI had a 5 fold higher odds ratio of MetS than men with BMI of 18.5-20.9. Likewise, women with high-normal BMI had 7.5 higher odds ratio than those with BMI 18.5-20.9. This data suggests that relatively minor weight changes could incur significant metabolic risk. This position is further supported by longitudinal studies indicating change in BMI is significantly correlated with changes in MetS parameters. In a 3 year follow-up study, Liese et al (97) found individuals with worsening MetS profile gained weight, while

those with improved MetS profile lost weight. This study found that a weight change of approximately 2 kg over 3 years was sufficient to alter metabolic profile. This data indicates that body weight may play a significant role in determining whole-body metabolic profile and that relatively minor weight changes may have a significant impact on health status.

Percent Body Fat. It has been suggested that risk associated with BMI is a complex phenomenon resulting from the interaction of health risks incurred by high levels of body fat and protective effects associated with high levels of lean body mass (LBM) (6, 17, 18, 133). In the Honolulu Heart Program (81), subjects with high skinfold measurements showed a linear increase in mortality with increasing BMI tertiles. However, individuals with low skinfold thickness showed decreased mortality with increasing BMI. This data suggests that lean body mass (LBM), not body weight per se, is protective. Furthermore, skeletal muscle strength as assessed by 1 repetition maximum has been shown to be inversely related to MetS prevalence and severity (78). Together, these observations offer indirect evidence that high levels of lean body mass may be protective against MetS.

Using bioelectrical impedence analysis (BIA), Bigaard et al (17, 18) demonstrated that mortality risk increases with body fat mass index (BFMI) and decreases with fat free mass index (FFMI). This finding has been replicated by others using skinfold measurements to assess BFMI and FFMI (6). This evidence suggests that body composition rather than weight, per se is responsible for increased health risk associated with increasing BMI. Segal et al (133) compared MetS profile among normal weight lean, overweight lean, and obese men. This study found similar CVD risk factor

clustering between normal weight lean and overweight lean men. However, obese men demonstrated significantly elevated diastolic blood pressure, fasting insulin, LDL-C, impaired glucose tolerance, and decreased HDL-C to total cholesterol ratio. This finding suggests that high levels of LBM seen in the overweight lean group were protective against the metabolic deterioration associated with obesity. Despite the association between increased adiposity and health risk, Simpson et al (135) found that body composition does not add improve mortality prediction beyond that of WC alone.

Assessing body composition by percent body fat in MetS has not been extensively explored in the literature. A study by Zhu et al (170) assessed MetS prevalence according to BMI and BIA assessed body composition. With respect to MetS prevalence, body fat percentages of 12, 21, 29, and 36% were comparable to BMI of 18.5, 25, 30, and 35, respectively for men. For women, these values were: 24, 31, 37, and 43%, respectively. This data shows MetS prevalence increases with increasing percent body fat. Therefore, assessment of body composition by percent body fat may be an alternative measure of obesity for diagnosis of MetS.

PHYSICAL FITNESS AND METS

Aerobic Capacity. Aerobic capacity has consistently proven to be a significant predictor of CVD (28, 96) and T2D (158). In addition, aerobic capacity has been shown to be the single best predictor of early mortality (27, 28, 96, 107, 109, 144, 157). Increasing aerobic capacity by 1 metabolic equivalent (MET) results in a 15% reduced risk of developing MetS (94) and a 25% reduced mortality risk (27). Furthermore, it has been shown that MetS does not increase risk of CVD or all-cause mortality after adjustment for aerobic fitness (83). Aerobic capacity has been shown to attenuate, but

not eliminate health risks associated with obesity (22, 27, 28, 83, 88, 96, 144). These data offer evidence that aerobic capacity may provide protection from health risks incurred from other risk factors, specifically obesity. Aerobic capacity is not negatively impacted by obesity per se (56), suggesting that aerobic capacity provides protection through a mechanism other than weight control. In addition to its protective effects against obesity, aerobic capacity is inversely related to non-traditional risk factors such as CRP (94). Despite the inverse relationship between aerobic capacity, and MetS clustering and mortality, current MetS definitions do not account for aerobic capacity.

Recently, evidence has emerged to suggest that aerobic capacity may be considered a diagnostic criterion of MetS (24, 38, 83, 88, 92, 93, 161). Several studies have shown an inverse relationship between aerobic capacity and MetS clustering (22, 24, 38, 88, 92, 161). This may be due to decreased expression of peroxisome proliferator-activator receptor γ coactivator 1α (PGC-1α), a regulator of mitochondrial biogenesis and function. PGC-1α expression has been found to be reduced in both diabetic and insulin resistant skeletal muscle (106). Cross sectional analysis shows individuals with the lowest levels of aerobic fitness are 7 times more likely to develop MetS than those with the highest level of fitness (38). Interestingly, there appears to be no difference in MetS prevalence among the 3 highest quartiles of fitness. Furthermore, exercise training resulting in increased maximal aerobic capacity has been shown to improve metabolic profile (47, 82, 111, 156). Factor analysis has shown low aerobic capacity to be a significant predictor of development of MetS (92, 119). One such analysis showed aerobic capacity loaded (inversely) heavily on the primary factor along with all current components of MetS (92). In fact, aerobic capacity (-.57) loaded more

heavily than FG (.50), systolic blood pressure (.41) and fasting triglycerides (.32), suggesting that aerobic fitness may have a more significant impact on MetS development than some current criteria. While it is obvious that aerobic capacity is inversely related to MetS, it is difficult to separate the benefits of fitness per se from those of other confounding variables such as decreased VAT or increased physical activity.

Physical Activity. Similar to aerobic capacity, PA has been inversely related to MetS prevalence (20, 24, 37, 77, 88, 92, 121, 136) with moderate to vigorous activity providing the most significant benefits (77, 121, 136). Laaksonen et al (88) found that risk of developing MetS was 48% lower in men engaging in over 3 hours per week of PA compared to sedentary men. This suggests that a sedentary lifestyle may be considered as a risk factor for developing MetS or possibly a criterion for diagnosis of MetS. This view has been supported by other authors as well (92). Additionally, it appears that individuals with high MetS risk may benefit the most from increased PA (20, 88). One study found that individuals in the lowest quartile of PA energy expenditure had significantly higher rates of MetS (37). However, individuals in the third quartile had MetS rates similar to the most active quartile, suggesting that moderate increases in PA offer significant protection against MetS development. This relationship was unaltered when adjusting for VO_2max. Additional evidence has suggested that PA may reduce the risk of MetS even in the absence of weight loss (47, 156) or improved aerobic fitness (20, 37).

Exercise training has proven to be an effective treatment for MetS. Okura et al (111) found that compared to diet alone, weight loss achieved by a combination of diet and exercise resulted in over 3.5 fold increase in odds ratio of improved MetS profile

after adjusting for age and body weight change. In the Studies of Targeted Risk Reduction Interventions through Defined Exercise (STRIDDE), it was noted that individuals living a sedentary lifestyle for 6 months had significantly worse metabolic profile and progression of MetS (77, 136). However, individuals engaging in moderate amounts of exercise displayed decreased number and severity of MetS risk factors (77). Those engaging in higher intensity exercise observed an even greater reduction in MetS, particularly decreased VAT (136). Wisloff et al (165) demonstrated similar progression in MetS progression in rats bred for low aerobic capacity. The fact that sedentary rats with naturally high aerobic capacity did not show progression of MetS suggests the beneficial effects of PA are largely attributable to improved aerobic capacity.

PROBLEMS WITH CURRENT METS DEFINITION

Discrepancy between Definitions. As mentioned earlier, numerous organizations have developed functional definitions of MetS including the World Health Organization (WHO), European Group for the Study of Insulin Resistance (EGIR), American Association of Clinical Endocrinologists (AACE), International Diabetes Foundation (IDF), and ATP III (34, 36). Of these definitions, WHO and ATP III have emerged as the primary definitions both in clinical practice as well as research settings (36). All definitions are somewhat similar with regard to which risk factors are included. However, there is significant discrepancy between definitions with regard to threshold values for each risk factor and methods used to assess risk factors. With regard to blood pressure, WHO considers 140/90 to be hypertensive while ATP III considers 130/85 to be inclusion criteria for MetS. Additionally, WHO considers HDL-C concentrations of <40mg/dl in women and <35mg/dl in men to be criteria for MetS. ATP III considers

HDL-C <50mg/dl in women and <40mg/dl in men to be criteria for MetS. Measurement techniques also vary between definitions. WHO considers either elevated WHR or BMI to meet the obesity requirement while ATP III considers only elevated WC. Additionally, WHO considers IGT, glucose intolerance, or T2D as an indicator of IR. Conversely, ATP III considers only FG ≥100mg/dl or use of glucose lowering medication to satisfy the IR requirement. Finally, some organizations require the presence of a single risk factor in order to diagnose MetS. WHO requires the presence of IR prior to diagnosis of MetS. ATP III, however, simply requires the presence of any 3 risk factors for classification of MetS. Taken together, the variation between definitions makes it difficult for both researchers and clinicians to determine which individuals are considered to have MetS.

Previous studies have compared predictive ability of the WHO and ATP III definitions. The majority of these studies have shown that overall prevalence was similar between definitions (65, 104). However, inter-study variation has shown MetS prevalence to range from approximately 15% (72) to over 30% (65) of the population. Additionally, MetS prevalence has been shown to be similar between men and women (72, 98, 113). Analysis of ethnic-specific MetS rates has revealed considerable differences in MetS prevalence (98). Lorenzo et al (98) demonstrated MetS prevalence of 13.9, 20.8, and 24.3% for black, Hispanic, and white Americans, respectively. The difference in MetS prevalence is primarily attributable to different rates of individual risk factors between ethnic groups. Black men tend to have higher HDL-C and higher BP than other ethnic groups. Similarly, white men tend to have lower HDL-C and higher TG. In women, blacks and Hispanics tend to have higher rates of obesity (98).

WHO has been shown to be superior to ATP III in predicting T2D (65, 72, 89), but not CVD (104). This is largely due to the fact that the WHO definition includes only individuals presenting with IR. It appears that ATP III definition has emerged as the preferred method for assessing MetS. According to this definition, an individual is classified as having MetS if 3 of the following 5 criteria are met: WC ≥102cm for men and ≥88cm for women, TG ≥150mg/dl, HDL-C <40mg/dl for men and <50 mg/dl for women, BP ≥130/85 (or on anti-hypertensive medication), and FG ≥100mg/dl (or on glucose lowering medication). However, the need to form a unified definition to assist both researchers and clinicians in diagnosing MetS persists.

Dichotomous Assessment. Another conflict with MetS is that individuals are dichotomously labeled according to the presence of 3 of 5 clinical thresholds. It has previously been shown that risk increases both with severity of each trait and the number of traits present (33, 100, 137, 164). However, current definitions of MetS do not account for this variability. Individual who do not meet the clinical threshold are not assigned any risk and those meeting threshold values have equal risk regardless of severity. A study by Wilson et al (164) demonstrated that relative risk of CVD and T2D associated with MetS was increased in individuals displaying only 1 or 2 of the 5 traits. Men with only 1 or 2 traits had a relative risk of 1.24 for total CVD and 4.16 for T2D compared to those with no MetS traits. For women these relative risks were 3.29 and 6.10, respectively. Therefore, it is obvious that risk is increased in individuals prior to diagnosis of MetS. It has also been shown that disease risk increases with increasing severity of each individual MetS trait. However, the current MetS definition does not account for this increase in risk until a clinical threshold is reached. Additionally, the

current MetS definition does not account for increased risk above these values. Therefore, individuals who barely reach the clinical thresholds are assigned the same risk as individuals who display much higher values for the same trait. Likewise, individuals who achieve marked reductions in MetS values are not assessed as having decreased risk unless a clinical threshold is reached. Due to these limitations, it is necessary to develop a system to evaluate MetS risk associated with increasing severity of individual traits and increasing number of traits. It is also likely that different combinations of traits result in different levels of associated risk.

Unweighted Variables. It is also well known that individual risk factors do not carry equal health risk. Current MetS definitions assign equal weight to each variable when a clinical threshold is reached. According to the ATP III definition, abdominal obesity and IR are believed to be the underlying risk factors for MetS development (59). This view is supported by previous factor analysis showing heavier loading for markers of both obesity and IR. The health consequences of obesity have been studied in great detail with consistent results indicating obesity is a major determinant of CVD, T2D, and early mortality. Obesity has been shown to be strongly correlated with all features of MetS and MetS prevalence increases across BMI tertiles. As mentioned previously, VAT is directly responsible for secretion of many cytokines such as TNFα and CRP. In agreement with this is that increasing quartile rank of VAT results in increasing prevalence of MetS regardless of BMI.

IR has also been proposed to be the causative factor of MetS. When the condition was first recognized, it was labeled as the Insulin Resistance Syndrome due to the pathological role of IR. Indeed, IR appears to be highly correlated to other features of the

syndrome and has been shown to have a higher loading in factor analysis studies. It has also been hypothesized that IR may predispose individuals to obesity rather than obesity inducing IR. A study by Petersen et al. suggests that IR may be the major cause of MetS. These authors found that in response to a glucose challenge, IR individuals displayed decreased muscle glycogen synthesis and increased hepatic lipogenesis with a resultant atherogenic profile (increased TG, decreased HDL-C). These changes were independent of changes in VAT suggesting that IR plays a more central role in MetS pathogenesis than obesity.

PREVIOUS ATTEMPTS TO QUANTIFY METS

Number of Components. Perhaps the simplest approach for quantifying MetS severity is to assess the number of traits present. Longitudinal studies have shown that incidence of CVD and T2D increases with increasing number of MetS traits. In a 5 year follow-up study by Klein et al (87), individuals with 0, 1, 2, 3, and ≥4 traits displayed odds ratio of 1.0, 1.95, 2.05, 2.70, and 5.86, respectively for CVD incidence. For T2D the odds ratios were 1.0, 1.75, 5.99, 9.37, and 33.67, respectively. Additionally, Solymoss et al (137) demonstrated found non-traditional risk factors such as HOMA, uric acid, apolipoproteins A1 and B increase with increasing number of MetS traits. In addition, these researchers showed number of MetS traits to be directly related to cerebrovascular disease, peripheral vascular disease, CAD severity, T2D and inversely related to exercise frequency. This data clearly illustrates worsening metabolic profile with increasing number of MetS traits. Wilson et al (164) demonstrated that incident CVD and T2D was increased 1.48 and 4.16 respectively in individuals with 1-2 MetS traits in 8 years of follow-up. Together, this data shows that mild MetS carries

significant health risk and health risks of severe MetS can be realized in as little as 5 years.

This system provides a simple method of assessing MetS severity and appears to reflect increased morbidity and mortality risk associated with severity of MetS. However, it is limited by heavy reliance on clinical thresholds to determine whether criterion values are achieved for each risk factor. Individuals with a poor metabolic profile may be classified as low risk provided few risk factors meet clinical threshold values. Additionally, this technique is limited by assigning equal weights to each MetS risk factor and thus assumes each individual trait contributes equally to disease risk.

Z-Score. Another previously employed method to assess severity of MetS is the development of z-scores for regression analysis (48, 77, 162). According to this method, values of each risk factor are transformed into standardized scores. Addition of these scores gives a summary score which is indicative of severity of MetS and associated disease and mortality risk. Using this scoring method, Wijndaele et al (162) found that MetS score was significantly higher in individuals with MetS than their healthy counterparts. Furthermore, this study determined that MetS score increases with increasing number of MetS traits. Other authors have used this technique to quantify MetS severity and found MetS score was inversely related to PA (48, 77) and aerobic capacity (48).

The benefit of this method is that it effectively establishes risk on a continuum rather than dichotomously labeling MetS, allowing effective comparison of individual risk compared to large sample sizes. Additionally, any improvement (or worsening) of MetS is reflected in the summary score. However, this method is not likely to be very

practical in a clinical setting due to the complexity of the statistical analysis. Additionally, risk stratification groups would likely be necessary in order for clinicians to effectively communicate MetS risk to patients. This technique is further limited by including only the current ATP III diagnostic criteria. However, it would be relatively simple to include non-traditional risk factors such as CRP, TNFα, body composition, and aerobic capacity into this analysis. Again, this method contributes equal weights to each individual risk factor. As discussed previously, it is likely that some risk factors and specific combinations confer increased risk than others. By standardizing scores and assessing risk based on a summary score, it is assumed that each risk factor contributes equally to the development of disease.

MU System. This lab has previously attempted to quantify severity of MetS based on severity of individual risk factors (149). According to this method, each risk factor was divided into quartiles with corresponding point values assigned (0, 1, 3, or 5) according to associated risk with higher point values indicating worsening metabolic profile and increasing risk. The sum of the quartile points indicates the Metabolic Syndrome Score, and theoretically, disease risk. Two scoring systems were created by this method: a 5 variable system including only the current MetS criteria and a 9 variable system that added CRP, BMI, percent body fat, and aerobic capacity. According to this system, the 5 variable score was correlated to FG (r=0.64), WC (r=0.63), TG (r=0.34), BP (r=0.34) and inversely correlated to HDL-C (r=-0.49). The 9 variable score was significantly correlated to BMI (r=0.84), WC (r=0.63), FG (r=0.57), CRP (r=0.51), percent body fat (r=0.38), TG (r=0.38), and BP (r=0.34). Additionally, this system was strongly inversely correlated to VO2max (r=-0.71). This system may be the first true

attempt to quantify disease risk in a clinically relevant and applicable manner. This system is beneficial because it assess risk associated with increasing severity of each MetS trait. Additionally, this system is easy to implement in either a clinical or research setting. However, this system once again contributed equal weights to each MetS risk factor.

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APPENDIX B
RAW DATA

Data for Mets traits for all subjects.

Sub #	Age	Gen	WC	SBP	DBP	HDL	TG	FG	Trait #	MetS	5score
1	45	M	117.5	132	100	50.1	104.5	76.8	2	0	17.5
2	44	F	118.0	122	84	43.1	65.7	112.4	3	1	24.5
3	42	F	94.0	126	85	52.8	99.7	116.6	3	1	23.5
4	48	F	96.7	122	80	71.7	67.0	106.7	2	0	13.0
5	35	M	120.5	122	68	47.5	104.8	92.1	1	0	18.5
6	42	F	104.3	110	62	75.1	165.0	87.5	2	0	15.0
7	23	F	94.0	126	80	73.0	144.5	67.6	1	0	8.0
8	20	F	112.0	112	68	57.7	135.0	90.0	1	0	17.5
9	46	F	97.5	110	66	101.1	195.0	86.0	2	0	11.0
10	34	F	99.4	124	70	40.8	103.8	83.0	2	0	15.5
11	48	M	124.0	110	66	36.7	195.7	124.9	4	1	30.5
12	38	F	92.0	112	76	60.0	92.3	95.0	1	0	9.5
13	48	F	119.7	130	68	51.4	66.8	115.5	3	1	25.5
14	49	F	123.5	108	80	44.9	213.1	112.0	4	1	29.5
15	26	M	98.0	130	82	44.5	100.9	102.0	2	0	16.5
16	18	F	114.3	126	78	62.6	176.9	105.2	3	1	21.5
17	46	F	130.0	122	64	106.6	129.0	99.0	1	0	14.0
18	50	M	98.8	128	84	40.5	96.2	119.0	1	0	17.5
19	23	F	87.0	116	76	69.2	232.0	95.0	1	0	10.5
20	29	M	94.0	126	88	55.6	80.7	106.4	2	0	10.5
21	22	F	117.3	122	82	38.7	136.0	111.4	4	1	25.5
23	42	F	90.5	122	78	52.3	63.0	105.0	2	0	17.5
24	35	M	102.0	122	82	44.0	102.0	106.0	2	0	18.5
25	35	F	124.0	118	82	49.4	92.1	110.0	3	1	24.5
26	41	M	94.0	126	80	51.0	110.0	103.0	1	0	9.5
27	23	F	110.0	116	66	45.6	93.0	100.0	3	1	23.5
28	40	F	117.0	122	84	36.4	132.9	105.7	4	1	25.5
29	35	M	110.5	128	74	39.97	157.0	117.0	4	1	24.5
30	46	F	89.0	114	74	58.6	117.3	94.5	1	0	17.5
31	28	M	107.0	110	82	46.1	79.4	100.8	2	0	17.5
32	24	F	99.0	110	70	35.6	186.0	119.0	4	1	26.5

Sub #	Age	Gen	WC	SBP	DBP	HDL	TG	FG	Trait #	MetS	5score
33	34	M	124.0	122	82	31.8	105.6	117.6	3	1	29.5
34	44	M	108.5	110	82	43.4	134.6	114.0	2	0	18.5
35	50	F	113.0	118	80	67.7	82.9	104.0	2	0	18.5
36	46	F	96.5	122	84	54.1	93.0	121.0	2	0	21.5
37	44	F	103.3	118	72	77.1	122.1	87.4	1	0	13.0
38	30	F	98.0	116	74	43.4	98.0	89.0	2	0	15.5
39	49	F	110.8	160	96	43.9	191.3	115.0	5	1	35.5
40	46	F	111.5	116	66	44.8	151.9	106.0	4	1	26.5
41	49	F	82.5	122	80	62.9	130.0	121.0	1	0	15.5
42	44	M	109.0	140	86	56.7	55.3	110.0	3	1	18.5
43	41	F	102.0	136	86	36.0	170.2	123.0	5	1	27.5
44	22	F	119.5	130	82	59.9	201.6	123.0	4	1	32.5
45	47	F	98.5	130	82	49.8	85.9	100.0	4	1	22.5
48	49	M	102.3	124	84	46.0	226.0	102.8	3	1	22.5
49	33	F	106.0	108	76	42.4	203.9	79.0	3	1	22.5
50	27	F	101.0	130	80	51.0	139.0	108.0	3	1	20.5
51	39	F	106.0	136	84	49.7	139.9	81.0	3	1	21.5
52	46	F	97.3	116	78	49.5	85.5	97.3	2	0	15.5
52	46	F	98.0	116	80	44.2	160.0	91.0	3	1	19.5
53	38	F	102.0	122	84	50.00	125.9	94.0	1	0	14.5
54	40	F	95.0	132	84	61.0	135.0	96.0	2	0	13.5
55	30	F	114.0	100	68	40.0	111.5	97.0	2	0	20.5
56	46	F	81.0	139	89	58.0	119.0	96.0	1	0	12.5
57	27	F	98.5	120	70	45.0	142.0	80.0	2	0	15.5
58	43	F	105.5	103	67	57.7	138.0	91.0	1	0	17.5
59	45	F	114.0	106	62	44.2	138.0	70.9	2	0	18.5
60	39	F	90.0	110	68	58.0	122.0	97.0	1	0	13.5
61	24	F	94.0	110	65	47.0	126.0	85.0	2	0	16.5
63	47	F	111.5	134	79	49.0	215.0	85.0	4	1	27.5
64	20	M	106.0	124	82	42.1	160.0	77.0	2	0	14.5
66	32	F	116.0	110	70	56.9	124.0	77.0	1	0	15.5

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Sub #	Age	Gen	WC	SBP	DBP	HDL	TG	FG	Trait #	MetS	5score
67	25	F	92.5	118	72	59.7	182.7	88.0	2	0	15.5
68	21	F	110.5	118	70	38.3	98.9	86.0	2	0	19.5
69	26	F	114.5	132	88	32.4	139.9	81.1	4	1	21.5
70	25	F	98.5	108	76	46.7	84.1	88.0	2	0	15.5
71	58	F	87.0	126	76	74.6	78.0	95.0	0	0	5.0
72	30	F	90.0	112	73	50.6	83.4	86.0	1	0	12.5
73	28	M	104.0	138	86	30.7	318.6	85.9	4	1	23.5
75	21	M	105.5	120	60	39.5	421.0	117.0	4	1	29.5
76	36	F	112.0	110	76	37.0	113.0	86.0	2	0	20.5
77	26	M	112.0	112	72	44.0	116.0	95.0	1	0	13.5
78	36	F	103.5	114	64	69.0	163.0	92.0	2	0	16.5
79	47	F	102.0	116	84	56.4	201.5	100.8	3	1	22.5
80	30	F	97.3	112	78	54.5	129.4	100.0	2	0	17.5
81	25	F	91.5	114	72	76.7	62.9	85.0	1	0	8.0
82	41	F	102.0	112	74	51.0	118.0	89.0	1	0	13.5
83	36	F	88.5	102	60	55.2	132.2	96.4	1	0	13.5
84	29	F	109.5	120	68	43.1	178.0	85.9	3	1	23.5
85	21	F	115.5	117	81	52.7	94.6	78.0	1	0	15.5
86	33	M	116.5	124	82	34.0	381.0	85.0	3	1	25.5
87	31	F	113.0	126	80	52.0	194.0	80.0	2	0	18.5
88	20	M	111.0	120	70	59.0	146.0	70.0	1	0	9.5
89	29	M	88.5	130	82	42.1	156.1	79.3	2	0	10.5
90	26	F	101.0	108	70	59.8	84.0	90.0	1	0	12.5
91	27	M	126.0	123	76	30.2	218.7	96.0	3	1	25.5
92	45	M	117.0	124	88	38.4	272.2	94.0	3	1	27.5
93	31	F	113.0	126	72	61.5	109.8	104.0	1	0	19.5
94	40	F	117.0	106	76	46.7	121.0	82.5	2	0	18.5
95	21	F	99.0	104	60	42.6	66.7	84.1	2	0	13.5
96	45	F	100.0	124	82	51.5	115.2	84.0	1	0	12.5
97	44	F	102.0	120	74	51.3	118.2	86.7	1	0	14.5
98	32	F	113.3	104	60	51.4	146.3	86.7	1	0	17.5

Sub #	Age	Gen	WC	SBP	DBP	HDL	TG	FG	Trait #	MetS	5score
99	38	F	100.5	120	72	49.4	123.6	89.0	2	0	17.5
100	43	F	97.0	134	86	57.0	162.9	79.7	3	1	16.5
101	21	F	94.5	120	80	56.3	94.9	88.0	1	0	13.5
102	42	F	98.5	117	59	55.1	115.0	95.0	1	0	13.5
103	26	F	125.0	132	78	45.9	80.0	74.0	3	1	20.5
104	41	F	103.5	126	80	52.6	140.4	79.9	1	0	16.5
105	43	M	110.0	116	76	37.8	262.4	81.5	3	1	18.5
106	36	F	84.0	104	61	52.1	81.8	103.0	1	0	12.5
107	28	F	87.0	99	60	46.5	74.3	93.0	1	0	11.5
108	45	F	101.5	124	70	40.2	172.5	90.8	3	1	19.5
109	39	F	106.0	112	68	44.4	126.3	88.4	2	0	20.5
110	47	F	101.0	120	74	44.8	81.5	85.0	2	0	16.5
111	42	F	99.0	115	82	49.8	90.0	98.0	2	0	16.5
112	47	F	122.0	112	74	45.7	346.9	138.0	4	1	32.5
114	40	M	98.0	122	82	34.1	256.2	121.7	4	1	25.5
115	42	F	98.0	125	84	60.1	100.0	91.0	1	0	11.5
116	23	M	127.0	125	78	49.4	102.9	98.0	1	0	18.5
117	46	F	110.5	110	78	56.0	96.1	82.0	1	0	14.5
118	42	F	122.5	106	66	41.0	82.0	89.0	2	0	19.5
119	46	M	116.0	123	81	45.0	85.0	95.0	1	0	17.5
120	23	M	106.0	118	82	43.0	112.0	98.0	1	0	14.5
121	42	M	109.0	114	76	23.9	182.5	101.8	4	1	22.5
122	38	M	118.5	118	77	39.5	196.0	137.0	4	1	30.5
123	37	M	107.0	132	84	50.6	64.0	109.0	3	1	16.5
124	42	M	118.5	134	94	45.0	155.0	96.0	3	1	24.5
125	44	F	100.5	112	74	51.0	145.0	113.0	2	0	17.5
126	40	F	118.5	126	84	74.0	147.0	108.0	2	0	18.0
127	34	F	93.7	114	78	69.0	253.0	109.0	3	1	18.5
128	26	F	109.0	112	66	38.9	158.0	90.0	3	1	22.5
129	44	F	87.0	112	71	74.4	193.3	101.3	2	0	15.0
131	39	M	130.5	124	82	49.8	109.7	99.8	1	0	18.5

Sub #	Age	Gen	WC	SBP	DBP	HDL	TG	FG	Trait #	MetS	5score
132	30	F	97.0	119	72	57.0	116.8	97.0	1	0	13.5
134	32	F	99.0	110	76	59.6	77.0	109.2	2	0	16.5
135	46	F	128.3	108	68	49.5	121.6	104.5	3	1	24.5
136	36	F	117.0	110	78	37.4	234.9	109.3	4	1	28.5
138	25	F	113.5	118	74	39.2	150.3	97.2	3	1	22.5
139	50	F	123.5	136	94	56.2	128.7	111.0	3	1	26.5
140	45	M	112.0	121	77	33.1	318.7	105.4	4	1	25.5
141	52	M	109.8	118	80	24.6	226.3	102.8	4	1	25.5
142	25	M	97.0	119	84	59.0	93.3	93.2	0	0	6.5
143	52	F	110.0	110	74	34.3	214.2	98.5	3	1	24.5
144	29	F	117.0	124	84	43.0	252.3	107.6	4	1	29.5
145	20	M	113.5	120	80	48.3	157.0	111.5	3	1	20.5
147	49	F	92.6	110	80	68.2	107.6	107.6	2	0	15.5
148	42	F	95.0	118	80	45.5	148.8	92.4	2	0	17.5
150	31	M	114.5	130	83	43.9	124.8	93.8	2	0	16.5
152	44	F	111.5	110	70	64.9	111.5	85.6	1	0	14.5
153	48	M	116.3	130	85	36.2	94.1	90.9	3	1	22.5
155	29	F	115.5	115	82	43.4	70.6	90.5	2	0	20.5
157	24	M	116.0	129	84	47.7	172.4	92.7	2	0	20.5
158	47	M	106.0	132	82	44.8	139.2	99.1	2	0	16.5
159	23	F	100.5	120	78	51.1	127.2	83.3	1	0	12.5
160	47	M	115.0	123	81	50.9	124.0	89.8	1	0	11.5
161	41	F	116.5	100	64	53.5	251.5	144.4	3	1	29.5
163	40	F	123.0	118	76	36.1	192.9	83.8	3	1	20.5
164	45	F	108.5	126	82	58.0	92.1	95.6	1	0	17.5
165	36	M	110.0	136	96	59.3	111.0	103.3	3	1	19.5
167	45	M	120.5	138	86	41.7	159.6	96.7	3	1	22.5
168	31	F	92.5	120	78	61.0	72.9	83.8	1	0	8.5
169	38	F	117.0	114	78	76.8	175.3	85.1	2	0	15.0
170	36	F	101.5	108	72	55.9	118.6	98.4	1	0	13.5
171	26	F	124.3	120	70	51.7	202.2	92.7	2	0	22.5

Sub #	Age	Gen	WC	SBP	DBP	HDL	TG	FG	Trait #	MetS	5score
172	34	M	116.5	110	76	56.8	177.9	96.0	2	0	16.5
173	34	M	102.5	112	74	40.6	104.9	92.3	1	0	13.5
174	33	F	106.0	116	79	32.1	203.0	96.0	3	1	24.5
175	42	F	103.0	100	64	74.6	76.4	94.1	1	0	12.0
176	47	F	88.0	108	82	65.9	94.8	88.0	1	0	10.5
178	53	F	111.9	120	74	52.7	171.3	82.1	2	0	18.5
179	19	M	113.0	128	68	33.0	336.2	116.7	4	1	29.5
181	53	M	100.0	122	78	61.3	75.0	89.1	0	0	6.5
182	41	M	103.0	124	84	42.8	111.2	86.9	1	0	14.5
183	37	M	127.0	126	70	34.9	558.7	96.1	3	1	25.5
184	51	M	105.0	129	86	25.6	549.7	98.7	4	1	21.5
185	40	F	105.0	110	72	59.7	58.4	87.4	1	0	16.5
186	31	F	103.0	110	82	60.7	55.3	80.3	1	0	12.5
187	48	M	113.0	116	76	37.3	123.9	108.7	3	1	20.5
188	36	M	115.0	114	82	56.9	155.9	101.9	3	1	15.5
189	19	F	97.5	104	62	60.5	124.9	79.0	1	0	8.5
190	50	M	105.5	150	86	29.8	343.6	91.1	4	1	25.5
191	28	F	110.0	118	72	49.5	72.4	82.1	2	0	17.5
192	40	F	110.0	124	84	58.4	127.6	84.1	1	0	16.5
195	22	F	117.5	112	72	70.3	85.8	91.5	1	0	12.0
196	54	M	117.0	128	82	52.5	140.4	92.3	1	0	15.5
197	29	F	103.5	124	81	56.5	134.9	93.4	1	0	14.5
199	43	M	111.5	142	100	48.0	115.6	102.6	3	1	22.5
201	37	M	108.0	142	92	46.2	123.8	95.6	2	0	18.5
202	38	M	106.5	122	82	69.8	76.4	103.4	2	0	13.0
301	37	M	120.7	119	82	37.0	286.0	97.1	3	1	25.5
302	37	M	102.2	121	75	44.0	100.0	81.4	1	0	12.5
303	39	M	110.5	129	83	33.0	192.0	149.5	4	1	27.5
304	40	M	90.2	118	81	46.0	96.0	128.6	1	0	15.5
305	35	M	116.2	136	93	45.0	307.0	103.6	4	1	30.5
306	48	M	102.9	111	80	32.0	148.0	131.4	3	1	25.5

Sub #	Age	Gen	WC	SBP	DBP	HDL	TG	FG	Trait #	MetS	5score
307	37	M	104.1	131	71	63.0	62.0	114.3	3	1	15.0
308	31	M	109.9	122	78	46.0	167.0	89.8	2	0	16.5
309	27	M	108.6	119	80	37.0	62.0	137.9	3	1	24.5
310	39	M	101.6	124	74	33.0	134.0	90.7	2	0	17.5
311	37	M	104.1	140	95	41.0	294.0	122.9	4	1	30.5
312	32	M	120.0	131	79	50.0	100.0	111.9	3	1	21.5
313	34	M	101.6	122	86	30.0	254.0	110.5	4	1	27.5
314	36	M	106.7	127	83	40.0	75.0	120.5	3	1	21.5
315	37	M	95.9	122	90	63.0	73.0	90.6	1	0	9.0
316	36	M	108.6	126	80	31.0	336.0	107.2	4	1	25.5
317	28	M	111.8	110	70	36.0	65.0	95.5	2	0	15.5
318	35	M	104.1	133	80	40.0	86.0	122.3	4	1	23.5
319	30	M	113.7	108	70	37.0	142.0	110.6	3	1	20.5
320	27	M	114.9	130	97	33.0	174.0	88.8	4	1	23.5
321	39	M	119.4	123	82	46.0	198.0	92.6	2	0	20.5
322	43	M	111.1	121	90	38.0	198.0	124.3	5	1	31.5
323	35	M	97.8	145	78	47.0	124.0	134.5	2	0	22.5
324	46	M	105.4	125	82	39.0	142.0	103.3	3	1	21.5
325	30	M	87.6	130	70	52.0	99.0	89.9	1	0	6.5
326	32	M	99.7	130	86	40.0	76.0	78.1	2	0	13.5
327	40	M	109.2	131	85	31.0	188.0	109.3	5	1	25.5
328	36	M	109.2	138	82	43.0	214.0	109.4	4	1	24.5

Gen=gender, WC=waist circumference, SBP=systolic blood pressure, DBP=diastolic blood pressure, HDL=high density lipoprotein-cholesterol, TG=triglycerides, FG=fasting glucose, Trait #=number of metabolic syndrome traits present, MetS=presence of metabolic syndrome according to ATP III definition. 5score calculated from proposed scoring system.