

## ABSTRACT

Title of Document: **IS A NEW WAIST CIRCUMFERENCE  
AND BMI NEEDED FOR AFRICAN  
AMERICANS FOR THE DIAGNOSIS OF  
METABOLIC SYNDROME?**

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African Americans are noted as having a low prevalence metabolic syndrome (MetS), which is partly attributed to a reported use of MetS criteria, such as waist circumference that is not appropriate for this population group. The purpose of this study was: 1) to investigate the gender specific optimal waist cut off points, which best identify individuals with metabolic abnormalities consistent with MetS, and are independent of body mass index (BMI) cutoff values; 2) to determine the gender specific cutoff values of BMI in relation to multiple metabolic risk factors; and 3) to assess the prevalence of metabolic syndrome. In this cross-sectional study, NHANES data from 1999-2006 was analyzed. 1445 participants had complete variables for metabolic syndrome criteria. The waist circumference of 95 cm for males and 98 cm for females were found as appropriate cut-off values to identify central obesity. Body

mass index at which metabolic syndrome was observed was 28 kg/m<sup>2</sup> for males and 32 kg/m<sup>2</sup> for females. Using our newly estimated waist circumference thresholds, the age-adjusted prevalence of MetS was 30.9% in males and 30.3% in females. The results indicate that for the early detection of metabolic syndrome in African American adult males, a lower cutoff value of 95 cm, rather than the 102 cm currently used is needed. The metabolic syndrome abnormalities appear at higher body mass index and waist circumference among women. Based on our findings, the prevalence of metabolic syndrome is currently underestimated among African American adult males.

IS A NEW WAIST CIRCUMFERENCE AND BMI NEEDED FOR AFRICAN  
AMERICANS FOR THE DIAGNOSIS OF METABOLIC SYNDROME?

By

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## **Dedication**

I dedicate this dissertation to my parents, the late Professor Dr. Mbarutso Etienne and Madame Mukakabano Emma-Marie; to the late Dr. Ntaganzwa Paul and Madame Kantengwa Veneranda; Dr. Nshimyumukiza Jotham; Dr. Sendashonga Seth; Mr. Turahirwa Gaspard; Mr. Mutsinzi Thomas; Mr. Gasangwa Boniface and all relatives whose dreams will never die.

I also dedicate this work to my sisters, brothers, nephews, and nieces, especially to Mutagoma Emma- Allene and Kwasi Bosompem for the support and encouragement during my graduate education.

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# CHAPTER 1: INTRODUCTION

The presence of metabolic syndrome is defined as 3 or more of 5 metabolic risk factors. The latter include high blood pressure, hyperglycemia, hypertriglyceridemia, low high density lipoprotein – cholesterol and large waist circumference (1, 2). Other factors including microalbuminuria, hyperuricemia, changes in clotting factors, chronic inflammation, and fatty liver have received attention in attempt to define the syndrome. It is recognized that the most prevalent form of the clustering abnormalities of the metabolic syndrome, linked to insulin resistance, is observed in subjects with abdominal obesity, in particular with excess visceral adipose tissue (3, 4). Abdominal obesity is measured by waist circumference (WC), which is considered a better marker of abdominal fat accumulation than the body mass index due to a higher correlation with visceral adipose tissue (5). However, there is still debate on appropriate population-based WC cutoff points.

Heterogeneity of abdominal tissue composition, in particular fat mass and skeletal mass, and its association with metabolic risk factors in different ethnic groups does not allow a universal WC cutoff value (6). Thus, successful prevention and management of increasing metabolic abnormalities and related cardiovascular and type 2 diabetes illnesses require accurate identification of high-risk individuals (1). There has been a growing research interest in practical, sensitive, screening cut-off values that are appropriate for different population groups worldwide. The overall objective of these research interests is to detect obesity and relative metabolic syndrome risk criteria.

The existing cut-off values for WC were adopted by International Diabetes Federation (IDF), and National Cholesterol Education Program - Adult Treatment Panel (NCEP-ATP III). They were based on studies of Europeans with limited sample size that related WC to BMI (2, 7, 8) in men and women. The NCEP-ATPIII waist circumference  $\geq 102$  cm in men and  $\geq 88$  cm in women were predicted from the BMI of  $30 \text{ kg/m}^2$ , and the IDF WC  $\geq 94$  cm in men and  $\geq 80$  cm in women were predicted from the BMI of  $25 \text{ kg/m}^2$ . Furthermore, the data did not take into consideration other metabolic syndrome components including high blood pressure, elevated fasting blood glucose, high levels of triglycerides, and low high density lipoprotein cholesterol (HDL-C). In addition, the age, gender and ethnic dependent relationship of waist circumference to abdominal adiposity were not addressed in the initial NCEP-ATP III guidelines. For instance in other studies, cutoff values developed by NCEP-ATP III were later found to be inappropriate for certain groups, such as Asians, whose WC/BMI display higher morbidity at lower cutoff points than European Americans (6). This led researchers to question the use of universal WC cut off values. Consequently, other research suggested that an evaluation was needed to determine if the current IDF and NCEP cutoffs are sensitive indicators of risk for other ethnic groups.

Given that waist circumference cutoffs have been found to be more predictive of body fatness, fat distribution (3, 9-11) and metabolic risk factors (12) in some population groups and inappropriate for others. IDF has recognized this and proposed to lower the waist circumference cut-offs for some ethnic groups. These new IDF ethnic cut-off values were not always validated against clinical outcomes and imaging

data of visceral fat (4). Also, previous studies on WC cut off points in African Americans were limited and not inclusive of the clustering of MetS abnormalities (13-17) and depended on BMI, indicating inadequate attention to high risk central obesity.

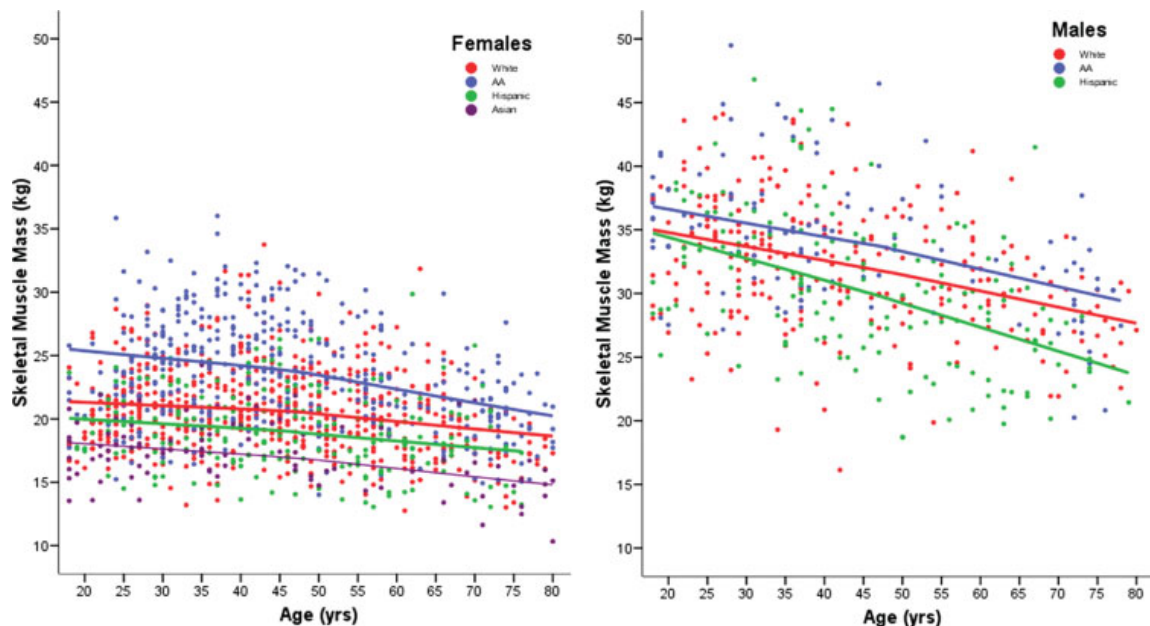
Studies show that there are health disparities between African Americans and other USA minorities indicating that they are at higher risk for morbidity and mortality from non-communicable chronic illnesses associated with metabolic syndrome. However, studies using the NCEP-ATPIII criteria report lower rates of metabolic syndrome in African Americans (AA) (12), and this is in contrast with observed disproportionately high prevalence of obesity, insulin resistance, type 2 diabetes, hypertension and heart disease (18,19). These lower rates of metabolic syndrome were attributed to lower levels of certain major components of metabolic syndrome, specifically serum high-density lipoprotein cholesterol (HDL), triglycerides (TG) (20, 21) and lower waist circumference (WC) particularly in men (7,16,17). The latter has been confirmed in a study which reported WC cutoffs 5-6 cm greater for European Americans (EA) than for AA men at every BMI level from 25 to 40 kg/m<sup>2</sup>, while no differences in WC for women was reported (16).

The use of WHO BMI to characterize CVD risk factors in determining WC was also a problem because the BMI cut off values of overweight (25 kg/m<sup>2</sup>) and obesity (30 kg/m<sup>2</sup>) had several limitations (10, 22). BMI does not separate fat mass from fat free mass (muscle, skeletal masses) (3). Also, studies have demonstrated that individuals with identical BMI values may have considerably different percentage fat levels, particularly if they vary in age, gender and ethnicity. African Americans in

particular, have been reported to have higher total bone density and muscle mass content compared to European Americans (10, 23). Other studies have observed higher values of skeletal muscle mass among African American males and females across their lifespan compared to other ethnic groups as illustrated in Figure 1 (24).

Recently, Flegal et al., 2009 investigated the relationship between BMI, WC, and waist-stature ratio (WSR) as proxies for adiposity with percentage body fat (% BF) in 12,901 individuals > 18 years of age from the 1999-2004 NHANES national sample. They confirmed differences in percentage body fat at the same BMI percentiles among different ages, sex, and ethnicity as stated previously. At a given BMI, the percentage of body fat, estimated using dual energy X-ray absorptiometry (DEXA) method, was lower in African Americans than in the European Americans, and further research was recommended to determine BMI, WC, and WSR that best classify individuals according to percentage fat (25).

**Fig1: SKELETAL MUSCLE FOR ETHNIC GROUPS BY AGE & GENDER**



(Source: Analiza M. Silva et al., 2009 - American Journal of Human Biology 1-7)

It is recognized that differences in body composition in ethnic/racial groups affect the cut off values for measurements of abdominal and overall obesity (6,26,27). Given the increased skeletal muscle mass and lower % BF, the relationship between % fat and BMI probably is different among African Americans. The change in this relationship suggests that African Americans, men in particular, may be at decreased metabolic risk compared with Europeans at a similar WC and BMI (12). Since these population groups may differ in the level of risk associated with a particular BMI/WC, research is needed to determine appropriate African American WC and BMI cut points to account for differences in (i) susceptibility to obesity-related metabolic risk factors, (ii) the relation of BMI to body fatness and fat free mass, and (iii) fat distribution.

This study focused on appropriateness of WC and BMI cut offs in African American males and females and determined optimum waist circumference and BMI based on their specific MetS risk factors. The results will contribute to the understanding of ethnic differences in metabolic syndrome profile and its implication in chronic disease disparities. To our knowledge, this will be the first study to assess the WC and BMI considering the unique characteristics of this group in terms of existent metabolic syndrome risk factors among African Americans, their higher muscle mass, bone density and lower body fat at a given BMI. It is anticipated that this study will initiate further interest to research the underlying metabolic syndrome differences and clarify the contribution of each MetS parameter to the higher prevalence of non-communicable chronic diseases among AA.

# Objectives

## Primary

1. To determine gender specific waist circumference cutoff values and body mass index for detecting the clustering of metabolic risk factors among African Americans  $\geq 20$  years independent of WHO BMI cutoff values;
2. To identify the cutoff values for waist circumference and BMI by ten-year age groups (20-29; 30-39; 40-49; 50-59; 60-69; and 70+).
3. To investigate whether there are differences in the likelihood of having metabolic syndrome based on the WC/ BMI cutoff values estimated by this study in comparison with the NCEP-ATP III, IDF and WHO cutoffs.

## Secondary

4. To identify differential metabolic risk characteristics among African Americans men and women that characterizes individuals with and without metabolic syndrome.
5. To determine the possible environmental and health determinants (dietary, nutritional biochemistries, hepatic fat accumulation markers, inflammation and thrombotic markers, hyperuricaemia, microalbuminuria, thyroid abnormalities, socioeconomic and lifestyle factors) that may contribute to MetS among African Americans adults  $\geq 20$  years when comparing those with and without metabolic syndrome.



## Research Questions

- 3.1.** What are the threshold values for waist circumference and BMI in adult African Americans that would predict the presence of individual and  $\geq 2$  metabolic syndrome risk factors (low HDL cholesterol level, high triglyceride level, high glucose level, and high blood pressure) by gender?
- 3.2.** Which WC cutoff values are appropriate among those suggested by current study, NCEP-ATP III, and IDF, for the criteria of WC as a component of the MetS syndrome among African Americans?
- 3.3.** Is there a statistically significant difference in age-adjusted prevalence of MetS among adult African Americans using a modified NCEP-ATPIII based on WC from question 3.1 compared with NCEP- ATPIII and the IDF definitions?
- 3.4.** What are the threshold values for waist circumference in adult African Americans that would predict the presence of  $\geq 2$  (3) metabolic syndrome risk factors by ten-year age groups and gender?
- 3.5.** How do the gender-specific cutoff values of WC/BMI for detecting  $\geq 2$  metabolic syndrome risk factors compare among cases with raised blood pressure (SBP  $\geq 130$  mmHg and/or  $\geq 85$  mmHg) and those without raised blood pressure using ROC analysis?
- 3.6.** Is there a statistically significant difference in MetS components and age-adjusted prevalence of  $\geq 2$  and 3 metabolic syndrome risk factors based on BMI from question 3.5 compared with WHO cutoff values ( $25\text{kg/m}^2$  and  $30\text{ kg/m}^2$ )?
- 3.7.** What are the predictors of MetS among African Americans men and women, and is there a statistically significant difference in concentration for TG and HDL among

African Americans diagnosed with  $\geq 2$  metabolic syndrome risk factors and those without MetS?

### **Supplemental Research Questions**

1. Is there a statistically significant difference in the dietary variables ( total Kcal, fat, carbohydrate, protein, fiber, vitamin C, Carotene, vitamin E, selenium, (antioxidants), Iron between individuals diagnosed with  $\geq 2$  metabolic syndrome risk factors and those without MetS?
2. Is there a statistically significant difference in serum vitamin C, Carotene, vitamin E, selenium, (antioxidants), Iron between individuals diagnosed with  $\geq 2$  metabolic syndrome risk factors and those without MetS?
3. Is there a statistically significant difference in relevant hepatic blood test - ALT alanine Aminotransferase, ALP alkaline phosphatase, GGT gamma glutamyl transferase between individuals diagnosed with  $\geq 2$  metabolic syndrome risk factors and those without MetS?
4. Is there a statistically significant difference in the inflammation and thrombotic markers, hyperuricaemia and microalbuminuria between individuals diagnosed with  $\geq 2$  metabolic syndrome risk factors and those without MetS?
5. Is there a statistically significant difference in socioeconomic variables (poverty income ratio, education, or marital status) and lifestyle factors (physical activity, alcohol, cigarette intake) between individuals diagnosed with  $\geq 2$  metabolic syndrome risk factors and those without MetS?

## CHAPTER 2: BACKGROUND AND LITERATURE REVIEW

### 2.1. Metabolic Syndrome

The term metabolic syndrome (MetS) has been developed with the purpose to assist in identification of individuals at high risk of type 2 diabetes and cardiovascular disease (CVD) in order to put in place preventative measures that can decrease their risks (28-30). Although no accepted central underlying mechanism has been agreed upon (31) for the pathogenesis of the Metabolic Syndrome, two features: the visceral obesity (32,33) and impaired insulin in particular (34-36) stand out as potential etiologies underlying the associated abnormalities of MetS. Additional independent mechanisms that have been considered as important contributors to the MetS include: prenatal and early-life influences (37); chronic stress; chronic activation of the immune system; the contributions of cytokines, hormones and other molecules produced by adipocytes; disorders of the hypothalamic–pituitary–adrenal axis; and altered glucocorticoid hormone action (31,38). Aging and hormonal changes (34) as well as potential multiple gene combinations (39) have also been implicated in the development of MetS.

Impaired insulin action in the liver, muscle and adipose tissues have been considered as the core disorders in the MetS and at the origin of risk factors that tend to cluster together as well as to occur commonly in insulin resistant individuals (36,40). The risk factors include hypertriglyceridemia, low high-density lipoprotein cholesterol (HDL-C), hyperinsulinemia, and high blood pressure (36). The simultaneous occurrence of these metabolic abnormalities has been shown to confer

higher cardiovascular disease (CVD) risk than each abnormality taken individually (41) or the sum of the abnormalities (42,43), even in the absence of hyperglycemia or diabetes (35). Patients with MetS have risk of developing CVD over the next 5 to 10 years is twice that of individuals without the syndrome. In addition, individuals with MetS have a 5 fold increase in risk for type 2 diabetes (29). A meta-analysis of longitudinal studies confirmed a 2 fold CVD risk for MetS which remained significant after controlling for classical CVD risk factors (44). Data from the NHANES III was used to quantify the increased prevalence of CHD among adults (> 50 years of age) by presence of MetS with or without diabetes. The results showed the lowest coronary heart disease (CHD) prevalence among individuals without metabolic syndrome regardless of diabetes status. A marked increase in prevalence of CHD was observed with the presence of metabolic syndrome, and the prevalence was highest when the diabetes and MetS co-exist (35). The risk of myocardial infarction, stroke, and coronary heart disease has been found to be much higher in individuals presenting with MetS than in those without the syndrome (45). Some studies, however, state that the MetS is not more useful than its collective component parts (46,47), while others argue that MetS has a longer-term prognostic value for CVD than that achieved by short-term global risk calculators (48).

The introduction of this complex of interrelated risk factors was originally called syndrome X or insulin resistant syndrome, and now it is referred to as metabolic syndrome. MetS is considered useful as a professional and public educational concept (53). Also, it represents an advance in health awareness and preventative medicine and goes beyond the classical risk factors, such as elevated

cholesterol, smoking, hypertension, and diabetes, in identifying high risk individuals (23). Although progress has been made in the management of the conventional risk factors, obesity and the metabolic syndrome have dramatically increased in the USA and other developed countries (4,49) and MetS is related to the increase in morbidity and mortality of cardiovascular diseases (32). Recent studies have shown an association between MetS and other clinical conditions including liver disease (50), cancer (51) and sleep apnea (52).

### **2.1.1 Clinical Criteria for Metabolic Syndrome**

One of the objectives of the World Health Organization (WHO) Action Plan for the Global Strategy for the Prevention and Control of Non-Communicable Disease is to develop simple strategies to identify high risk individuals, and suitable and cost effective interventions (53). The metabolic syndrome has been advocated as a simplified screening tool and as a framework for the exploration and understanding the pathophysiological association between metabolic abnormalities. The MetS allows us to quantify the comparison between different risk levels (relative risk) and to predict chronic disease risk factors within populations. Also, this screening tool facilitates comparisons between countries, guides clinical management decisions, and provides a public health message for the need to assess related risk factors (54). A recent “Debate” report of a WHO Expert Consultation has recommended that the metabolic syndrome be considered as a pre-morbid condition (54) rather than a clinical diagnosis, and should thus exclude individuals with established diabetes or known cardiovascular disease (CVD).

In the same line of preventative measures for CVD in particular and clinical management of high blood cholesterol and intensive treatment of patients with CHD, the NCEP –ATP III updated existing recommendations and added a new major feature which focuses on the primary prevention in individuals with metabolic syndrome. The preventive approach is to primary use intensified therapeutic lifestyle changes (1, 2), then drug treatment on the individual components if the latter fails (1). Moreover, NCEP-ATPIII recommended a complete lipoprotein profile (HDL cholesterol, triglycerides, total, and LDL) screening once every 5 years for individuals 20 years or older, as opposed to the initial test for HDL and total cholesterol alone.

Currently, there is no universally accepted definition of metabolic syndrome. A number of independent organizations WHO (55), NCEP-III (32), the European Group for the Study of Insulin Resistance (56) and the IDF (1) have proposed clinical criteria for clinicians for identification of high-risk individuals and for research (30). All groups agree on the core criteria of the MetS including dyslipidemia, obesity, insulin resistance, and hypertension (57). The most widely used clinical criteria for diagnosing the MetS are those proposed by IDF, and the NCEP -ATPIII. Their definitions include the risk factors listed in table I, and there is use of different cut-off points for the WC risk factor.

**Table I Clinical diagnosis of the metabolic syndrome based on criteria from the NCEP ATP III, WHO, and consensus criteria for NCEP-ATPIII and IDF**

	NCEP ATP III <sup>a</sup>	WHO <sup>b</sup>	NCEP ATP III <sup>a</sup> IDF <sup>a</sup>
<b>Fasting blood glucose</b>	≥100 mg/dL	IFG/IGT/T2DM	≥100 mg/dL (5.6 mmol/L) Or treatment of elevated glucose If above 100 mg/dL (5.6 mmol/L), OGTT strongly recommended but not necessary
<b>Abdominal obesity</b>			
□en	≥102 cm WC	>0.90 WHR (or BMI ≥30 kg/m <sup>2</sup> )	* Ethnicity specific Europids ≥ 94 cm South Asians/Chinese ≥ 90 cm Japanese ≥ 85 cm
Women	≥88 cm WC	>0.85 WHR (or BMI ≥30 kg/m <sup>2</sup> )	Europids ,South Asians/Chinese ≥ 80 cm Japanese ≥ 90cm
<b>Triglycerides</b>	≥150 mg/dL	≥1.7 mmol/L	≥150 mg/dL (1.7 mmol/L) treatment for this lipid abnormality as alternative indicator
<b>HDL Cholesterol</b>			
Men	<40 mg/dL	<0.9 mmol/L	<40 mg/dL (1.03 mmol/L) or drug treatment for reduced HDL-C
Women	<50 mg/dL	<1.0 mmol/L	<50 mg/dL (1.29 mmol/L)
<b>Blood pressure</b>	≥130/85 mm Hg	≥140/90 mm Hg	≥130/85 mm Hg Treatment of previously diagnosed hypertension
<b>Microalbuminuria</b>	-	Yes	-

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; T2DM, type 2 diabetes mellitus; NCEP ATP III, National Cholesterol Education Program Adults Adult Treatment Panel III; WC, waist circumference; WHO, World Health Organization.

WHR, waist-to-hip circumference ratio

<sup>a</sup>Three or more criteria.

<sup>b</sup>IFG/IGT/T2DM plus ≥2 criteria.

According to the WHO definition of MetS proposed in 1998, MetS is diagnosed on the basis of insulin resistance as defined by impaired fasting glucose, type 2 diabetes, or glucose intolerance plus two additional risk factors. The other risks include high body mass index or waist-to-hip circumference ratio; elevated plasma triglyceride; decreased plasma high density lipoprotein cholesterol; hypertension; or elevated urinary albumin (58).

The International Diabetes Federation (IDF), and the NCEP ATP III definition both consider that a person with MetS has at least 3 of the 5 metabolic abnormalities: elevated triglycerides, low HDL cholesterol, hypertension, elevated

fasting blood glucose or impaired fasting glucose or type 2 diabetes mellitus, and ethnic specific abdominal obesity (2,29,57). Individuals on medication for high blood pressure, type 2 diabetes, and dyslipidemia are included in the diagnosis of MetS (1). The most recent (2003) fasting blood glucose of 5.6 mmol/L or 100 mg/dL was adopted by both IDF and NCEP –ATPIII. However, the shortcoming of this new definition of impaired fasting glucose is that it would not capture a substantial number of individuals with impaired glucose tolerance as the oral glucose tolerance test (OGTT) is not required (59). Other components commonly observed among individuals with MetS such as inflammatory and thrombotic markers, hyperuricemia and microalbuminuria have been suggested to be included in further studies as criteria of the MetS (60).

Concerning the WC, IDF recommends a threshold for WC  $\geq$  94 cm for men and  $\geq$  80 cm equivalent to a BMI of 25 kg/m<sup>2</sup> for women of European origin. Ethnic specific WC thresholds included in the IDF definition were based on data linking WC to diabetes status for Asian Indians, and WC to obesity related multiple risk factors for other Asian populations (61-63). In contrast, the AHA/NHLBI recommends the WC  $\geq$  102 cm and  $\geq$  88 cm values for men and women, respectively, to define abdominal obesity. The latter values are consistent with the definition of abdominal obesity found in National Institutes of Health obesity guidelines (64), and are equivalent to a BMI of approximately 30 kg/m<sup>2</sup>. The NCEP-ATPIII recognizes that some male patients may be genetically predisposed to insulin resistance and can be diagnosed with multiple metabolic abnormalities when their waist circumference is



only marginally increased (94 -102cm). As a result, they should be targeted to change life habits (2).

In an attempt to unify the criteria, a 2009 meeting of the IDF, NHLBI, American Heart Association, World Heart Federation, International Atherosclerosis Society, and the International Association for the Study of Obesity reached an agreement that both the IDF and NCEP-ATPIII consider as alternative MetS indicators drug treatment for elevated fasting glucose, triglycerides, blood pressure and for reduced high density lipoprotein cholesterol (HDL-C) in their definitions (29). They also approved that there should not be an obligatory component and waist circumference should continue to be a useful preliminary screening tool (29). Additionally, recommendations were made that a single set of cutoff values would be implemented for the components of MetS except WC for which further research is required. For the WC, it was recommended that the IDF WC cut off values be used for non-Europeans until more data is available. For people of European origin either the AHA/NHLBI or IDF should be used. Further cross-sectional and longitudinal studies were recommended to explore the relation of WC thresholds to metabolic risk factors for both CVD and type 2 diabetes, and to reach more reliable WC cut off values for different ethnic groups, especially for women. Meanwhile, national and regional cut off values for WC would continue to be in use and three out of the 5 MetS criteria would qualify an individual as having metabolic syndrome (29).

Despite the many advantages of the MetS to identify people in both the community and clinical settings at increased risk of CVD and diabetes (1); in predicting CVD morbidity, CVD mortality, type 2 diabetes and all-cause of mortality

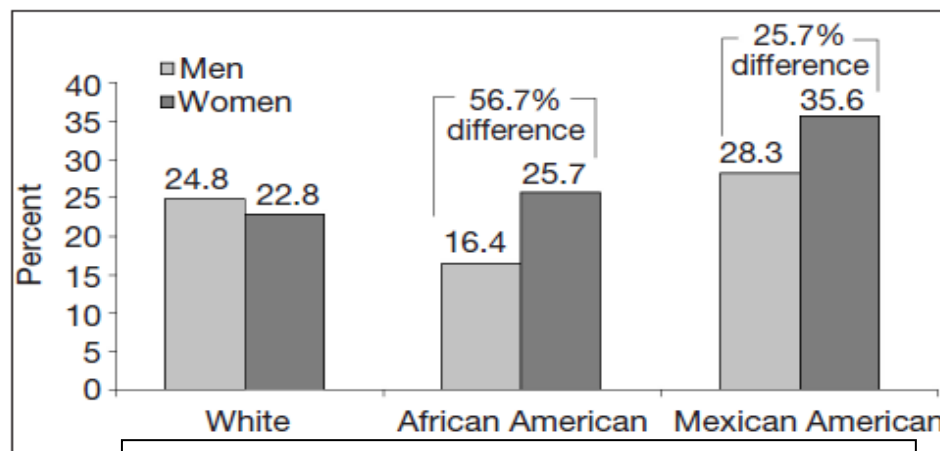
(38); and in guiding relative risk prediction and management decisions, the concept has been subjected to criticism for the lack of agreement upon a single unifying pathophysiological mechanism. Other denunciations include the omission of some risk factors for predicting diabetes and CVD (e.g., direct measure of insulin resistance, family history, C - reactive protein), and lack of established risk factor cutoffs across different populations (65). The concept has not been widely adopted in formal diagnosis and national guidelines for the prediction of DM and CVD. In 2008, however, the Japanese Government initiated a national screening program using the MetS as the point of entry in identifying people at high risk, who can benefit from intervention to reduce CVD risk (66). The recent publication of a consensus statement on the definition of the MetS, representing the views of six major organizations and societies, may prove to be a pivotal point in the development of the MetS as a tool for clinical and public health use (67).

### **2.1.2 The Prevalence of Metabolic Syndrome**

Studies have shown that the prevalence of MetS differs between genders, and among ethnic groups and countries. The condition is becoming increasingly common in many populations in developing world, and among younger age groups including overweight/obese adolescents (68,69). Differences in genetic background, diet, levels of physical activity, population age and sex all influence the prevalence of the MetS and its components (57). The MetS prevalence estimates, using different definitions, have been often found to be similar in some populations; however, in others, rates vary from one ethnic group to another (70,71).

The NHANES 1988-1994 data shows that the age-adjusted prevalence of MetS, based on ATP III criteria, was 24% in the adult US Population (2). Based on NHANES III and NCEP-ATP III criteria, the MetS affects 47 million people in the United States, with the highest rates observed in Mexican American women and the lowest rates observed in African American men. The age-adjusted prevalence of MetS was 21.6% among African Americans and similar to that of the overall US population (23.7%). However, African American women presented with higher MetS occurrence of 25.7% than their male counterparts of 16.4% (Figure 2) (72). It has been observed that the higher prevalence of MetS, among African American women, is mainly related to the disproportionate rates of high blood pressure, overall obesity, and type 2 diabetes. The data based on NHANES 1999-2000 has shown a statistically significant increase in age-adjusted national prevalence of MetS from 24% to 27.0%, with higher increase particularly observed among women. Increases in high blood pressure, waist circumference, and hypertriglyceridemia accounted for much of the raise in MetS (87).

**FIG.2. Age-adjusted prevalence of three or more risk factors for the metabolic syndrome among US adults.**



Source: J Am Med Assoc 2002; 287:356-359.

In a succeeding study that used the NCEP and the revised IDF 2005 definitions with elimination of WC as a requirement for the diagnosis of MetS, the prevalence of any 3 of 5 risk factors were estimated among US adults  $\geq 20$  years of age from NHANES 1999-2004 data (12). For the NCEP definition, the unadjusted prevalence of MetS was 35.5% for women and 34.8% for men. For the revised IDF definition, the prevalence was 38.3% and 41.9% respectively in women and men. With the use of NCEP ATPIII higher WC cut points (102cm), a lower proportion of individuals were diagnosed as having MetS compared to the revised IDF 2005 lower WC threshold. African Americans had the lowest age-adjusted prevalence of MetS (24.5%) compared to African American women and other ethnic groups (>35%). Additional data shows that in the USA, the metabolic syndrome is very common, and an estimated 44% of the adult population over 50 years of age met the NCEP criteria (35).

A recent study on racial differences in kidney function among 37,107 males with BMI  $\geq 30$  kg/m<sup>2</sup> and metabolic syndrome (73), found that European Americans were more likely to have MetS components. Hypertension was 87.1% vs. 84.8%, dyslipidemia was 81.6% vs. 66.7%, and diabetes was 42.7% vs. 34.9% in EA vs. AA respectively. However, African Americans men were more likely to have abnormal microalbuminuria levels (73).

## **2.2 Insulin Resistance**

### **2.2.1. Insulin and Macronutrient Regulation**

Insulin is an important hormone and its binding to the receptor on the liver, adipose and skeletal muscle cells, initiates activation of the downstream signaling

molecules and pathways that mediates the effects of insulin on glucose, protein, lipid metabolism and cell division, differentiation and growth (74,75). Insulin regulates the whole body glucose homeostasis by promoting glucose uptake in the muscle, adipose tissue, and inhibiting glucose production through the process of glycogenolysis and gluconeogenesis in the liver. For the regulation of lipid metabolism, insulin increases esterification of free fatty acids and fatty acid synthesis. Insulin also reduces hormone sensitive lipoprotein lipase activity that result in decreased lipolysis and free fatty acid in the circulation, and inhibits the rate of Apoprotein B and very low density lipoprotein (VLDL) synthesis in the liver (76). It is also evident that insulin increases protein synthesis and DNA replication by regulating the amino acid uptake and decreasing proteolysis (77).

In insulin resistance, the normal production of insulin does not lead to normal insulin response. As a result pancreatic beta cell secretes more insulin to compensate for the hyperglycemic status commonly observed among individuals with MetS and type 2 diabetes. Animal and human studies have suggested that hepatic insulin resistance is the underlying cause of the MetS (78) and its related metabolic abnormalities, namely dyslipidemia, and increased inflammatory factors.

### **2.2.2 Insulin Resistance, Central Obesity, and Metabolic Syndrome**

Series of metabolic studies have revealed that increased adipose tissue is associated with high levels of free fatty acids and insulin resistance (23,79). Although visceral fat depots account for a low percent of total body fat, for instance 15% in obese men (80), subjects with large visceral fat present the most severe metabolic risk profile and insulin resistance state (81,82). Studies have demonstrated that the

inflammation status associated with the increased secretion of adipokines from excess adipose tissue (49), and the alteration in free fatty acid metabolism are involved in insulin resistance pathogenesis by disrupting the insulin signaling cascade (83,84). This defect in post-receptor signaling has been indicated to be the primary cause of reduced insulin sensitivity of targeted tissues (85). Consequently, insulin resistance is then characterized by skeletal muscle and liver insulin resistance as well as the beta-cell abnormalities (86), essential elements in the pathophysiology of type 2 diabetes. Additionally, insulin resistance is associated with an increase in adipose tissue lipolytic rate, which plays an important role in pathogenesis of dyslipidemia associated with MetS (49) as discussed in the subsequent paragraph. Among obese individuals, the increased plasma insulin concentration lacks the ability to compensate for insulin resistance in adipose tissue, and these subjects present with high basal lipolytic rates and plasma NEFA concentrations (72). Insulin resistance can also cause vasoconstriction and renal sodium reabsorption, leading to high blood pressure (49).

### **2.2.3 Insulin Resistance and Dyslipidemia**

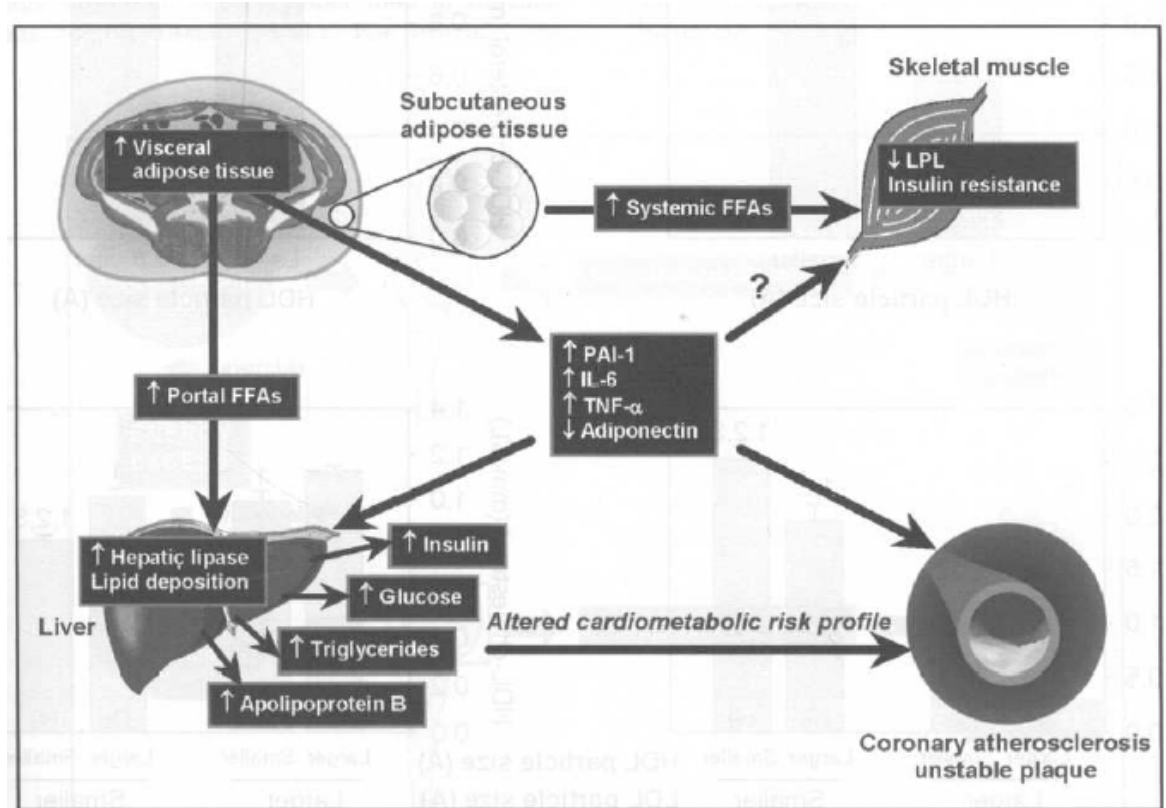
The atherogenic dyslipidemia in patients with MetS consists of a reduced level of high density lipoprotein cholesterol and elevated serum triglycerides (2,72,88). Although not cited as criteria for the diagnosis of MetS, other lipoprotein abnormalities associated with insulin resistance and increased CVD risk include an increase in small low density lipoprotein particles, apolipoprotein B, small HDL particles and postprandial accumulation of triglycerides rich remnant proteins

(29,89,90). They have also been shown to be associated with increased CVD risk (91-94).

In a normal state, the hydrolysis of triglycerides to fatty acids and glycerol in fat cells is a process regulated by several hormones and parahormones which act on cyclic adenosine monophosphate (c-AMP) formation or breakdown. In turn the c-AMP influences the activity of hormone sensitive lipase (HSL), which stimulates hydrolysis of triglycerides. The rate of lipolysis is highest in the visceral adipose tissue (VAT), intermediate in the subcutaneous abdominal fat, and low in the subcutaneous gluteal/femoral region (95).

The alteration of free fatty acid metabolism condition is characterized by adipocyte resistance to the antilipolytic effect of insulin and the impairment of FFA esterification (96, 97). Thus, the excessive non-esterified free fatty acids (NEFAs) from the lipolysis of fat cells alter the ability of insulin to (i) stimulate muscle glucose uptake, (ii) inhibit hepatic glucose production - contributing to impaired glucose tolerance (98,99), and (iii) diminish the hepatic insulin clearance as discussed earlier. Additionally, increased free fatty acid, mainly released from visceral adipocytes into the portal vein then to the liver, leads to an increase in hepatic secretion of triglycerides rich lipoproteins (VLDL) (23,100-101), in elevated plasma triglycerides concentration (102), in decreased hepatic degradation of apoprotein B and insulin - resulting in hyperapoprotein B and hyperinsulinemia. The lipid deposition and hepatic lipase in the liver are also increased (Figure3).

**Figure 3: Altered Lipid Metabolism and Insulin Resistance**



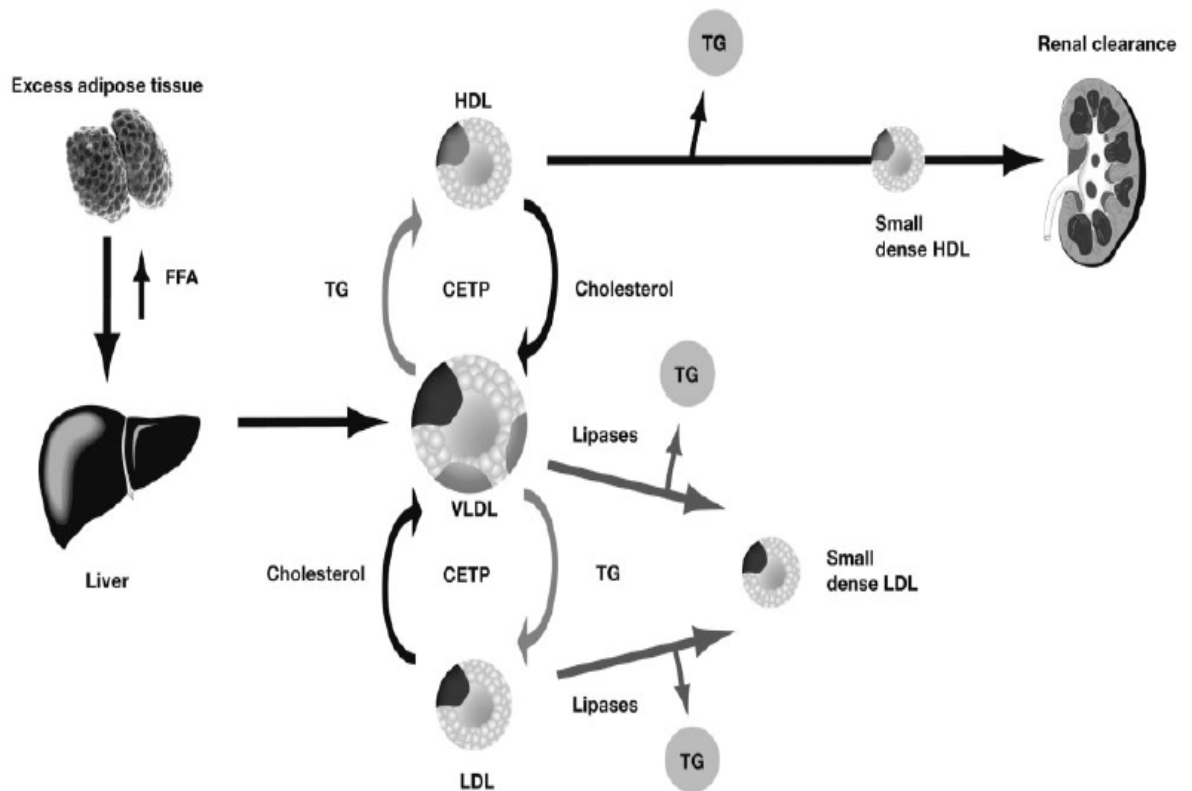
Jean Pierre Despres, *Annals of Medicine* 2006; 38: 52-63.

The high concentration of triglycerides rich lipoproteins, as seen in individuals with high visceral fat, enhances the transfer of triglycerides from VLDL to LDL and HDL, in exchange for cholesteryl esters. The effect of the increased cholesteryl ester transfer protein (CETP), in obesity, on the transfer of cholesteryl esters is presented in Figure (4). This process results in LDL and HDL particles high in TG, which are subject to lipolysis by the hepatic lipase enzyme. The increased activity of this enzyme, in viscerally obese patients (23), enhances the formation of cholesteryl ester depleted small LDL and HDL particles. This is largely responsible for the observed higher clearance of HDL and its decrease in plasma found in MetS condition (103). The discussed pattern of dyslipidemia characterized by three lipid



abnormalities: increased plasma triglyceride levels, decreased HDL-cholesterol concentrations and the presence of small, dense LDL particles are also referred to as the “atherogenic lipid triad”. They are observed in individuals with MetS or type 2 diabetes (104). It has been suggested that the clinical importance of the atherogenic lipoprotein phenotype probably exceeds that of LDL-cholesterol, due to many more patients with coronary artery disease that are found to have this trait than hypercholesterolemia (105).

**Figure 4: Mechanisms of cholesteryl ester transfer protein**



A.Bakhai et al., 2008 QJ Med 2008; 101; 767-776

It has been suggested that the role of the insulin resistance and abnormal fat distribution may vary depending on ethnic group (57). Hyatt et al., 2009 study in

premenopausal, healthy and overweight women, showed that African Americans are more hyperinsulinemic than European Americans, independent of obesity, fat distribution, and inflammation (106). The insulin resistance in AA has been reported to be highly associated with subcutaneous adipose tissue, thus the overall body fatness could be the important mediator in disease process (82,107) among African Americans men and women.

Although issues have been raised concerning the absolute cut points of plasma TG and HDL –C proposed by the NCEP-ATP III, there is ample data suggesting that these atherogenic dyslipidemia criteria are characteristic of insulin resistance and highly predictive of CVD risk, and their treatment lead to a decrease in incidence of CVD (108). In general, the distribution of triglycerides, HDL-C and TG/HDL-C ratio appear the same between adult US males and females. However, African Americans have lower levels of triglycerides and small LDL particles than EA (109), and AA men have higher levels of HDL-C than their EA counterparts (28). Among females, AAs seem to have similar or lower triglyceride concentrations and comparable HDL-C concentrations to EA females (20,110). The coexistence of insulin resistance and lower levels of triglycerides in AA has been associated with the lack of the effect of insulin resistance to hinder the increased lipoprotein lipase activity to clear the TG (20).

Stein E. et al. 2007 reported that among a sample of African Americans, only 10% of the sample (n=185 non diabetic AA 30-50 years of age) had TGs  $\geq 150$  mg/dL. Individuals with TG levels of 110-149 mg/dL ( $>110$ mg/dL) presented insulin resistance equivalent to that of the high – TG  $\geq 150$  mg/dL group and concluded that

the TG levels below the current ATPIII MetS cut off value are associated with insulin resistance. The authors suggested that a TG value of  $\geq 110$  mg/dL increased the detection of the MetS at different levels of insulin resistance (21).

#### **2.2.4. Insulin Resistance, Adipokines and Atherosclerosis**

The adipose tissue stores and releases energy rich fatty acids, and it is now recognized as an important secretory organ of bioactive proteins, namely adipokines. Increased abdominal obesity with a predominance of visceral adipose tissue is associated with an increase rate of lipid metabolism and adipokines secretion than in subcutaneous fat. The cytokine molecules produced by the adipose tissue, although many of them are produced by other cells and tissues, include interleukin-6 (IL-6), angiotensinogen, resistin, plasminogen activator inhibitor (PAI-1), and tumor necrosis factor-  $\alpha$  (TNF- $\alpha$ ). Leptin and adiponectin are exclusively produced by adipose tissue. In contrast to other adipokines, the levels of adiponectin, an anti-inflammatory and insulin sensitizer are decreased in obese individuals (112).

The rise in plasma level of the proinflammatory cytokines secreted by adipose tissue (TNF-  $\alpha$ , IL-6, and leptin, PAI-1, angiotensinogen, resistin) as well as acute-phase proteins such as c-reactive protein (CRP) increases along with increasing adipose mass. It is more evident that this state of chronic inflammation may contribute to the chronic illnesses associated with obesity, namely atherosclerosis, dyslipidemia and insulin resistance (113). Additionally, CRP is emerging as an independent and strong predictor of cardiovascular diseases (114,115).

Adipokines play crucial roles in the development of atherosclerotic plaques and insulin resistance (Figure1). The adipokines raise the migration and attachment of

monocytes in the blood vessel wall and their conversion into macrophages. The macrophages phagocytose oxidized LDL resulting in formation of lipid laden foam cells. As the foam cells accumulate in the vessel wall, they form fatty streaks which develop into atherosclerotic plaques (116). Adipokines have been shown to contribute to the increased release of non-esterified free fatty acids (NEFAs), and high levels of adipokines and NEFAs from the excess adipose tissue lead to insulin resistance (117,118). The tumor necrosis factor  $\alpha$  adipokine down regulates the insulin signaling cascade, including the expression and translocation to the cell membrane of the GLUT 4 glucose transporters. Thus, this results in impaired ability of insulin to stimulate glucose uptake by muscles and adipocytes, (117) and the ability of insulin to suppress hepatic glucose production is impaired (119).

#### **2.2.5. Insulin Resistance and Non-Alcohol Fatty Liver Disease**

Non-alcoholic fatty liver disease (NAFLD) refers to liver damage that ranges from simple fatty liver to steatohepatitis, characterized by advanced fibrosis and cirrhosis. NAFLD is defined by the accumulation of fat in the liver  $>5\%$  per liver weight with a minimum  $< 10$  g daily alcohol intake (120). Approximately 33.6% cases of NAFLD have been diagnosed in a population based on a cohort study in the USA (121). NAFLD is strongly related with insulin resistance and metabolic syndrome (122). Waist circumference, TG level and insulin resistance have been shown to be independently associated with NAFLD. The latter is the most frequent reason of elevated liver enzymes in the USA among individuals diagnosed with 2 diabetes, obesity and hyperlipidemia (123). The excess fat deposition in the liver has been associated with increased free fatty acids delivery from adipose tissues, elevated

synthesis of fatty acid via the de novo pathway, high consumption of dietary fat, and reduced clearance of VLDL particles (120).

Currently, the liver biopsy is the “gold standard” procedure to diagnose NAFLD. Due to its invasive nature, the magnetic resonance spectroscopy/imaging and the computer tomography are used instead. There are no specific biochemical markers for NAFLD, however, an increase of alanine aminotransferase (ALT) is often used. Prospective studies have indicated an increase in gamma glutamyltransferase (GGT) with NAFLD and could be considered as a surrogate marker of NAFLD (124,125).

#### **2.2.6. Hypertension and Metabolic Syndrome**

Approximately one in four persons in the United States presents with hypertension, which is twice more common in adults with diabetes than others. Obesity is possibly the common link between the two conditions; however, other factors namely autonomic dysfunction and insulin resistance may also be involved (127-129). Insulin resistance has been proposed as a strong predictor for the development of hypertension (130). It has also been documented that patients with hypertension vs. those without it, have higher proportional frequency of some established cardiovascular risk factors, namely obesity, BMI, and family history of coronary artery disease. There is emerging evidence regarding a relationship between C-reactive protein (CRP) and hypertension (131).

Elevated blood pressure contributes to microvascular and macrovascular complications, and to prevent those risks, reduction in blood pressure has been suggested. Guidelines from the American Diabetes Association and National Kidney

Foundation recommend that blood pressure be reduced to less than 130/80 mm Hg, with an optimal target of below 120/80 mm Hg in individuals with renal insufficiency and proteinuria (132,133). A new category of hypertension classification has been introduced by the 7th report of the Joint National Commission (JNC-7) on High blood pressure. systolic blood pressure between 120-139 mmHg or diastolic blood pressure that ranges between 80-89 mmHg are indicative of prehypertension, which is a strong predictor for the development of hypertension (134). Subjects with prehypertension have clinical characteristics of insulin resistance syndrome and tend to be more obese, have higher levels of fasting triglycerides and fasting insulin level > 12.2  $\mu$ U/mL, an established marker for IR (130).

Studies demonstrate that there are striking hypertension disparities among ethnic groups. High blood pressure is more common in racial/ethnic minority groups than in European Americans and the consequences of hypertension-related illnesses are greater in these groups, particularly in African Americans. African Americans develop hypertension at an earlier age and the overall mortality owed to high blood pressure and its consequences is 4 to 5 times more likely in AA than in EA (135). This is due to a combination of genetic and mainly environmental factors.

## **2.3 Abdominal Obesity**

### **2.3.1. Waist Circumference and Metabolic Syndrome**

In epidemiologic studies, WC is used as a simple measure of total abdominal size, and is considered as a valid marker of visceral fat (13), with thresholds that are gender and ethnic-group specific whenever available (29). Waist circumference is useful beyond the information provided by the BMI, and helps to identify the

subgroup of overweight/obese likely characterized by a greater accumulation of abdominal fat – the high-risk obesity phenotype (136). The WC is influenced by body composition, adipose tissue distribution, and body weight (3). Relationships between gender, sex hormones, parity, menopause, and age with WC have also been noted (137,138). Based on NHANES data, the WC is larger in adult males than females except among AA (139), and larger in older adults (60-69 years) compared to younger adults (20-29 years) up to the age of 70 (140). Accumulation and redistribution of fat from subcutaneous to visceral fat have been observed from late middle age (141) and there seems to be a preferential accumulation of visceral fat post- pregnancy (142). Other factors such as smoking and alcohol consumption have been found to be independently associated with increased WC in a longitudinal study (143).

Waist circumference has been determined to be better correlated with the abdominal visceral fat, estimated by computer tomography (5) than either BMI or WHR (8,139,144), and visceral fat has been shown to be more metabolically active than other fat stores. Visceral fat is highly associated with metabolic abnormalities including glucose intolerance, hyperinsulinemia, hypertension, high LDL, high triglycerides, and high total cholesterol. Recently, Non-Alcohol Fatty Liver (NAFL) has been identified with respect to elevated metabolic risk (145). Consequently, large WC likely reveals increased NAFL and visceral adipose tissue (VAT). The WC ability to provide a crude but effective measure of intra-abdominal fat has not been observed in all subjects. However, in the presence of an increased waist measurement, high levels of fasting triglycerides may constitute a simple but useful

marker of the inability to store the extra energy in subcutaneous adipose tissues (145). There is now evidence that the simultaneous presence of a high WC and fasting triglyceride levels, described as hypertriglyceridemic waist, may be a first step approach to identify a subgroup of individuals at higher risk of having features of the MetS such as atherogenic metabolic triad (high apolipoprotein B, small LDL, and hyperinsulinemia) (146).

Increasingly, studies have reported that central obesity is a more powerful predictor of chronic diseases, mainly hypertension, type 2 diabetes, and dyslipidemia, than overall obesity estimated with BMI (8,147-148). The abdominal obesity is highly correlated with insulin resistance and strongly correlated with the other MetS components than any other metabolic risk factor (33, 149). Among equally overweight or obese individuals, those characterized by an increase waist circumference are at increased risk of Type 2 diabetes and CVD (151), independent of the risk predicted by increased BMI. Furthermore, it has now been documented in prospective and case-control studies that individuals with a normal BMI, nevertheless, characterized by an excess visceral adipose tissue show the features of the MetS and have a two to three fold increase in CVD (152,153). Various studies have also shown that the association between WHR or waist to height ratio (WTR) and impaired glucose metabolism of type 2 diabetes was associated with larger waist circumference and smaller hip or thigh circumferences (154,155).

With the development of imaging techniques to accurately estimate abdominal adiposity and to discriminate subcutaneous fat from visceral, several studies have shown that central fat accumulation accompanied by an excess of intra-abdominal



adipose tissue is predictive of the features of the MetS (33,156), and the studies confirmed that individuals with an excess of visceral adipose tissue are characterized by the most severe metabolic abnormalities (5). Conversely, other studies found that subcutaneous abdominal fat is more closely related to insulin resistance than visceral fat (80,107).

The hypotheses relating abdominal fat stores to the MetS focus on the established and emerging understanding that visceral adipose tissue in particular is a source of tumor necrosis factor-alpha (TNF- $\alpha$ ) and of FFA directly released into the portal vein, that impair insulin action in skeletal muscle (157). In addition, excessive adipose tissue is associated with a decreased production of adiponectin which may impair insulin sensitivity (158). The adiponectin is an adipose specific collagen-like molecule, which has been found to have anti-atherosclerotic, antidiabetic, and anti-inflammatory functions. However, much work remains to be done to elucidate the complex interactions between central obesity and other MetS risk factors (159).

### **2.3.2. NCEP-ATPIII and IDF Adopted WC Cutoffs**

Waist circumference cutoffs are unrelated to height and age, and closely related with total body fat and BMI (3,281,147,160). The waist circumference values were originally determined based on a study of Europeans relating WC to BMI to identify subjects that would benefit from weight management. A random sample of men and women were recruited from the general population of North Glasgow and their WC was measured mid-way between the iliac crests and the lowest rib. The cross tabulation between WC and BMI at  $\geq 25$  kg/m<sup>2</sup> and  $\geq 30$  kg/m<sup>2</sup> was assessed. The sensitivity and specificity for WC cutoff values were subsequently estimated.

For the BMI  $\geq 25$  kg/m<sup>2</sup>, the WC were 94 cm and 80 cm, respectively, for men and women. Corresponding WC for the BMI  $\geq 30$  kg/m<sup>2</sup> were 102 cm and 88 cm. Both action levels of WC showed high sensitivity (>94%) and specificity (97%) for identifying individuals who required weight management. The lower WC thresholds of 94 cm and 80 cm represent the cut points at which health risk were increased especially for young men. The upper WC cut off values of 102 cm and 88 cm coincide with the points at which the overweight related arthritis symptoms and signs of breathlessness started to develop (144).

The cut-points for central obesity adopted in the USA by the National Institutes of Health clinical guidelines for obesity are 102 cm for men and 88 cm for women. These cut points are employed by NCEP - ATP III to define central obesity (2). In Europe, the WC of 94 cm in men and 80 cm in women are being used (57). The issue of whether these cutoff points might not be appropriate for different ethnic groups has not been settled, and the relationship between WC and BMI in Europeans may not apply to other ethnic groups (7,13,108,161). In recent years, some countries and organizations have estimated ethnic specific WC guidelines for instance for Asians and central and south Americans (7).

### **2.3.3. Prevalence of Abdominal Obesity and Average WC in the USA**

An earlier study (Osokun et al, 2000) using NHANES III data shows ethnic differences in the prevalence of central obesity (102cm) across age groups (17-39; 40-59, and 60-90). European Americans (EA) men had significantly higher prevalence of central obesity (14.1%, 30.5% and 50.6%) compared to African Americans (AA)

(5.5%; 11.7%, 37.6%). Among women, the prevalence of central obesity (88cm) was 50%, 57.8%, and 57.4%, respectively, in EA, AA, and Hispanic Americans (HA) (17).

A recent study, comparing ten year trends in WC and BMI in the USA, shows that for both NHANES III (1988-1994) and NHANES 1999-2004, AA men have a lower mean WC than EA (91.9 and 95.7 cm in AA vs. 96.3 and 100.9 in EA). Over time, the difference in mean WC seems to have widened when comparing European Americans to African Americans (e.g., 4.4 cm vs 5.2 cm in men). Conversely, among females, the highest increase in mean WC was observed among AA (92.6 -98.4cm) vs. the EA (88 -92.7 cm) and the disparity in mean WC increased from 4.6 to 5.7 cm. Moreover, the ten year trends assessment in WC and BMI showed that the largest absolute increase in mean of WC and BMI in the USA population was constantly observed among the youngest adult (20-29 years), those aged 60-69, and AA females ( 162).

#### **2.3.4. Racial Differences in Visceral and Subcutaneous Adipose Tissue**

Ethnic differences in the relationship of body fat and visceral adipose tissue have been reported. At any level of total body fat, European Americans are more prone to elevated visceral fat deposition than African Americans (163). In the Health, Risk Factors, Exercise Training, and Genetics (HERITAGE) study of 723 healthy and sedentary AA and EA adults, Despres et al., 2000 observed an average VAT of 109 and 74 cm<sup>2</sup> among EA men and women respectively, while the corresponding numbers were 74 and 67 cm<sup>2</sup> for AA. Within the African American group, despite higher total body fat among African American women than men, there was no gender

difference in absolute amount of visceral fat, and women were less prone to visceral fat accumulation than were men. Although both AA and EA men had similar body fat mass and BMI, EA showed significantly higher VAT than AA men. Among women, both EA and AA groups had similar levels of VAT. However, AA women had higher BMI, body fat, subcutaneous fat, body weight, WC, and %BF than their EA counterparts. Other studies have also reported that AA women had lower amounts of VAT for a given waist circumference, BMI, or waist to hip ratio (WHR) than EA women (164,165).

The findings comparing AA and EA were confirmed in a recent small sample study among both men and women from AA and EA. Although age, BMI, WC, WHR, and sagittal diameter did not differ among groups in either men or women, VAT was significantly lower in AA men and women (174). In addition, similar or greater concentrations of selected inflammatory biomarkers (fibrinogen, CRP, IL -6) were observed among AA. The researchers also found that SAT was more consistently associated with inflammatory markers after controlling for age, and VAT; suggesting a relationship between increased rates of inflammation and related diseases, including insulin resistance and type 2 diabetes. Further research was recommended to assess the generalizability of their findings in a larger sample of different age, health status and locations.

### **2.3.5. Estimated WC among African Americans**

In the Sumner et al., 2008 study, the authors determined the WC in African Americans which would best predict the insulin resistance (IR) based on a relatively small, convenient sample of healthy individuals 20-50 years old. Their focus was on

the relationship of WC to insulin resistance (IR) and not MetS markers. Their rationale was that due to close association of visceral fat with both IR and WC, they could speculate that WC could be a marker of IR. Sixty eight men and 63 women participated in the study and their WC was measured and a mean of three measurements was recorded. WC and BMI cut-points that identified IR, as well as the WC prediction of BMI were investigated. WC was examined at 2 cm increment from  $\geq 80$  to  $\geq 108$  cm. The WC thresholds that optimally predicted the IR were 102 cm in men and 98 cm in women. This study did not consider all the MetS risk factors, and suggest a different WC for women. This study could not show that those individuals with WC consistent with IR were at highest risk of MetS (13).

Other studies have also suggested different WC cutoff values. Diaz et al., 2007 examined the differences in the prevalence of diabetes and its association with WC, WHR, and BMI in different ethnic groups for adults  $\geq 20$  years of age, using NHANES 2003-2004 and Health Survey for England data. Unweighted samples were used. The data was stratified into two age groups ( $< 40$  and  $\geq 40$  years) as above 40 years there is an increased risk of developing diabetes. The sample of individuals  $< 40$  years who had diabetes was too small to predict the WC cutoff values for this group. The optimum cut points predicting diabetes among adults  $\geq 40$  years old was 108.9 cm (42.9 in) for AA men and 104.6 cm (41.2 in) for AA women. In terms of BMI the cut points were 31.7 kg/m<sup>2</sup> for men and 27.7 kg/m<sup>2</sup> for women (14).

Okosun et al., 1999 utilized the NHANES III data to assess the ability of the NCEP ATPIII WC cut points of 102cm and 88 cm in predicting correctly dyslipidemia, type 2 diabetes, and hypertension in only overweight adults (BMI 25-

29.9 kg/m<sup>2</sup>) who were 20-90 years of age. WC had been measured at midpoint between the rib and the top of the iliac crest. The other metabolic markers were defined as: total cholesterol  $\geq 240$ mg/dL; HDL  $< 35$  mg/dL; LDL-C  $\geq 130$  mg/dL; triglycerides  $\geq 200$ mg/dL; fasting blood glucose  $\geq 126$  mg/dl or use of hypoglycemic medication or insulin; a 2 hour post load oral glucose tolerance test  $>200$  mg/dL; systolic blood pressure  $\geq 140$  and diastolic blood pressure  $\geq 90$  or current use of anti-hypertensive medication. The analyses were performed by age groups including young (17-39), middle age (40-59), and elderly (60-90years). Among AA men the sensitivity of the 102 cm was only elevated for the LDL (46-80), and lower for the other metabolic risk (20- $<40$ ). However, sensitivity tended to increase with age. Given the low sensitivity of the WC measures, the study recommends further studies to determine the specific WC cut-points by ethnic group (15).

Another study from Okosun et al., 2000 examined the abdominal fat or WC values associated with the established BMI cut off points for overweight and obesity among individuals 17-90 years, using NHANES III data. Linear regression analysis was carried out to estimate the gender and ethnic specific WC corresponding to 25-29.9kg/m<sup>2</sup> and  $\geq 30$  kg/m<sup>2</sup>, also a ROC curve technique was run to determine WC corresponding to BMI cutoff values specified above. The results show that AA men had similar BMI and mean weight compared to EA, but AA women had significantly higher BMI and mean body weight than their EA counterparts. AA men and women had lower WC values at given levels of overweight and obesity. For the overweight individuals, the authors recommended the WC of 86-87 cm and 91-92 cm,

respectively, in women and men. The analogous values for obesity were 97 cm for women and 101-103 cm for men (17).

Zhu et al., 2005 assessed the WC cut off values for identifying one or more of the three cardiovascular disease risk factors in different ethnic groups based on NHANES III data. The risk factors were defined as high blood pressure SBP  $\geq$  140 mmHg and DBP  $\geq$  90 mmHg or current use of anti-hypertensive medication; high plasma glucose  $>$  125mg/dL or use of medication; dyslipidemia : Low HDL  $<$  35 mg/dL for men and  $<$  45 mg/dL for women, and LDL concentrations  $\geq$  160 mg/dL or currently on hypercholesterolemia medications. The WC corresponding to conventional BMI of 18.5, 25, 30, 35, 40 kg/m<sup>2</sup> with one or more CVD were similar in AA, EA and Mexican American women and were 70, 83, 94, 104, and 115 cm respectively. The equivalent values in men varied among different ethnic groups. The WC cut offs were 5-6 cm higher for EA than for AA at every BMI level between 25-40 kg/m<sup>2</sup>. The authors also estimated the WC corresponding to 25 and 30 kg/m<sup>2</sup> when one or more Metabolic syndrome parameters were present. Among overweight AA, the WC were 86 cm for men and 83 cm for women, while for obese individuals the estimated WC were 97 cm for men and 91 cm for women (16).

Based on the above studies, some age categories and/or non-overweight or obese individuals with high WC and increased MetS risk were excluded from the analysis. There is need to identify WC on the basis of their empirical relation with obesity related metabolic risk factors, rather than WC values that identify cut off values corresponding to BMI from European populations. Additionally, in both females and males, WC increases with age largely due to gain in body weight and the WC are

also seen with aging in the absence of weight gain. As the age increases so do risk factors of chronic illnesses, thus, an assessment of the need for age specific WC cutoffs in adults will be carried out in consideration of disease risk factors. I propose to (1) investigate the sex specific optimal waist cut points which best identify individuals with metabolic abnormalities consistent with the metabolic syndrome among African Americans  $\geq 20$  years old independent of BMI cutoff values; (2) evaluate which WC cutoffs are appropriate among the different cutoff points, including those proposed by the NCEP and IDF; (3) determine the gender specific cutoff values of BMI in relation to multiple metabolic risk factors among African Americans; (4) identify the threshold values for waist circumference and BMI by ten-year age groups (20-29; 30-39; 40-49; 50-59; 60-69; and 70+). (5) Compare the discriminate gender specific cut off values of WC and BMI for detecting metabolic risk factors between cases with and without elevated blood pressure. Raised blood pressure is the most common component of the MetS among AA. We will assess if the metabolic features differ between those who have raised BP and those who do not.

## **2.4 Obesity**

### **2.4.1. Body Mass Index Categories**

Excessive body fat, overweight and obesity are associated with increased mortality and morbidity (166). In the absence of simple methods to measure total body fat, the assessment and classification of overweight and obesity are dependent on practical definitions that have been established based on body mass index or Quetelet's Index which relates weight to height (weight/(kg)/height (m<sup>2</sup>). As there are



no established cut-off points for fat mass or % body fat to translate into cut-offs for BMI, The WHO Expert Committee (167) and the 1997 WHO Expert Consultation (161) reports led to the classification of the categories of BMI (Table).

### CLASSIFICATION OF BMI

CLASSIFY ACCORDING TO BMI	Principal cutoffs BMI Kg/m <sup>2</sup>	Additional cut-offs BMI Kg/m <sup>2</sup>
<b>NORMAL</b>	18.50-24.99	18.50-22.99 23.00 -24.99
<b>OVERWEIGHT</b> <b>Pre-obese</b>	<b>≥25.00</b> 25.00-29.99	<b>≥25.00</b> 25.00-27.49 27.50-29.99
<b>OBESE</b> <b>Class I</b>	<b>≥ 30.00</b> 30.00-34.99	<b>≥ 30.00</b> 30.00-34.99 32.50-34.99
<b>Class II</b>	35.00-39.99	35.00-37.49 37.50-39.99
<b>Class III</b>	<b>≥40.00</b>	<b>≥40.00</b>

Sources: WHO 1995, WHO, 2000 and WHO 2004.

The WHO recommends international use of the BMI cut-offs with awareness that the health risk at a given BMI would vary in association with body build and proportions, also within and across populations (161). Moreover, BMI cut-off points should be interpreted in combination with other morbidity and mortality risk factors (HTN, serum lipids, impaired glucose metabolism, type of fat distribution, smoking, disease etc...) (167) to limit the misclassification due to non-similar contributions of bone mass, muscle mass, and fluid to body weight (168).

The rationale behind the BMI definitions is based upon epidemiological data that shows increased mortality with BMI above 25 kg/m<sup>2</sup> (167,169-172). The increase

in mortality, however, appears modest until a BMI of 30 kg/m<sup>2</sup> is attained. Individuals with a BMI of  $\geq 30$  kg/m<sup>2</sup> have a mortality rate from all causes, and CVD in particular, 50-100 percent above those with normal range of BMI – 20-25 kg/m<sup>2</sup> (167,171). These cut points were derived primarily in European populations to correspond to risk thresholds for a wide range of chronic diseases and mortality (173) and there has been ongoing debate as to whether these criteria for obesity and overweight are appropriate for non-European populations as they do not account for difference in body fat distribution, and the relation of body size and composition with health outcomes (25).

Some of the concerns have been that the cutoff points for overweight and obesity considerably underestimate obesity related health issues among Asian populations and might overestimate risk in Pacific populations (79), consequently the BMI should be lowered for Asian, and BMI standards should be higher for the Pacific Island populations (Samoa) than those recommended by WHO (174). In 2000, the International Association for the Study of Obesity (IASO), the International Obesity Task Force (IOFT), and the WHO proposed the cutoff points of 23 to 24.9 kg/m<sup>2</sup> for being overweight and  $\geq 25.0$  kg/m<sup>2</sup> for obesity in adult Asians (175). In 2002, the WHO expert consultation reported lack of universal BMI values for overweight and obese in all Asian populations. In an addition to the established cut-off points WHO, the expert committee provided in 2002 new cut-off points of  $\geq 23$  kg/m<sup>2</sup> as increased risk and  $\geq 27.5$  kg/m<sup>2</sup> for high risk thresholds for public health intervention. (79).

Among African Americans, available cohort studies state that adiposity may be a less important predictor of mortality among AA than among EA, especially

among women. In individuals who never smoked and without history of disease, the association between a high BMI and elevated risk of death was observed to be more moderate among AA men and women, a small increase in risk of death was found only at BMI 35.0 or higher (176). Two large U.S. surveys – the NHANES and the NHIS showed that the BMI-related to increased mortality begins at a 1 to 3 kg/m<sup>2</sup> higher BMI level among African Americans than among European Americans. The BMI associated with minimum mortality was 26.8 kg/m<sup>2</sup> for AA women and 27.1 kg/m<sup>2</sup> for AA men compared to 24.3 kg/m<sup>2</sup> and 24.8 kg/m<sup>2</sup> in EA women and men respectively (177). Among African American women, high BMI has been suggested to be less hazardous to health (WHO 1995- 3) and central obesity may be less strongly associated with CVD and DM risk factors among AA women compare to EA (167).

#### **2.4.2. BMI and Aging**

Longitudinal studies have demonstrated the association of body fat gain with age across cohorts with different age ranges. In general, the average BMI increase was largest in the younger subjects and African American women (mean age 29 years). This increase of BMI throughout the greater part of adulthood was related to the increase in both muscle mass and body fat (3). In the Coronary Artery Risk Development in Young Adults study of a young cohort (18-30 years), the average increase in BMI over 10 years period was 2-4kg/m<sup>2</sup> (178). Among African Americans males and females, the increase was 3.2 kg/m<sup>2</sup> and 4.1 kg/m<sup>2</sup>, respectively. Corresponding BMI increase among European Americans were 2.3 kg/m<sup>2</sup> in males

and 2.4 kg/m<sup>2</sup> in females. In the Atherosclerosis in Communities study, the middle aged 45-64 years group had a BMI increase on average 1kg/m<sup>2</sup> and was larger in the younger participants after 9 years of follow up (179).

BMI appears to increase with age until the 70 years of age and then is reversed at older age (180). At older age, the changes in BMI are associated with the decrease in muscle mass, and fat mass is often increasing (181). Other studies have shown a decline in size of adipose depots with aging probably due to the reduced capacity of pre-adipocytes to mature. This is accompanied by accumulation of fat outside adipose tissue such as in muscles, liver and other sites possibly leading to the dysfunction of those tissues (150).

## CHAPTER 3: RESEARCH DESIGN AND METHODS

### 3.1. Survey Description and Sample Design

The National Health and Nutrition Examination Surveys (NHANES) program produces health and nutritional data on children and adults in the United States. The program was initiated in 1960s by the National Center for Health Statistics (NCHS), which is part of the Centers for Disease Control and Prevention (CDC). Since early 1960s NHANES has conducted a series of periodic surveys, however, in 1999, the program was designed to become a continuous annual survey with evolving focus to address emerging health and nutritional needs. The NHANES uses complex, stratified, multi-stage, clustered samples of civilian, non-institutionalized populations. Yearly, a nationally representative sample of about 7,000 individuals of all ages is selected in households across the United States. African Americans, Mexican Americans, adolescents aged 12-19 years, and persons aged  $\geq 60$  years are oversampled to generate more precise estimates for these groups. A detailed description of design specifications can be obtained elsewhere (182).

The survey consists of an interview in the household followed by a clinical examination in a mobile examination center (MEC). The NHANES questionnaires are administered using Computer Assisted Personal Interviewing (CAPI) and the Audio Computerized Self-Administered (A-CASI). The questions include demographic, socioeconomic, dietary, and health-related questions. At the completion of data collection, the interview data files are transmitted electronically to a central survey database system. In mobile examination center, the examinations are conducted by a physician and other highly trained medical personnel. The medical

tests include physical examination, blood and urinary laboratory tests, X-rays, and other health measurements and interviews. Detailed information on administering questionnaires, examination instructions, specimen collection and processing, and quality control systems are discussed in the Survey Operations Manuals and Consent Documents (183-186). NHANES studies undergo institutional review board approval and the respondents sign a Household Interview Consent form prior to the start of the interview. Other Consent/Assent and Parental Permission for the Examination at the Mobile Exam Center and for Specimen Storage and Continuing Studies are completed by participants as well.

### **3.2. Data Availability and Use of Sample Weights**

The NHANES datasets and related documentations are available on the following website [http://www.cdc.gov/nchs/nhanes/nhanes\\_questionnaires.htm](http://www.cdc.gov/nchs/nhanes/nhanes_questionnaires.htm) and were downloaded for analysis. Data are released in two year cycles described as NHANES 1999-2000, NHANES 2001-2002, NHANES 2003-2004 etc, and in component-specific data files. For the analysis of data, 4 year cycles of the continuous NHANES were combined, hence increasing the sample size and analytic options. Variables included in this study were extracted from the demographics, examination, laboratory, and questionnaire data files. The variables were selected based on the waist circumference/BMI association with the metabolic abnormalities as already discussed in detail in the literature review section. The sequence or identification numbers allowed the extraction of variables of interest from each of the data files and were merged to form the final data set. The variables include age, gender, poverty income ratio, WC, BMI, MetS components, dietary variables, hepatic

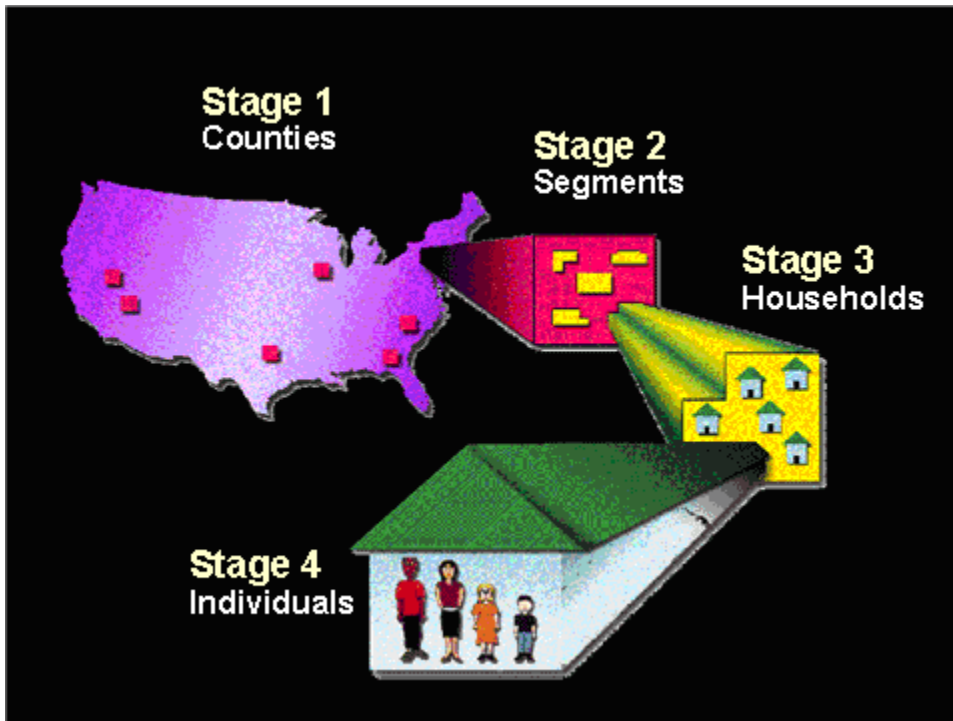
markers for nonalcoholic fatty liver disease, C - reactive protein and prothrombotic state, microalbuminuria, and hyperuricemia.

During sampling, each participant did not have the same probability of selection; there was large oversampling of adolescents aged 12-19 years, African Americans, Mexican Americans, low income European Americans and older persons (187). Because of the complex multi-stage probability sample design, the sample weights were applied in data analysis to produce unbiased population estimates (188). These sample weights can be considered as measures of the number of persons the particular sample observations represent in the population. They also reflect the differential probabilities of selection and the adjustment for non-response and post-stratification to match the 2000 U.S. Census population (187).

Additional aspects of the design that were taken into consideration in data analyses are the strata and primary sampling units (PSUs) pairings from the sample design. The strata were defined by geography and proportions of minority populations and most strata contain two PSUs. The primary sampling units were normally single counties, with small counties combined to meet a minimum population size. The PSUs were further divided into segments and a sample of households and individuals are randomly drawn within each segment (Figure 5). The strata and PSU represent the sampling units and were used to produce unbiased variance and sampling error estimates (214). Currently, the National Center for Health Statistics (NCHS) recommends the utilization of the Taylor Series Linearization methods (TSL) to estimate variance in all NHANES surveys. Statistical software packages for instance

STATA, SAS, SPSS and SUDAAN can all be utilized to estimate the variance by TSL methods (189).

**Figure 5: NHANES Sampling Procedure**



Source: NHANES

### 3.3. Statistical Analysis

#### 3.3.1. Statistical Software Package

SAS 9.2 software was used to prepare data for analysis, including sorting, extracting, merging, and assumptions testing of the data. STATA 10.1 or 11.1 versions were also utilized in data analysis and have advanced tools to manage specialized data such as survey data with complex sampling structure (191).



### **3.3.2. Study Sample**

A Nationally representative cross-sectional sample of 4415 adults African Americans civilian  $\geq 20$  y were selected from the NHANES 1999-2006 data. Participants with at least one missing parameter in anthropometric, blood pressure or metabolic criteria measurements were excluded from all analyses. Subjects who would have fasted less than 8 hours prior to blood tests were not included in the analysis. Pregnant as well as subjects with cancer were also excluded during data analysis.

### **3.3.3. Variables**

#### **Definition of multiple metabolic risk factors**

In order to determine the WC/BMI among African Americans, participants with two or more of the four NCEP-ATP III metabolic syndrome criteria were defined as having multiple risk factors. The criteria include hyperglycemia (fasting blood glucose  $\geq 100$  mg/dL or use of hypoglycemic medication); dyslipidemia (Triglycerides  $\geq 150$  mg/dL, HDL-cholesterol  $< 40$  mg/dL for men and  $< 50$ mg/dL for women, or current antidyslipidemia medication), and high blood pressure (SBP  $\geq 130$  mmHg and or DBP  $\geq 85$  mmHg, or use of antihypertensive medication). We considered the presence of multiple MetS risk factors as an outcome variable of the ROC analysis to obtain waist circumference cutoffs.

#### **Anthropometric, laboratory measurements, and body composition**

The NHANES weight, height were captured electronically from the measuring instruments to minimize possible data entry errors. Experienced trainers and observers monitored technician performance in the field. Standards procedures that

were followed for the anthropometric measurements have been reported in the Anthropometry Procedures Manual and the Anthropometric Standardization Reference manual (183). Body mass index was calculated using the weight (kg) divided by the square of height (m<sup>2</sup>). Abdominal obesity (WC) was measured to the nearest 0.1 cm using a steel measuring tape at the high point of the iliac crest during minimal respiration. Up to four blood pressure readings were measured using a standard mercury sphygmomanometer, with a subject sitting on a chair after at least a five-minute rest. For participants with three or four readings, the average of the last two was used to establish the blood pressure status. The reported average was used in this analysis. When only two measurements were taken, the last one was used.

Details of the laboratory procedures for MetS components are discussed elsewhere (190). Fasting blood glucose concentration was quantified using an enzymatic reaction. HDL-C was estimated after the precipitation of other lipoproteins using a heparin-manganese chloride mixture. Serum triglyceride levels were measured enzymatically after hydrolyzation to glycerol. C reactive protein concentrations were measured by latex-enhanced nephelometry on a BN II nephelometer (Dade Behring Inc., Deerfield IL).

The whole-body DEXA scans were obtained using a Hologic QDR 4500A fan-beam densitometer (Hologic Inc, Bedford, MA). Pregnant subjects were excluded from scanning. A number of participants had missing valid DXA data related to implants (pacemakers, stents, breast augmentation and hip replacements) and higher BMI levels. DXA scanner cannot penetrate much thicker than 15 cm adiposity and some of the implants would have been appeared as dense bone and additional lean

soft tissues. Because data were not missing at random DXA missing values were estimated. Multiple imputations (M=5) were performed using sequential regression multivariate imputation within 10 age-by-sex groups.

### **Supplemental Analysis Variables**

Supplementary analysis was carried out to compare individuals with presence of MetS and those without MetS in terms of dietary, serum nutrients, socio-economic, lifestyle factors, inflammation and thrombotic markers, hyperuricemia, microalbuminuria, hepatic biomarkers related to nonalcoholic fatty liver disease (NAFLD).

### **Dietary Variables**

Dietary and lifestyle variables related to the WC and BMI was considered. These include total Kcal, fat/saturated fat, carbohydrate, protein, fiber, and antioxidants (vit C, carotene, vit E, and selenium). Lifestyle factors included physical activity, alcohol, and cigarette intake. Studies have suggested that the accumulation of excessive body fat has been associated with increased oxidative stress, a potential early instigator of obesity associated metabolic syndrome (217). Thus, nutrition biochemistries of antioxidants namely serum vitamin C, carotene, vitamin E, selenium were also utilized during analysis and compared among individuals with and without MetS.

### **Socio Economic Variables**

To assess the socio-economic status of a family, poverty income ratio (PIR), education, and marital status variables were utilized. PIR values for NHANES participants were computed using the family income divide by the family's appropriate poverty threshold (US Census Bureau, 2007). A PIR value of less than

1.0 is below the official poverty threshold while the PIR of  $\geq 1.00$  indicate income above the poverty level.

**HEPATIC MARKERS FOR NAFLD:** In the general population, all MetS components have been shown to correlate with fatty liver, a characteristic of the nonalcoholic fatty liver disease (NAFLD) (50). The latter has been called the hepatic component of MS (192-194). Most cases with NAFLD present with an elevated alanine aminotransferase (ALT) enzyme activity, thus ALT is used as a marker of NAFLD (195). Recent studies have also indicated that gamma-glutamyl transferase (GGT) is also associated with NAFLD, and ALT, GGT, and alkaline phosphatase (AP) are strongly correlated to the prevalence of the MetS (194,195). The strongest contributors for the association of MetS with hepatic enzymes have been shown to be central obesity, elevated triglycerides and fasting glucose. For AP, low HDL – cholesterol concentrations have been found with significant impact (197). The level of ALT, GGT and AP enzymes were assessed in the study.

**C-REACTIVE PROTEIN:** is one of the measures of the body's response to inflammation from chronic conditions such as arthritis, and environmental exposure to agents such as tobacco smoke. Also, the CRP reflects the acute phase response to an infectious disease or other causes of tissue damage and inflammation. Cytokines generated by inflammatory cells enter the systemic circulation where they stimulate the liver to release C - reactive protein. Levels of the inflammatory marker CPR are increased in subjects with MetS, and are associated with the individual components of the MetS (198). Studies have shown that AAs have higher levels of CRP than EA. The CRP levels have been shown higher in AA women than AA men, EA men and

women with a median CRP of 3.5 vs. 2.1, 3.2 and 1.7 mg/l, respectively (199). The significance was  $p < 0.001$  for each comparison to AA women.

**PROTHROMBOTIC STATE:** An increase in plasminogen activator inhibitor-1 and coagulation factors, referred to as a prothrombotic state, tends to occur more frequently in AAs. Fibrinogen is an essential blood-clotting factor and is also involved in other functions including smooth muscle proliferation and platelet aggregation. It is emerging as an important risk factor for CVD and this measure was included to assess its association with MetS syndrome. Fibrinogen levels have been found to be higher among African Americans than EA, particularly in subjects with a family history of diabetes and CHD (200,201). However, fibrinolysis levels have been found to be enhanced in African Americans (200) as well. In the NHANES data fibrinogen values are available for participants aged 40 years and older.

**MICROALBUMINURIA:** reflects transvascular albumin leakage related to abnormalities of endothelial function (202). Microalbuminuria has been linked to a great risk for future CVD and mortality, atherosclerosis, renal disease, and all-causes of mortality (203). Several studies have disclosed that MetS is independently associated with an increased risk for chronic kidney disease and microalbuminuria (204,205). The prevalence of microalbuminuria increases with the number of components of MetS, and particularly high plasma glucose, high blood pressure and obesity have been shown to be the major risk factors for microalbuminuria (203). The inclusion of microalbuminuria as part of MetS has been suggested in some studies (203,206) and WHO definition of MetS include microalbuminuria as one of the components.

**HYPERURICEMIA:** It has been suggested as a simple marker of the metabolic syndrome (207,209), and the serum urate increases with the number of components of the MetS condition. Insulin resistance has been noted to induce the low excretion type hyperuricemia (210) thus; the reduced renal excretion of urate among patients with the metabolic syndrome may explain the increased frequency of hyperuricemia. Additionally, studies have shown that visceral fat accumulation has been found to cause the hyper synthetic type hyperuricemia through elevated fatty acid influx into the liver (211,212).

### 3.3.4. Data Analysis

The distribution and normality of continuous variables was assessed and necessary variable transformation applied. Basic descriptive statistics including mean values for general characteristics, anthropometric profiles, body composition values, and the 5 components of MetS were estimated by gender and age groups. Age was grouped by ten year age categories starting from 20-29, and for older adults age in years was top coded at  $\geq 70$  years of age. The age grouping was related to differences in absolute increase in WC and BMI in the population (149). To assess differences in the weighted values of means and frequencies between women and men, and individuals with and without MetS, student's t-test and Rao-Scott chi-square test were carried out.

The receiver operator characteristics (ROC) curve analysis was used to determine cutoff points of WC/BMI by gender and by ten-year age groups corresponding to; (i) whether participants have individual or  $\geq 2$  MetS risk factors defined by NCEP-ATPIII (except for WC) such as high blood pressure,

hyperglycaemia, raised triglycerides, and low HDL-cholesterol; and (ii) whether participants stratified by high blood pressure status ( raise BP : SBP  $\geq$  130 mmHg and/or DBP  $\geq$  85 mmHg and non-raised BP) have  $\geq$  2 MetS risk factors. ROC analysis was also used, in addition to simple regression, to identify WC values corresponding to the determined BMI cut-off values in comparison with WHO overweight (25 kg/m<sup>2</sup>) and obesity (30 kg/m<sup>2</sup>) thresholds in both men and women.

The methods to identify optimum cutoff points of WC/BMI using sensitivity, specificity, and the ROC curves were applied. These methods include the distance from the upper left corner of the point on the ROC curve [(1-Sensitivity)<sup>2</sup> + (1-Specificity)<sup>2</sup>] and the value of the Youden index (sensitivity + specificity-1) (213,214). Furthermore, other measures of diagnostic accuracy, such as the positive predicted value (PPV), the negative predicted value (NPV), the total accuracy, and the ROC curve area were considered. The above enumerated measures of accuracy can be defined as follows. Sensitivity and specificity for given cutoffs are the probabilities of correctly identifying cases with a certain condition (or disease) and true non-cases that do not present the condition (or illness) respectively. PPV is the proportion of those with the condition among all individuals the test classified as positive, while the NPV is the proportion of true non-cases among individuals without the condition. The total accuracy is the sum of true cases plus non cases accurately predicted by the tests expressed as a percentage of the total sample (213).

A measure of WC/BMI with maximum sensitivity and specificity, which shows the minimum distance from the upper left corner of the ROC curve and the maximum Youden index, correspond to the optimal cutoff points (2212-214). In the

case of a WC with higher sensitivity and NPV, it was selected over another measure with higher specificity when both measures have the same total accuracy. The area under the ROC curve (AUC) was used as a measure of the overall accuracy of performance of the ROC curve and to examine the predictive value of WC/BMI for MetS components. The AUC takes values between 0 and 1, where an AUC of 1 is a perfect screen test. The null hypothesis that the AUC is equal to 0.5, which represents a test equal to chance, will be tested. The additional AUC values of  $\geq 0.7$  but  $< 0.8$ ,  $\geq 0.8$  but  $< 0.9$ , and  $\geq 0.9$  have been suggested as reflecting the acceptable, excellent, and outstanding levels of discrimination (216). Statistical tests for a comparison of AUCs within gender and all pairs of age groups was performed by the t-test and p value  $< 0.05$  will be considered statistically significant. The measures of diagnostic accuracy from the study was compared with existing WC values such as the NCEP, IDF and previous studies (13,17).

Furthermore, weighted means of MetS criteria, weighted proportions of subjects with abdominal obesity and overall obesity, and weighted prevalence of MetS were estimated using the proposed optimal cutoff values of WC/BMI and were compared with the existing cutoff values from NCEP, IDF and WHO. T-test was applied to compare continuous variables, and chi-square test assessed the differences in categorical variables. Statistical significance was set at p value  $< 0.05$  for the t-test and chi-square tests.

Logistic regression analyses was applied to estimate gender specific odd ratio of having MetS risk factors versus not having the risk factors for the estimated WC and BMI, controlling for covariates such as age, education, poverty-income ratio,



diet, physical activity, smoking, alcohol consumption, CRP and menopausal status. The WC and BMI reference values were set as the value below the estimated WC and BMI in question 3.1. Gender – specific and weighted Pearson correlation were run between each pair of the BMI/WC, and body composition (fat and fat free mass) variables and MetS components adjusting for age and anthropometric measures as appropriate. Multiple regression analysis was used to examine the possible variables that contribute to the variation in BMI. Variables with  $\geq 10\%$  missing data were eliminated before running the regression analysis. Logistic regression was performed to assess whether there are significant differences among AA men/women with and without MetS with respect to the selected predictors of MetS.

Statistical differences in environmental and health determinants that may contribute to MetS among AA adults were assessed when comparing individuals with and without metabolic syndrome. Unless otherwise mentioned, the appropriate sample weights, stratum variable and primary sampling unit (PSU) variable were applied to all analyses to account for the complex design effect and non-response.

## Chapter 4: RESULTS

### PAPER 1: NEW WAIST CIRCUMFERENCE CUT-OFFS FOR AFRICAN AMERICANS ACCORDING TO THE CLUSTERING OF METABOLIC SYNDROME RISK FACTORS, NHANES 1999-2006

#### Abstract

**Background:** Although central obesity is highly associated with metabolic syndrome criteria, reliable cutoff values for waist circumference independent of BMI<sup>1</sup> are still lacking among African Americans.

**Objective:** The objective was to determine the gender specific cut-off values of waist circumference (WC)<sup>2</sup> for screening African Americans, which optimally predict the clustering of two or more metabolic syndrome risk factors.

**Methods:** The study consisted of 2136 females and 1908 males African American participants in the NHANES<sup>3</sup> (1999-2006) study. The metabolic syndrome components were defined according to the NCEP/ATPIII<sup>4</sup> criteria. The WC values for detecting the gender specific metabolic risk factors were tested using receiver operating characteristics analysis (ROC)<sup>5</sup>. The Youden Index and the minimum distance values from the upper left corner of the ROC curve were calculated to determine the WC thresholds with an optimal combination of sensitivity and specificity.

**Results:** The mean age of subjects was 46 years ranging between 20-85 years with a BMI of 29.9 (SE=7.4), in the range of 15.8-67.3 kg/m<sup>2</sup>, and a WC of 98.5 (SE=16.9),

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<sup>1</sup> BMI- Body Mass Index

<sup>2</sup> WC- Waist Circumference

<sup>3</sup> NHANES: National Health and Nutrition Examination Survey (NHANES)

<sup>4</sup> NCEP/ATPIII-National cholesterol Education Program/Adult Treatment Panel III.

<sup>5</sup> ROC-Receiver Operating Characteristics

in the range of 60.4-163.1cm. The WC cut-off values were 94.7 cm with 76 sensitivity and 67 specificity for males and 97.6 cm with 70 sensitivity and 61 specificity for females. These WC cutoff values did not differ substantially by age categories.

**Conclusion:** For the early detection and management of the metabolic syndrome in African Americans, the WC of 95 cm for males and 98 cm for females are suggested as appropriate cut-off values to identify central obesity.

### **Introduction**

Metabolic syndrome (MetS)<sup>6</sup> is comprised of multiple risk factors that include hyperglycemia, hypertension, abnormal fat distribution, low HDL<sup>7</sup> cholesterol, and high triglyceride levels. These criteria have been related to insulin resistance and visceral adiposity. Individuals with MetS are considered to have high risk for type 2 diabetes and cardiovascular diseases (29,218). The MetS criteria have been defined by WHO, and other groups such as National Cholesterol Education Program-Adults Treatment Panel III (NCEP-ATPIII) and (IDF)<sup>8</sup> (2,4,29,218). There are differences in how IDF and NCEP-ATPIII diagnose central obesity, measured as waist circumference (WC) (**Table 1**). With regard to WC, the NCEP-ATPIII definition does not take into account ethnic differences, thus the heterogeneity of abdominal obesity and its association with metabolic risk factors. The WC threshold criteria, chosen by NCEP-ATPIII and IDF for the diagnosis of abdominal obesity, are based on the study of Lean et al. (1995), which related WC to BMI in a European

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<sup>6</sup> MetS- Metabolic Syndrome

<sup>7</sup> HDL- High Density Lipoprotein

<sup>8</sup> IDF- International Diabetes Federation

population (8). Current National Institutes of Health guidelines suggest that for any body mass index (BMI) category, normal to obese, the presence of a WC  $\geq$  102 cm for men and  $\geq$  88 cm for women is indicative of a greater risk for cardiovascular and metabolic diseases than lower WC values (64).

Central adiposity is recognized to be highly associated with increased risk of cardiovascular disease, the presence of hypertension, dyslipidemia, and type 2 diabetes independent of overall obesity (3,4). A WC cutoff value based on the relationship of WC to BMI has not been shown to be an optimal method of identifying the pathological effect of central obesity (6). Successful prevention and management of increasing metabolic abnormalities and related cardiovascular and type 2 diabetes illnesses require accurate identification of high-risk individuals based on their unique risk factors. In response to this need, IDF and certain Asian populations have defined central obesity thresholds based on ethnic differences (6). In acknowledging insufficient information on best WC cutoffs that predict risk in African Americans, IDF recommends that people of African descent use the European values until more specific data are available (218).

Previous studies on WC cut off points in African Americans were limited and either lacked sufficient sample size or used convenience samples. In addition, some were not inclusive of the clustering of NCEP-ATPIII MetS abnormalities (13-17) and depended on existing values of WC corresponding to BMI cutoffs, which might not be optimal for the African Americans (8). The inconsistent results among African Americans have provided varied optimal cutoff points of waist circumference that range from 89.0-108.9 cm for men and 83.0-104.6 cm for women (7). Given the

paucity of existing data, more reliable cutoff values for WC in African Americans need to be proposed independent of existing BMI categories.

The present study used a large and nationally representative sample of African American adults to: (1) determine optimal cutoff points of waist circumference for detecting the individual and cluster of metabolic risk factors by gender and age group; (2) ascertain which waist circumference thresholds are appropriate among varied values including those recommended by NCEP and IDF; (3) compare the gender specific cutoff values of WC for detecting metabolic risk factors between cases with and without raised blood pressure.

## **Methods and Procedures**

### ***Subjects***

This study analyzed data on African American subjects from the NHANES 1999-2006, who participated in both interview and clinical examination in a mobile examination center (MEC). The NHANES uses complex, stratified, multi-stage, clustered samples of civilian non-institutionalized populations (219). A total of 4044 subjects (2136 women and 1908 men) aged  $\geq 20$  years were studied. Pregnant, lactating women, individuals using insulin and with missing values were excluded from the study. In addition, subjects who had fasted less than 8 hours prior to blood tests or who had cancer were excluded during data analysis. Of the 4044 subjects, data were collected on 1445 participants (males and females) for all of the NCEP ATP III criteria and these subjects were therefore eligible for the ROC analysis. Detailed description of institutional review board approval, design specifications,

survey operations manuals and consent documents for NHANES can be obtained elsewhere (183-184).

### ***Anthropometric measurements and blood pressure monitoring***

With an electronic scale, weight was measured in pounds and converted to kilograms in the automated system. Height was measured with a fixed stadiometer to the nearest 0.1 cm. The WC was evaluated with a measurement of the abdominal circumference at the high point of the iliac crest. The measurement was recorded to the nearest 0.1 millimeter using a measuring steel tape around the trunk at the end of a normal expiration (body measure link). BMI was calculated as weight (kg) divided by the square of height (m<sup>2</sup>). Systolic and diastolic blood pressure readings were recorded four times using a standard mercury sphygmomanometer, with subjects sitting on a chair after at least a five-minute rest. For participations with three or four readings, the average of the last two was estimated and used in this analysis. In case of two measurements, the last reading was considered as the average. When only one blood pressure reading was available, that reading served as the average (221).

### ***Blood Examination***

For fasting blood glucose and triglycerides, data were collected on a subsample of the 4044 of participants. This subsample is nationally representative and corresponding sample weights were estimated to reflect this stage of sampling and the no response. For the determination of WC and BMI thresholds, the subsample and its relative sample weights were used in the analysis.

The biochemical measurements were obtained at the mobile examination center and blood glucose concentration was quantified using a hexokinase enzymatic

reaction (223). The serum concentration of HDL cholesterol (Heparin-Mn<sup>+2</sup> method and direct method) and triglycerides (Enzymatic reactions) were measured using an Hitachi 704 Analyzer (Roche Diagnostics, Indianapolis, IN) (224).

***Definition of multiple cardiovascular risk factors to obtain WC cutoffs***

Several studies have suggested that WC may be a better anthropometric predictor of many MetS risk factors, which aggregate in an individual, compared to BMI or waist hip ratio (5,225). For this study, multiple metabolic syndrome abnormalities were defined as the occurrence of two or more of the following criteria: 1) fasting blood glucose values  $\geq 100$  mg/dL or the use hypoglycemic agents; 2) high concentrations of serum triglycerides ( $\geq 150$  mg/dL) or treatment for this lipid abnormality as alternative indicator; 3) high blood pressure (systolic  $\geq 130$  mmHg, diastolic  $\geq 85$  mmHg, or the use of antihypertensive medications); and 4) low concentration of serum HDL  $< 40$  mg/dL for males and  $< 50$  mg/dL for females or drug treatment for reduced HDL. The presence of at least two of these multiple risk factors was considered as an outcome variable of the ROC analysis to obtain the WC cutoffs.

**Statistical Analysis**

Data were analyzed using SAS 9.2 and STATA software to account for the complex survey design and incorporate cluster, strata and sample weights in the analysis. SAS statistical software (release 9.2) was used for data cleaning and computation of descriptive statistics for the general characteristics, the anthropometrics, and MetS risk factors. The data are presented as means ( $\pm$  S.E.) and

percentages for categorical variables. T-test and Rao Chi-square test were applied to compare males and females. The statistical significance was considered at  $P < 0.05$ . Continuous variables not normally distributed were transformed and geometric means were used for the means of serum triglycerides, HDL, and systolic blood pressure because of their right skew distribution.

ROC analysis was performed using STATA 10.1 for Windows (STATA, College Station, TX) to find appropriate gender specific WC cutoff values for detecting the individual and the clustering of  $\geq 2$  metabolic syndrome risk factors defined by NCEP-ATPIII (except for WC). The sensitivity and specificity were estimated at each 1 cm increment of WC. The models were reanalyzed with age (categorized by 10-year age groups) and by hypertension status adjustments (raised BP: SBP  $\geq 130$  mmHg and/or DBP  $\geq 85$  mmHg and non-raised BP). We defined the best cut off values of WC with the optimal combination of sensitivity and specificity based on the maximum Youden's index (sensitivity + specificity - 1) (214) and the minimum distance from the upper left corner of the point on the ROC curve [ $(1 - \text{sensitivity})^2 + (1 - \text{specificity})^2$ ]. Additional measures of diagnostic accuracy such as total accuracy, positive predictive value, negative predictive value, and ROC curve area were also calculated. A WC with higher sensitivity and negative predictive value (NPV) was selected over a WC with higher specificity when both values had identical total accuracy. The areas under the ROC curves were calculated to assess the overall accuracy of performance of the ROC curve and to determine the ability of WC to predict the presence of the cluster of MetS indicators. The measures of diagnostic



accuracy (AUC) from the newly estimated WC were compared with those of existing WC values from NCEP, IDF and previous studies (15).

## Results

### *Participant characteristics*

Subjects characteristics are provided in **Table 2**. The average age of the subjects was 42.9 years ( $\pm 0.43$ ; range: 20-85) for females and 41.8 years ( $\pm 0.42$ ; range: 20-85) for males. The distribution of age groups shows a higher proportion of individuals between 20-29 and 40-49 years of age, 22% and 23% respectively. At the youngest age range, more males (21%) than females (16%) were observed while the opposite was observed after 70 year of age (9% males vs.13% females). For the other age groups 30-39 y, 50-59 y and 60-69 y, the proportion of participants was 14%, 16%, and 19%, respectively.

Consistent with known gender differences, males had higher weight, height, SBP and DBP, compared with female participants. BMI and WC were significantly lower in males than in females. The TG was statistically significant different between males and females (T value=4.06,  $P < 0.001$ ). The geometric mean for males for TG was 100.5 mg/dL (SE=2.437) with a confidence interval ranging from 95.8 to 105.5 mg/dL. The corresponding values for females were 86.5 mg/dL (SE=2.168) with a confidence interval of 82.3-91.0 mg/dL. The HDL geometric mean was 49.9 mg/dL (SE=0.451) with a CI of 49.0-50.8 mg/dL. Females had a significantly higher (T value= -13.27,  $p < 0.001$ ) mean of 56.5 mg/dL (SE=0.466) than males, with a CI of 55.6-57.4 mg/dL.

28-31% of the subjects did not have an abnormal MetS risk factor. At least two abnormal indicators of the MetS were present in 39% for males and 41% for females. The prevalence of MetS criteria and the number of risk factors were not significantly different between males and females (**Table 2**).

### ***The frequency of MetS criteria by gender and age categories***

The assessment of the prevalence of each individual criterion by gender revealed that high blood pressure was the most frequent risk factor, being present in 46.9 and 47.3% for females and males, respectively (**Figure 1**). Low HDL cholesterol was present in 34% of the females compared to 23% of the males. High fasting blood glucose was almost equally present in males and females (31.2 & 32.6%). The lowest frequency was observed for high triglycerides (11.9-19.4%). The frequency of the individual criteria was statistically significantly different between male and female subjects except for high fasting blood glucose ( $\geq 100$  mg/dL) and high blood pressure ( $\geq 130/85$  mm HG).

**Figure 2** portrays the prevalence of at least 2 metabolic risk factors (except WC) across age categories and by gender. The risk factors include elevated blood pressure, triglycerides, fasting blood glucose, and low HDL levels. Males and females, 40-49 and 60-69 years of age, had the highest prevalence of at least 2 risk factors (24% and 27%, respectively), while the younger and the oldest groups had the lowest (7% and 15%) prevalence followed by the 50-59 year age categories (17%). The percentage of at least two of the metabolic components was higher in females compared to males between the age cluster of 50-59 and 60-69 years. The young age

categories of 20-29 and 30-39 years had a lower proportion of females vs. males with 2 or more risk factors.

***The mean average for anthropometric and medical profiles by age categories***

The anthropometrics and medical examination profiles in **Table 3** show a generalized and marked increase of the mean for all the MetS components between 20 & the 60th decade in both males and females. However, a decline was observed in the seventh decade except for SBP and HDL, which were at their highest at  $\geq 70$  years of age. For the  $\geq 70$  year group, the SBP reached 147.9 for females vs. 143.1 mmHg for males. HDL was 65.1 and 54.4 mg/dL for females and males, respectively. In terms of gender related differences, the average of the MetS risk factors were found to be higher in males than females with the exception of WC, BMI, and HDL. The gap difference disappeared after the 5<sup>th</sup> decade for TG and narrowed for WC. Among females, there was a mean increase of 5-6 kg after 20-29 yrs and a decrease of close to 4 kg after the 70<sup>th</sup> birthday. The change in weight was less pronounced in males (1-3 kg increase after 20-29 year category). However, significant body weight loss was recorded after 70 years and above (7.5 kg).

***WC cut-offs points for the detection of high blood pressure, hyperglycemia, triglyceridemia and low HDL by gender***

The WC cut-off levels were determined by relating them to the individual MetS component. **Table 4** summarizes the sensitivity and specificity for each WC level for the identification of elevated blood pressure, high fasting blood glucose, raised triglycerides, HDL levels and the presence of at least 2 of those criteria.

In males, the optimal combination of sensitivity and specificity was at 95 cm for high blood pressure and fasting blood glucose, at 97 cm for raised triglycerides, and at 98 cm for low HDL. The values ranges between 95 and 98 cm, with an optimal cut-off value found at ~ 95 cm for the presence of at least 2 of the criteria. In females, the optimal combination of sensitivity and specificity were at 96 cm for high blood pressure, at 99 cm for fasting blood glucose and at 98 cm for high triglycerides and low HDL. The presence of at least 2 of the metabolic risk factors was identified at ~ 98 cm.

#### ***Appropriate waist circumference determination***

Based on the Youden Index and minimum distance from the upper left corner of the ROC curve, the male WC cut off value that best predicts two or more metabolic risk factors was 94.7 cm. At this WC, sensitivity and specificity rates were 76 and 63 % respectively (**Table 5**). The 102 cm waist circumference currently in use for males had a sensitivity of 53% and specificity of 77% (**Table 5 & figure 4**). For females, the threshold associated with the optimal combination of sensitivity and specificity was 97.6 cm, corresponding to sensitivity and specificity values of 71 and 62% (**Table 5**). The current NCEP ATPIII WC cut point of 88 cm corresponds to a sensitivity and specificity of 91 and 37% (**figure 4**). **Figure 3** represents the ROC curve for the newly estimated cut off values for both males and females. The ROC area for males was 0.74 with a confidence interval of 0.70-0.78 while for females, the ROC was 0.72 and a confidence interval is 0.68-0.76. AUC was not statistically significant between males and females (P=0.554).

### *Characteristics of participants by blood pressure status and their WC cutoffs*

**Table 6** compares the characteristics of subjects with and without elevated blood pressure. The mean age was significantly lower among people without raised blood pressure than those with raised blood pressure in both males and females. A lower percentage of young people 20-39 as well as those 50-59 years of age had raised blood pressure in both males and females. The proportion of people who had high blood pressure significantly decreased with age. The mean BMI and WC were significantly higher in participants with raised blood pressure than those without for both genders. The percentage of people who had the clustering of risk factors was also significantly higher among those with elevated blood pressure than those without high blood pressure in both males and females.

**Table 7** shows the comparison of WC cutoff values for predicting the selected cluster of MetS risk factors using ROC analysis between subjects with and without elevated blood pressure. WC thresholds for males with and without high blood pressure were 95 cm and 94.7 cm, respectively. Corresponding values among females were 99 cm and 97.6 cm. The WC cut offs did not differ between those with and without hypertension in both males and females. However, the values appeared slightly higher among those without raised blood pressure.

### **Discussion**

The purpose of this study was to determine gender specific optimal cut off values of WC that best predict indicators of a cluster of metabolic risk criteria in a large, nationally representative sample of African American adults. The WC thresholds that best predict the cluster of metabolic risk factors in African American

males and females were found to be 95 cm and 98 cm, respectively. Compared to IDF ( $\geq 80$  for females and  $\geq 94$  cm for males) and NCEP/ATP III ( $\geq 88$  in females and  $\geq 102$  cm in males) definitions of central obesity (2,29), the threshold suggested for males (95 cm) was similar to the IDF cut off value of 94 cm, but lower than the NCEP ATP III currently used WC of 102 cm. Among females, in contrast to the IDF (80 cm) and NCEP III (88 cm), the cut off value was higher and equivalent to 98 cm. Females developed metabolic risk factors at higher WC in comparison to males. Overall, we observed that our cutoff values of WC for males yielded maximum sensitivity and specificity (Figure 4).

The lower cut off value for WC in males compared to the 102 cm (8), which predicts the obesity BMI in Europeans, highlights the heterogeneity in values of WC and associated metabolic risk factors in different ethnic groups and populations. Indeed, other groups such as Asians who develop MetS at lower cut off values have revised their criteria (226) and new thresholds have been suggested. In addition, lower WC values in African Americans (16), particularly among males, below the levels of WC estimated from BMI in European Americans have challenged the long held assumptions of a similar WC threshold across ethnic and racial groups in assessing MetS criteria (17). Thus, there is no support for choosing a WC threshold predicted from BMI cut-offs among African Americans. WC recommendations should be based on WC and its relationship to metabolic risk factors.

Although sampling methods, measurements and indicator differences preclude direct comparison of our findings with previous studies, a recent study of Sumner et al (2008), to determine the WC in African Americans that best predict the insulin

resistance based on convenient sample of adults 20-50 years old, suggested a similar WC threshold of  $\geq 98$  cm in females (13). An earlier study of Okosun et al (2000) using NHANES III to determine the WC associated with established BMI cut off values suggested a WC of 97 cm for females and 101-103 cm in males (17). The same authors also assessed the ability of 102 cm and 88 cm in predicting MetS risk factors (15), and their findings confirm our current study, which found lower sensitivity at 102 cm for males (41-56%) for the different MetS components, and a very low specificity for the 88 cm in females (31-37%). Zhu et al, (2005) estimated WC corresponding to the established overweight and obese values when one or more metabolic syndrome components were present. The authors suggested 91 cm for females and 97 cm for males, however, the MetS criteria they used had different values than ones we used in this study. All the previous studies suggested a higher WC for females than the current 88 cm and the current study identified the optimal cut off values that are associated with both individual and the cluster of MetS risk factors.

The major limitation of this study was the lack of availability of data for 2007-08 to increase the sample size of the subsample for triglycerides and fasting blood glucose. This might have affected the lack of significant differences in WC thresholds by age categories (not reported) and for individuals with and without high blood pressure. Secondly, this study is a cross-sectional design and gives limited information on the susceptibility to MetS risk factors. A longitudinal study would be needed to determine the association between WC and incidence of the MetS criteria. Furthermore, this study did not assess the intra- abdominal distribution of adipose

tissue in relation to WC and metabolic risk factors. Further research would be needed to compare intra-abdominal adipose distribution between genders & its relationship with MetS.

### **Conclusion**

In summary, we used the ROC curve analysis to determine appropriate WC cut off values for individuals with multiple metabolic risk factors among African Americans. Findings showed that the WC thresholds, with relatively high sensitivity and specificity, are 95 cm for males and 98 cm for females, respectively. The present findings suggest that those cutoffs be used for the early detection and management of MetS. Since this study was cross-sectional in nature, further investigation of long-term morbidity/mortality data are needed to confirm the appropriate definition of central obesity in African Americans.



**Table 1. Metabolic syndrome criteria based on NCEP-ATPIII and IDF consensus**

	<b>NCEP ATP III<sup>a</sup></b>	<b>IDF<sup>a</sup></b>
<b><u>Waist circumference</u></b>		
<b>Men</b>	>102 cm WC	Europids $\geq$ 94 cm* South Asians/Chinese $\geq$ 90 cm* Japanese $\geq$ 85 cm*
<b>Women</b>	>88 cm WC	Europids ,South Asians/Chinese $\geq$ 80 cm* Japanese $\geq$ 90cm*
<b><u>Triglycerides</u></b>	$\geq$ 150 mg/dL (1.7 mmol/L) or treatment for this lipid abnormality	
<b><u>Blood glucose</u></b>	$\geq$ 100 mg/dL (5.6 mmol/L) or treatment of elevated glucose >100 mg/dL (5.6 mmol/L), OGTT strongly recommended but not necessary	
<b><u>HDL</u></b>		
<b>Men</b>	<40 mg/dL (1.03 mmol/L) or drug treatment for reduced HDL	
<b>Women</b>	<50 mg/dL (1.29 mmol/L) or drug treatment for reduced HDL	
<b><u>Blood pressure</u></b>	$\geq$ 130/85 mm Hg or treatment of previously diagnosed hypertension	

NCEP-ATPIII: National Cholesterol Education Program-Adult Treatment Panel III; IDF: International Diabetes Federation; WC: waist circumference; OGTT: Oral Glucose Tolerance Test; HDL: High Density Lipoprotein Cholesterol; \* Population and country specific waist circumference; Source: Circulation.2009; 120:1640-1645.

**Table 2. Characteristics of the study population**

Characteristics	Men		Women	
	(n =1458)	Range	(n = 1439)	Range
Age (years)	41.8 ±0.42	20-85	42.9±0.43	20-85
Weight (kg)‡	87.5 ±0.54	38.9-156.4	82.5 ±0.57	38.9-163.0
Height (m)‡	177.1±0.15	151.7-204.1	162.9±0.19	149.9-184.7
BMI (kg/m <sup>2</sup> )‡	27.8 ±0.16	16.1 -47.4	31.1 ±0.23	17.4-57.6
WC (cm)‡	95.7±0.39	62.4-144.7	98.0 ±0.57	60.4-145.0
SBP (mmHg)‡	127±0.38	90-217	125±0.74	79-266
DBP (mmHg)‡	75±0.43	35-116	72± 0.41	40-112
LHDL- C (mg/dL)	49.9±0.45	48.9-50.8	56.5±0.47	55.6-57.4
LTG (mg/dL)	100.5±2.44	95.8-105.5	86.5 ±2.17	82.3-91.0
FBG (≥ 100 mg/dL)	n	32%	n	30%
subjects with risk factors*	(n=567)		(n=571)	
no risk	178	31%	158	28%
1 risk factor	172	30%	183	32%
2 risk factors	134	24%	136	24%
3 risk factors	55	10%	74	13%
4 risk factors	28	5%	20	4%

Mean ±SE or number of subjects and proportion of subjects (%)

‡AGE t value -4.16 p = 0.001; weight t value 6.64 p=0.0001; Height t value = 59.26 p <0.0001; BMI -12.38 p < 0.0001; WC -3.68 p < 0.0005; DBP t value 4.95 P =<.0001, TG t value = 4.06 p =0.000.

BMI: Body mass index = Body weight (kg) / height (m)<sup>2</sup>; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; LHDL, log of high density lipoprotein cholesterol; LTG, log of triglycerides.

\*Risk factors: raised triglycerides, low HDL-C, elevated fasting blood glucose, and raised BP blood pressure.

**Table 3. Anthropometric profiles and medical examinations results by gender and 10 years age category, NHANES 1999-2006**

	<b>Females (n= 1408)</b>					
<b>Age ( years)</b>	<b>20-29 n=230</b>	<b>30-39 n=262</b>	<b>40-49 n=321</b>	<b>50-59 n=198</b>	<b>60-69 n=225</b>	<b>≥70 n=172</b>
<b>Weight (kg)</b>	78.7 ± 1.5	84.4 ± 1.5	84.1 ± 1.0	84.8 ± 1.3	84.3 ± 1.2	74.8 ± 1.3
<b>Height (cm)</b>	163.1 ± 0.4	163.9 ± 0.5	163.4 ± 0.4	163.0 ± 0.5	161.9 ± 0.5	158.8 ± 0.5
<b>WC (cm)</b>	92.6 ± 1.3	97.4 ± 1.4	99.1 ± 0.9	100.3 ± 0.9	102.7 ± 0.9	98.1 ± 1.1
<b>BMI ( kg/m<sup>2</sup>)</b>	29.5 ± 0.5	31.3 ± 0.6	31.5 ± 0.5	31.8 ± 0.5	31.9 ± 0.4	29.6 ± 0.5
<b>SBP (mmHg)</b>	111.6 ± 0.9	116.8 ± 1.1	125.4 ± 1.5	131.4 ± 1.3	141.1 ± 1.3	147.9 ± 2.2
<b>DBP (mmHg)</b>	67.1 ± 0.7	72.4 ± 0.7	75.5 ± 0.9	76.1 ± 0.7	74.3 ± 0.8	67.15 ± 0.9
<b>TG (mg/dl)</b>	86.6 ± 5.2	86.5 ± 4.5	96.3 ± 4.5	130.5 ± 12.8	120.1 ± 6.1	108.5 ± 5.4
<b>HDL(mg/dl)</b>	54.9 ± 1.1	56.3 ± 1.1	58.7 ± 0.8	61.9 ± 1.1	60.1 ± 1.3	65.1 ± 1.8
<b>FBG (mg/dl)</b>	89.7 ± 1.1	94.1 ± 1.8	97.0 ± 1.3	110.4 ± 5.4	110.6 ± 3.6	111.6 ± 4.2
	<b>Males (n = 1436)</b>					
	<b>20-29 n=296</b>	<b>30-39 n=263</b>	<b>40-49 n=321</b>	<b>50-59 n=205</b>	<b>60-69 n=217</b>	<b>≥70 n=134</b>
<b>Weight (kg)</b>	86.5 ± 1.2	89.4 ± 1.3	88.2 ± 1.0	87.5 ± 1.4	87.3 ± 1.4	79.0 ± 1.2
<b>Height (cm)</b>	178.4 ± 0.4	177.4 ± 0.4	177.3 ± 0.3	176.8 ± 0.5	175.7 ± 0.5	171.8 ± 0.6
<b>WC (cm)</b>	90.4 ± 0.9	95.6 ± 1.1	96.9 ± 0.8	98.5 ± 1.0	101.6 ± 1.2	98.6 ± 0.9
<b>BMI ( kg/m<sup>2</sup>)</b>	27.1 ± 0.4	28.3 ± 0.4	28.0 ± 0.3	27.9 ± 0.4	28.3 ± 0.4	26.7 ± 0.4
<b>SBP (mmHg)</b>	120.1 ± 0.7	122.7 ± 0.8	127.2 ± 0.9	133.7 ± 1.4	135.0 ± 1.6	143.1 ± 2.1
<b>DBP (mmHg)</b>	69.6 ± 0.9	74.3 ± 0.8	78.9 ± 0.8	80.1 ± 1.0	74.1 ± 0.9	71.4 ± 1.4
<b>TG (mg/dl)</b>	97.5 ± 5.1	140.9 ± 13.8	131.8 ± 7.9	126.4 ± 0.1	122.4 ± 7.7	105.6 ± 6.6
<b>HDL(mg/dl)</b>	51.0 ± 0.9	50.1 ± 0.9	51.2 ± 0.9	54.4 ± 1.2	52.9 ± 0.9	54.4 ± 1.4
<b>FBG (mg/dl)</b>	93.4 ± 1.9	98.3 ± 1.4	101.5 ± 2.4	112.5 ± 3.7	127.5 ± 6.5	109.3 ± 4.9

Values mean and standard errors WC: Waist circumference; BMI: Body mass index; SBP: systolic blood pressure, DBP: diastolic blood pressure; TG: triglycerides; HDL-cholesterol: high density lipoprotein cholesterol; FBG: Fasting blood glucose

**Table 4. Estimated waist circumference which predicts the cluster of metabolic syndrome in African Americans; NHANES 1999-2006.**

<i>WC (cm)</i>	<i>J value</i>	<i>Minimum Distance</i>	<i>Diagnostic accuracy</i>	<i>PPV(%)</i>	<i>NPV(%)</i>	<i>Sensitivity (%)</i>	<i>Specificity (%)</i>
<b>Men</b>							
≥ 89	0.38	0.512	62	48	89	88	50
≥ 92	0.35	0.488	62	48	84	79	56
<b>≥ 94.7<sup>a</sup></b>	<b>0.39</b>	<b>0.440</b>	<b>67</b>	<b>52</b>	<b>83</b>	<b>76</b>	<b>63</b>
<b>≥ 95</b>	<b>0.39</b>	<b>0.441</b>	<b>67</b>	<b>52</b>	<b>83</b>	<b>75</b>	<b>64</b>
≥ 98	0.36	0.459	70	54	79	64	71
<b>≥ 102<sup>b</sup></b>	<b>0.29</b>	<b>0.534</b>	<b>73</b>	<b>54</b>	<b>75</b>	<b>52</b>	<b>77</b>
≥ 105	0.28	0.560	75	56	75	47	81
≥ 109	0.19	0.68	79	55	71	34	86
<b>Women</b>							
≥ 83	0.22	0.744	51	43	93	97	26
<b>≥ 88<sup>b</sup></b>	<b>0.29</b>	<b>0.624</b>	<b>56</b>	<b>46</b>	<b>88</b>	<b>91</b>	<b>38</b>
≥ 93	0.32	0.526	60	49	83	82	51
<b>≥ 97.6<sup>a</sup></b>	<b>0.33</b>	<b>0.476</b>	<b>64</b>	<b>52</b>	<b>79</b>	<b>71</b>	<b>62</b>
<b>≥ 98</b>	<b>0.32</b>	<b>0.481</b>	<b>64</b>	<b>52</b>	<b>78</b>	<b>70</b>	<b>62</b>
≥ 103	0.30	0.504	69	54	75	58	72
≥ 105	0.29	0.520	71	56	74	55	75

WC = waist circumference. Jvalue = Youden Index. Minimum distance from the upper left corner of the point on the ROC curve. NPV: negative predictive values. PPV: positive predictive values. <sup>a</sup> author's recommendations. <sup>b</sup> National Cholesterol Education Program-Adult Treatment Panel III recommendations.

**Table 5. Sensitivity and specificity of metabolic syndrome criteria by gender; NHANES 1999-2006**

MEN										
WC cut-off (cm)	BP≥130/85 MmHG		FBG ≥100 mg/dL		Triglycerides ≥150 mg/dL		HDL ≤ 40 mg/dL		MetS	
	Sens	Spec	Sens	Spec	Sens	Spec	Sens	Spec	Sens	Spec
90	73	50	84	47	87	43	82	40	88	49
91	71	53	82	50	83	45	78	43	85	52
92	68	55	79	54	76	47	78	47	80	54
93	66	57	77	56	73	49	78	50	79	57
94	63	59	76	59	72	53	76	52	76	60
95	<u>61</u>	<u>62</u>	<u>74</u>	<u>63</u>	72	55	75	54	<u>76</u>	<u>63</u>
96	56	64	71	65	68	58	72	58	72	66
97	55	67	67	66	<u>65</u>	<u>60</u>	69	60	68	67
98	53	69	66	69	61	62	<u>67</u>	<u>63</u>	65	70
99	50	71	63	71	57	65	64	65	63	72
100	46	73	57	73	51	67	61	69	57	74
101	44	74	56	74	50	69	59	69	55	75
102	41	76	54	76	49	71	56	71	53	77
103	40	76	51	77	48	72	54	72	51	78
<b>AUC (95% CI) 0.65 (0.61-0.69) 0.72 (0.67-0.76) 0.66 (0.61-0.71) 0.69 (0.63-0.74) 0.74 (0.70-0.78)</b>										
WOMEN										
WC cut-off (cm)	BP≥130/85 MmHG		FBG ≥100 mg/Dl		Triglycerides ≥150 mg/dL		HDL ≤ 50 mg/dL		MetS	
	Sens	Spec	Sens	Spec	Sens	Spec	Sens	Spec	Sens	Spec
85	88	26	94	26	96	21	89	23	95	28
86	85	29	94	28	95	24	88	25	95	30
87	84	33	92	34	93	26	84	27	92	33
88	82	35	91	36	92	30	82	31	91	37
89	80	38	88	38	92	30	82	31	90	40
90	78	39	85	39	91	34	81	35	87	41
91	77	40	84	42	90	36	78	37	86	43
92	73	46	83	46	89	39	76	40	85	47
93	72	46	81	49	89	42	74	42	83	49
94	71	50	79	50	87	44	71	45	81	52
95	69	53	78	54	85	47	70	48	79	55
96	<u>66</u>	<u>56</u>	76	55	85	49	69	50	77	57
97	<u>65</u>	57	73	59	80	51	65	52	74	58
98	61	60	71	60	<u>77</u>	<u>53</u>	<u>63</u>	<u>55</u>	72	61
99	57	62	<u>68</u>	<u>63</u>	70	55	60	56	68	63
100	56	63	65	63	68	57	57	59	65	65
<b>AUC (95% CI) 0.65 (0.61-0.68) 0.71(0.67-0.75) 0.68 (0.63-0.72) 0.62 (0.57-0.67) 0.72 (0.68-0.76)</b>										

WC: waist circumference; BP: blood pressure; FBG: fasting blood glucose; HDL: High density lipoprotein; MetS: presence of ≥ 2 metabolic criteria (BP, FBG, low HDL, high triglycerides); Sens: sensitivity; Spec: specificity.

**Table 6 . Comparison between participants with and without raised blood pressure NHANES 1999-2006**

	<i>Men (558)</i>		<i>Women(549)</i>	
	Without HBP*	With HBP	Without HBP	With HBP
# observations	282	276	261	288
Age ( years)	36.5±0.63	47.3±0.77	36.5±0.58	53.9±0.87
Age categories				
20-29 yr	90 (32%)	27 (10%)	77 (30%)	6 (2%)
30-39 yr	79 (28%)	38 (14%)	85 (33%)	26 (9%)
40-49 yr	63 (22%)	63 (23%)	61 (23%)	67 (23%)
50-59 yr	21 (7%)	36 (13%)	19 (7%)	47 (16%)
60-69 yr	20 (7%)	64 (23%)	12 (5%)	84 (29%)
± 70 yr	9 (3%)	48 (17%)	7 (3%)	58 (20%)
Body mass index *	26.8±0.31	28.6±0.49	30.0±0.40	33.1±0.54
Waist circumference *	91.9±0.93	99.4±1.37	95.1±0.94	103±1.00
Clustering risk factors **	42 (15%)	170 (62%)	40 (15%)	191 (66%)

Mean ±SE or % of participants

\*Body weight (kg)/(m)<sup>2</sup> ; waist circumference (cm); HBP high blood pressure (mm Hg)

\*\*subjects with 2 or more of MetS risk factors: raised systolic BP and/or diastolic BP, high triglycerides, reduced HDL-C and raised fasting plasma glucose

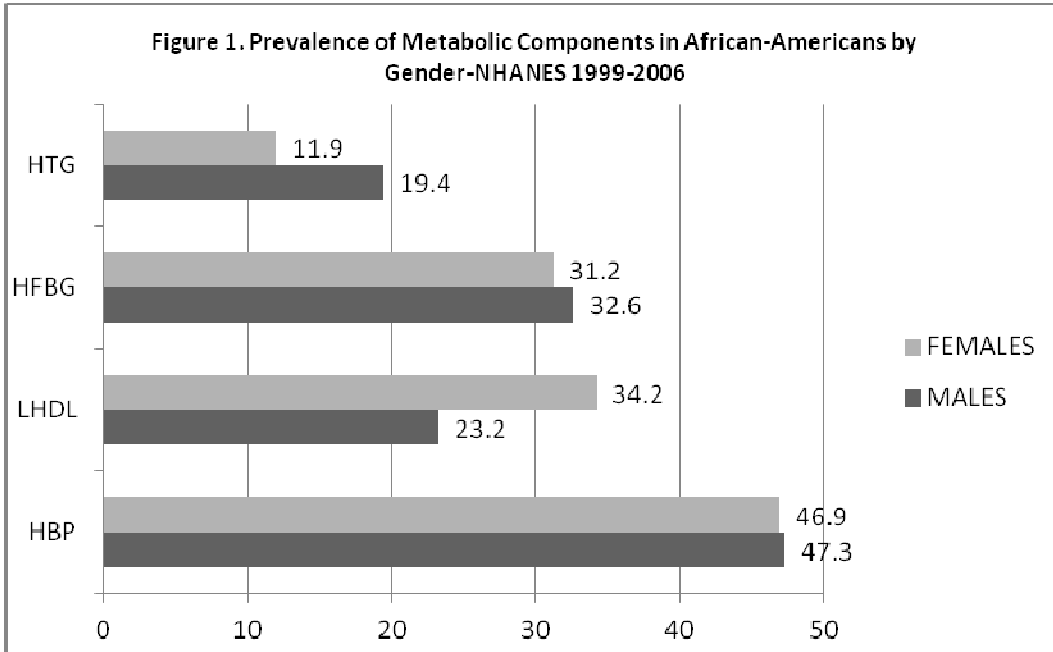
**Table 7. Gender –specific WC cutoffs for detecting clustering of MetS risk factors including patients with and without raised HBP**

	<i>Men</i>		<i>Women</i>	
	Without HBP	With HBP	Without HBP	With HBP
WC (cm)	95	94.7	99	97.6
Least distance values*	0.443	0.442	0.479	0.478
Youden index	0.383	0.386	0.322	0.329
Sensitivity	75	75	67	71
Specificity	64	63	65	62
AUC	0.739	0.702	0.706	0.703
95% CI of AUC **	(0.649-0.813)	(0.639-0.758)	(0.629-0.772)	(0.640-0.760)

WC: waist circumference (cm); HBP: high blood pressure; \* Least distance from upper left to ROC curve

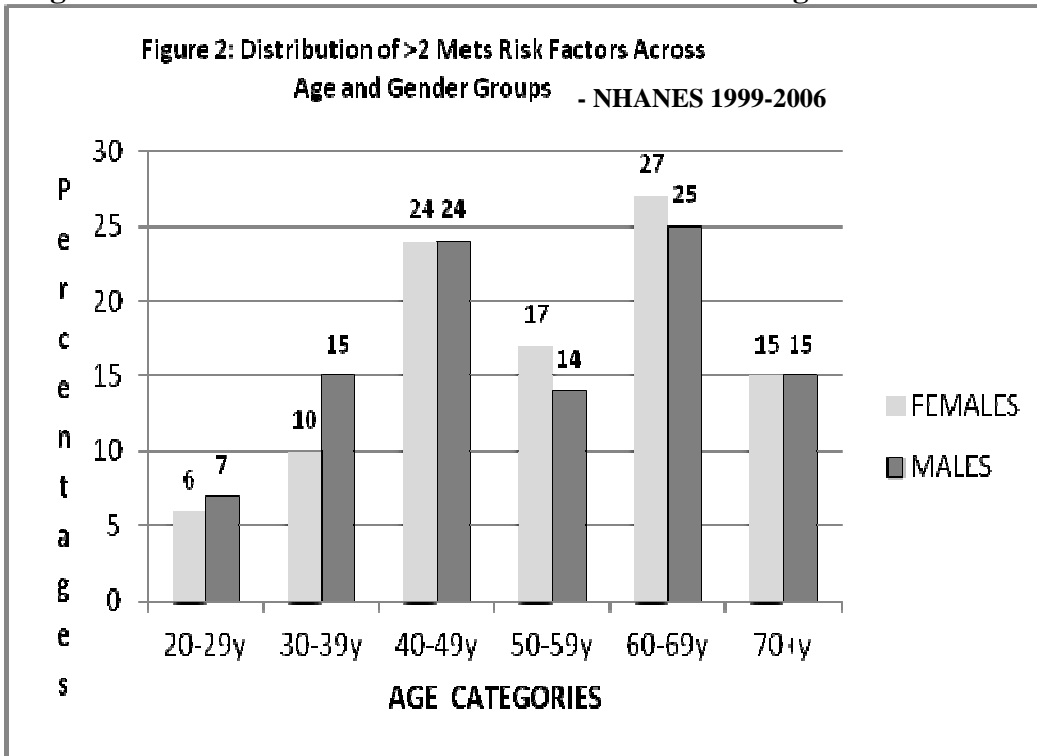
\*\* 95% CI confidence interval; AUC: area under the receiver operating characteristics (ROC) curve.

**Figure 1. Prevalence of Metabolic Components in African Americans by Gender-NHANES 1999-2006**

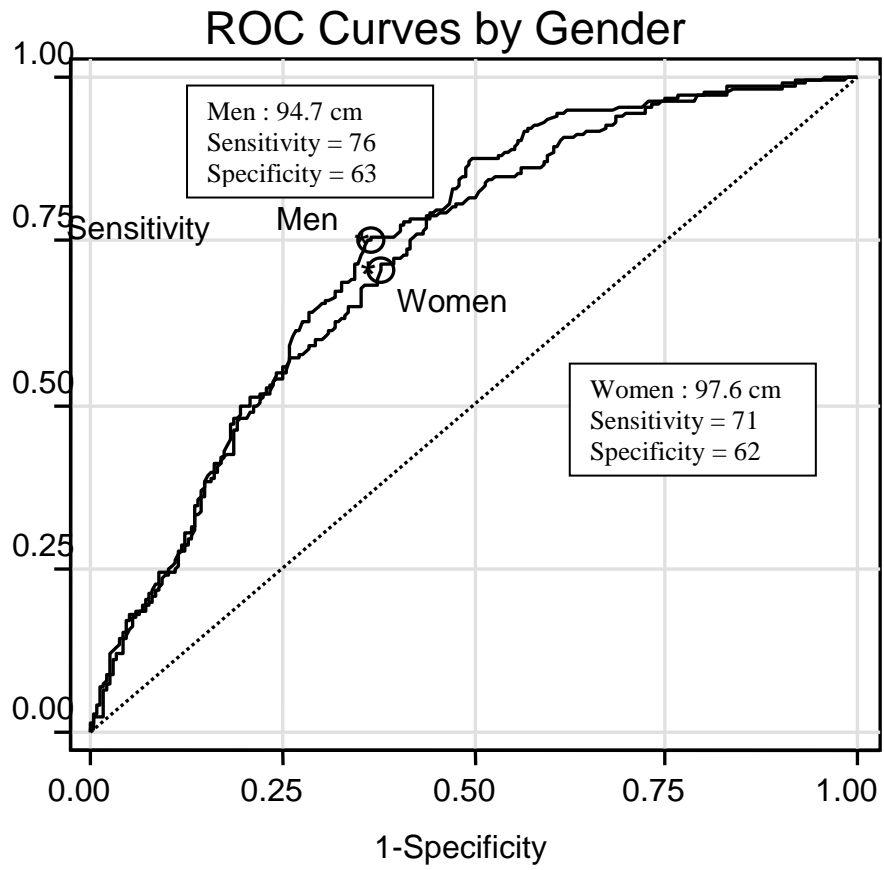


HTG: high triglycerides; HFBG: high fasting blood glucose; LHDH: Low high Percentage terol; HBP: high blood pressure.

**Figure 2. Distribution of > 2 Mets Risk Factors Across Age & Gender Groups**



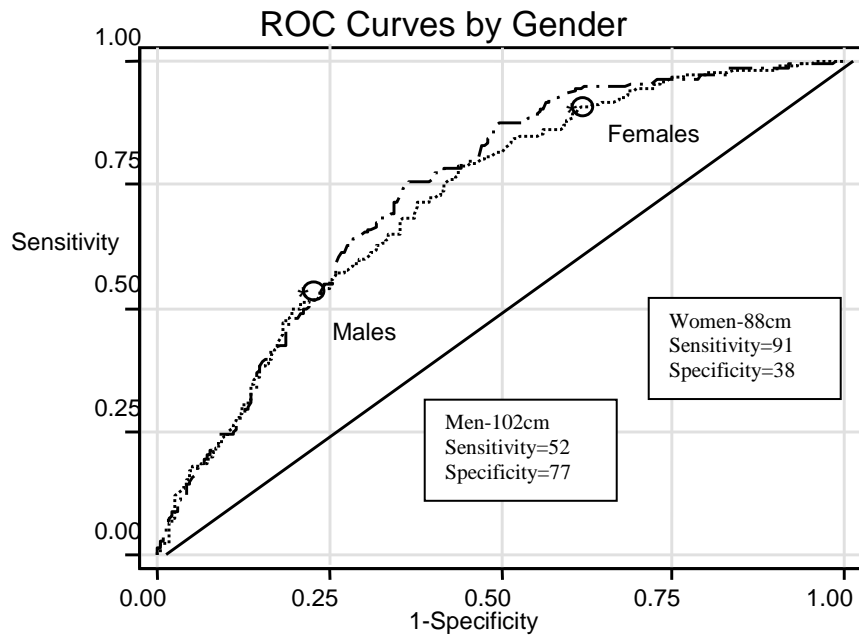
**Figure 3. New Waist circumference cut off points for the detection of the cluster of high blood pressure, hyperglycemia, triglyceridemia and low high density lipoprotein cholesterol – NHANES 1999-2006**



3



**Figure 4. NCEP/ ATP III Waist circumference cut off points for the detection of the cluster of high blood pressure, hyperglycemia, triglyceridemia and low high density lipoprotein cholesterol NHANES 1999-2006.**



## **PAPER 2: APPROPRIATE BMI AND COMPARISON OF THE BMI THRESHOLD VALUES IN PREDICTING METABOLIC SYNDROME RISK FACTORS**

### **Abstract**

Existing BMI cut off values have been debated as to whether they are appropriate across different population groups as they do not account for body fat distribution and their association with health outcomes remains unclear in certain groups.

The purpose of the study was to determine appropriate African American (AA) body mass index (BMI) cut points to account for differences in obesity related metabolic risk factors. It also studies the gender differences in the relationship of BMI to body composition.

The study comprised of 4415 of adults aged 20 and older and 49% were males. Males were younger than females (41.7 years vs. 43.9 years, respectively) and their average age increased correspondingly with BMI categories, ranging from 36.7 – 44.6 years.

The opposite was observed in females, where the age slightly decreased with increasing BMI values. From receiver operating characteristics analysis (ROC), the optimal cut-off points for BMI were found to correspond to 28 kg/m<sup>2</sup> in males and 32 kg/m<sup>2</sup> in females. The BMI cut points predicted from the presence of MetS risk factors are lower in males and higher for females than the currently defined cut off values of 30 kg/m<sup>2</sup>. WC corresponding to the newly estimated values of BMI in males and females were tested using simple linear regression and ROC and were 96 cm and 99 cm, respectively. The findings differed from the current NCEP-ATPIII WC values in males (102 cm) and in females (88 cm) predicted from the BMI.

In summary, the current study results show the need to consider ethnic background in defining the BMI cut-off values that predict the presence of health risk factors. Higher BMI among AA corresponds to lower WC in males and to higher WC in females.

### **Introduction**

Body Mass Index (BMI) is used to assess overall heaviness (227). There are no established cut-off points for fat mass or percentage body fat (%BF) that translate into cut-offs for BMI, which relates weight/(kg) to height (m<sup>2</sup>). The World Health Organization (WHO) defines overweight as a BMI 25-29.9 kg/m<sup>2</sup> and obesity as BMI  $\geq$  30 kg/m<sup>2</sup>. Such recommendations were promulgated primarily for European populations to correspond to risk thresholds for a wide range of chronic diseases and mortality (161). The epidemiological data show increased mortality at BMI  $\geq$  25 kg/m<sup>2</sup> (167-169, 172). This increase, however, appears modest until a BMI of 30 kg/m<sup>2</sup> is attained. Individuals with a BMI of  $\geq$  30 kg/m<sup>2</sup> have a mortality rate from all causes, and cardiovascular disease (CVD) in particular, 50-100 % above those whose BMI fall in the normal range of BMI 20-25 kg/m<sup>2</sup> (167,171).

Among African Americans (AA), available studies suggest that adiposity may be a less important predictor of mortality than in European Americans (EA), especially among females (228). In individuals who never smoked and without history of disease, the association between a high BMI and elevated risk of death was observed to be more moderate among AA males and females. A small increase in risk of death was found only at BMI 35.0 or higher (228) among AA females. Two large

U.S. surveys – the National Health and Nutrition Examination Survey (NHANES) and the National Health Interview Survey (NHIS) showed that the BMI-related to increased mortality begins at a 1 to 3 kg/m<sup>2</sup> higher BMI level among African Americans than among European Americans. The BMI associated with minimum mortality was 26.8 kg/m<sup>2</sup> for AA females and 27.1 kg/m<sup>2</sup> for AA males compared to 24.3 kg/m<sup>2</sup> and 24.8 kg/m<sup>2</sup> in EA females and males, respectively (229).

The use of WHO BMI cut off values for overweight (25 kg/m<sup>2</sup>) and obesity (30 kg/m<sup>2</sup>) has limitations (10, 22). The BMI measurement is disputed because its correlation with body fatness is inconsistent across populations (24-27). In addition, there has been ongoing debate as to whether these criteria (for obesity and overweight) are appropriate for non-European populations as they do not account for differences in body fat distribution and the relation of body size and composition with health outcomes (25). BMI does not separate fat mass from fat free mass (muscle and skeletal masses). Studies have shown that individuals with identical BMI values may have considerably different percentage fat levels, particularly if they vary in age, gender and ethnicity. Compared to other ethnic groups, African Americans have been reported to have higher total bone density and muscle mass content (24) across the lifespan. Using dual energy X-ray absorptiometry (DEXA), the percentage of body fat (BF) estimated at a given BMI was lower in African Americans than in European Americans. Thus, the relationship between percentage fat and BMI is probably different among African Americans, given the increased skeletal muscle mass and lower percentage BF. It is not surprising that a change in this relationship may

suggest that African American females in particular may be at decreased metabolic risk compared with Europeans at similar BMI levels (12).

Since population groups may differ in the level of risk associated with a particular BMI, research is needed to determine appropriate African American BMI cut points to account for differences in (i) susceptibility to obesity-related metabolic risk factors, (ii) the relation of BMI to body fatness and fat free mass, and (iii) fat distribution. This study focuses on appropriateness of BMI cut offs in adult African American males and females. The optimum BMI levels based on their specific Metabolic Syndrome (MetS) risk profiles will be determined. The results will contribute to our understanding of ethnic differences in metabolic syndrome and its implication for chronic disease disparities.

## **Research Design and Methods**

### **Data source and sample size**

The study analyzed data from the National Health and Nutrition Examination Survey (NHANES) data collected between 1999 and 2006 on African Americans (230). NHANES survey comprises a series of cross-sectional studies, which uses a complex, multistage probability, stratified and cluster sampling design survey. It was designed to monitor and evaluate the nutritional and health status of a representative sample of the non-institutionalized U.S. population. The assessment is based on health-related household questionnaires, laboratory tests and physiological measurements. Detailed information on NHANES data collection procedures are available elsewhere (231). Individuals aged  $\geq 60$  years of age, low income European

Americans, Mexican Americans and African Americans were oversampled to ensure accurate estimates in those population groups.

This NHANES sample comprised of 4415 AA adults  $\geq 20$  years. Of the total number, 3842 subjects were interviewed and completed the clinical examination in a mobile examination center (MEC). After the exclusion of pregnant and lactating women, those using insulin and others who reported having cancer, 3124 remained in the analysis.

The final sample consisted of 1445 subjects, with complete data on all the MetS criteria, were used to determine the BMI threshold values to predict MetS risk factors.

### **Socio demographics and economic status**

Socio-economic variables such as age, gender, education, marital status and poverty income ratio (PIR) were included in the analysis. Education level was categorized into three groups:  $< 8$  yr, 8-12 yr, and  $> 12$  yr of education. Poverty income ratio from NHANES was computed as a ratio of income to the family's pertinent poverty threshold established by the US Census Bureau in a given year calendar (232). The following NHANES definitions were used, a  $PIR \geq 1.0$  is indicative of income above the poverty level while  $<1.0$  is below the official poverty threshold. The PIR categories were defined as  $<1.85$  indicating low,  $\geq 1.85-3.5$  as medium, and  $>3.5$  as high socioeconomic status. Age was grouped into 6 categories: 20-29, 30-39, 40-49, 50-59 and  $\geq 60$  years of age.

### **Dietary and lifestyle factors**

Smokers were designated as current, past, and never smokers. Individuals who had smoked  $\geq 100$  cigarettes during their lifetimes and who reported not currently smoking were considered as past smokers. Drinking was classified into three groups: Heavy, moderate, and non-drinkers. Heavy drinkers were individuals who ever drank  $\geq 5$  alcoholic beverages per day or drank daily at least one beer, wine, or hard liquor for the past month. Dietary habits were coded on the basis of energy intake from fat ( $< 25\%$ ;  $25\text{-}35\%$ ,  $> 35\%$ ) and carbohydrate ( $<45\%$ ;  $45\text{-}65\%$ ,  $& > 65\%$ ). Physical activity was based on three levels of average level of physical activity per day as defined by NHANES (230). Sitting during the day with not much walking was defined as sedentary. Standing or walking a lot during the day was considered as moderate. The most active participants were those who climbed stairs or hills often, did heavy work or carried loads (233).

### **Measures: Biochemical and Definition of metabolic risk factors**

Biochemical samples were collected during the MEC examination. Fasting blood glucose was determined by the glucose oxidase method quantified using hexokinase enzyme (234). Serum triglyceride was measured enzymatically with the hydrolysis of glycerol. High – density lipoprotein was measured after the precipitation of other lipoproteins with heparin-manganese chloride mixture or with direct method. Biochemical analyses were carried out using Hitachi 706 (serviced by Roche Diagnostics, Indianapolis, IN) (235).

For this study, participants were considered to have a high risk for MetS if they had at least any two of the following 4 components: 1) dyslipidemia – high

triglycerides  $\geq 150$  mg/dL and low HDL 40 mg/dL for males and  $< 50$  mg/dL for females; 2) hyperglycemia  $\geq 100$  mg/dL or oral treatment for diabetes; 3) hypertension – systolic blood pressure (SBP) and /or diastolic blood pressure (DBP) of  $\geq 130$  mmHg and  $\geq 85$  mmHg, respectively, or they were on treatment for any abnormal indicator.

### **NHANES Physical & anthropometrics measure**

The blood pressure was measured using a standard mercury sphygmomanometer to the nearest two mmHg on the right arm with the subject seated and having rested for at least 10 minutes. The average of the last two readings was taken as the subject's blood pressure. When there were only two readings, the last reading was considered as the individual's blood pressure. The waist circumference (WC) was measured using a steel tape at the top of the iliac area. Electronic scale was used to measure the body weight in kilograms, while the height was estimated using a calibrated stadiometer. Body mass index [weight (kg)/height ( $m^2$ )] was calculated for every subject on the basis of collected weight and height (236), and was categorized into 6 groups ( $<23$ , 23-27.49, 27.5 – 29.99,  $\geq 30$  and  $\geq 40$ ) (237). Post-menopausal status was described as having complete cessation of menses for  $\geq 12$  months.

During data collection in NHANES /MEC, a whole body scan was administered for eligible subjects during the 3-year cycles of 1999 - 2004 using Hologic QDR-4500A fan-beam densitometer (Hologic Inc., Bedford, MA). Pregnant females, individuals who reported nuclear medicine studies, use of barium contrast in the past 7 days, a weight  $> 300$  lbs or height  $> 6$  ft 5 were excluded from the DXA tests. The test



provided lean and bone tissue measurements for the total body. Data on total mass (g), fat mass (g), lean mass (g), bone mineral content (g), bone area (cm<sup>2</sup>) and bone mineral density (g/cm<sup>2</sup>) were recorded. Percentage body fat (BF %) was calculated as total body fat mass over total mass X 100, and is a direct measure of an individual's relative body fat. Using sequential regression imputation methods (IVEware software), multiple imputation of the DXA data were made and five complete records were created for each participant. The imputation was to prevent bias that could result from the nonrandom missing data and ensure a more accurate standard error estimation. Pregnant Women and participants with amputations other than fingers or toes were excluded during the process. Detailed description of the multiple imputations can be found in the NHANES 1999-2004 technical documentation (238).

### **Statistical Analysis**

Statistical analysis was carried out using SAS statistical package (version 9.2; SAS Institute Inc, Cary, NC) and STATA statistical software (Version 10.1 for Windows; Stata Corporation, College Station, TX) with adjustments for the complex sample design unless specified otherwise. The survey design variables include a 8 year estimated sampling weight, the primary sampling units (PSU), and the strata. First, the distribution of body composition (%BF, TBF, FFM), anthropometrics and biochemical variables by sex was examined and logarithmic transformations were performed to correct departures from normality on some of the body composition measures. A chi-square test was used to examine the differences in prevalence of MetS criteria by gender and BMI categories (<23, 23-25, 25-27.49, 27.5-29.99, ≥30 and ≥ 40 kg/m<sup>2</sup>) as defined by WHO. Based on the Rao-Scott Chi-Square test with

adjusted F statistics, the test of independence was considered statistically significant at  $p$  value  $< 0.05$ .

Next, Receiver Operating Characteristic (ROC) analysis (215) was carried out separately for males and females to determine BMI values related to the presence of individual or  $\geq 2$  MetS risk factors. The components of MetS risk factors were used as outcomes. The best BMI thresholds and their corresponding sensitivity and specificity were defined based on the minimum distance from the upper left corner of the ROC curve and the Youden's index values. Area under the ROC Curve (AUC) was used as a measure of the overall accuracy of performance of the ROC test in predicting BMI cut off values for MetS criteria. The AUCs values of  $\geq 0.7 - <0.8$ ;  $\geq 0.8 - <0.9$ ; and  $\geq 0.9$  correspond to the acceptable, excellent and outstanding classification (216,239). Then, using simple regression and ROC analysis, the WC values corresponding to the newly estimated and existent BMIs thresholds in males and females were determined.

Logistic regression was used to assess the association between increased risk of metabolic syndrome and BMI while adjusting for selected lifestyle and demographics variables. Two dummy variables were used to code low and high BMI. The BMI values estimated by this study as optimal BMI in predicting MetS risk corresponded to 28 kg/m<sup>2</sup> and 32 kg/m<sup>2</sup> for males and females, respectively. The low BMI ( $< 28$  and  $< 32$  kg/m<sup>2</sup>) served as the reference to facilitate the test of nonlinear relationship between BMI and MetS criteria while adjusting for covariates. Comparisons were made between the odds ratios and 95% CI for specified low and high BMI  $\geq$  kg/m<sup>2</sup> while adjusting for age, education, smoking, alcohol intake,

dietary and physical activity. A value of  $p < 0.05$  indicated statistical significance.

The logistic regression models were modeled separately for males and females. Two way interaction terms were examined in each gender specific model and were dropped when there were not statistically significant.

Weighted correlation between BMI/WC and blood glucose, blood pressure, and lipid profiles was run by gender while adjusting for age. Furthermore, Pearson's correlation analysis was used to assess the degree of linear association between WC and BMI, as well as body composition (fat and fat free mass). Subsequently, multiple linear regression analysis was performed to evaluate the relation between BMI and body fat and fat free mass measures. This was done to assess their contribution to the variation in BMI among African Americans. All regressions were done separately for males and females while controlling for age. Statistical tests were conducted at the p-value less than 0.05 significance level. For the analysis of the 5 multiple imputation NHANES data, the "mim" estimation procedure was carried out to take imputation into consideration (240).

## **Results**

### **Subject Characteristics**

A total of 4415 participants met study criteria and 49.1% were Males.

Demographic characteristics are summarized in **Table 8** by gender and body mass index categories. Males were younger than females (41.7 years vs. 43.9 years, respectively) and their average age increased correspondingly with BMI categories, ranging from 36.7 – 44.6 years. The opposite was observed in females, with the average age slightly decreasing with an increase in BMI values. Between 43.7 –

72.5% of Males had up to high school education level. Males with a BMI of  $\geq 40$  kg/m<sup>2</sup> showed the lowest percentage of individuals with greater than high school (27.5%). For females, the education attainment of high school and > than high school was on average 47%. In the case of females who completed more than high school, the education rate was similar across BMI categories with variation at BMI values of 23-25 kg/m<sup>2</sup> (53%) and 27.5-29.9 kg/m<sup>2</sup> (38%). A statistically significant association (p value <0.05) between PIR and BMI categories was observed among males. The lowest PIR (< 1.85) was recorded in 49-53% males with lower BMI categories of 25 kg/m<sup>2</sup> and below. On average, 37.5% of males with a BMI > 25 kg/m<sup>2</sup> had a PIR > 3.5, while those with a PIR < 1.85 were 32%. In general, among females, a greater percentage (49%) had a lower PIR < 1.85 compared to Males (39%). A higher percentage (32.3-38.8%) of females with a BMI below 25 kg/m<sup>2</sup> had a PIR > 3.5 compared to those (21-25%) with BMI 25 kg/m<sup>2</sup> and above.

### **Prevalence of MetS criteria across BMI categories**

Variations in prevalence of MetS risk factors by gender and across BMI categories are shown in **Figure 5 and 6**. There was a statistically significant association in MetS criteria with the BMI categories in males and females. In males, high fasting blood glucose (HFBG), high blood pressure and low HDL showed an increase percentage with high BMI categories. On the other hand, high triglycerides showed a similar trend but a decrease after BMI of 30 kg/m<sup>2</sup>. High blood pressure had the highest prevalence rate in males and females. In females, the highest rate of MetS criteria were high blood pressure, low HDL and high fasting blood glucose (HFBG).

Among the MetS criteria, triglycerides showed the lowest prevalence rate with a proportionate decrease in both females and males after the BMI of  $\geq 30 \text{ kg/m}^2$ .

### **BMI cut-offs values based on the presence of MetS risk factors**

**Table 9 & 10** summarize gender specific BMI thresholds related to the presence of individual or two or more MetS risk factors. Among males, the BMI thresholds for individual MetS components range between 27- 29  $\text{kg/m}^2$ . The cut off value of having a cluster of the risk factors showed optimal combination of sensitivity and specificity at close to 28  $\text{kg/m}^2$ . Compared to males, the MetS criteria in females were observed at higher ranges of BMI. As illustrated in the **Table 9**, high blood pressure was noted at BMI between 29-30  $\text{kg/m}^2$ , high fasting blood sugar was at 31-32  $\text{kg/m}^2$ , and high triglycerides and low HDL at 32-33  $\text{kg/m}^2$ . Consequently, in females, the findings based on sensitivity and specificity suggest a BMI of 32  $\text{kg/m}^2$  as the most appropriate cut off value to identify the cluster of metabolic syndrome.

Sensitivities, specificities and Areas under the ROC curve to identify BMI thresholds are shown in **Figure 7**. It is noted that a BMI of  $\sim 28 \text{ kg/m}^2$  was the most sensitive and specific to identify male participants with MetS conditions, whereas in females the corresponding value was higher and equal to  $\sim 32 \text{ kg/m}^2$ . Using ROC curve analysis, the newly estimated BMI cut off values correspond to the waist circumference of 96.3 cm (sens=0.87, spec=0.86) for males and 99.2 cm (sens=0.86, spec=0.89) for females. The estimated WC for females was also higher than males under this analysis. Based on a simple regression analysis model, the WC values based on the following equations:  $\text{WC} = 25.105 + 2.545 * \text{BMI}$  for males and  $\text{WC} =$

37.944+1.938\*BMI for females were similar (96.3 cm for males and 99.9 cm for females) to ROC values.

### **Adjusted association between MetS criteria and BMI**

Logistic regression was used to assess the association between BMI and the likelihood of having MetS among African Americans 20 years and older after adjusting lifestyle and demographic covariates. The independent covariates which were examined for incorporation into the final model included age, education, smoking, alcohol consumption, dietary and physical activity. It appears that among males, each of the following predictors in the multivariate models: MetS criteria, age categories, fat intake and smoking status had significant or marginally significant relationship with the probability of having a high BMI (28 kg/m<sup>2</sup>) after adjusting for the relationships of the other predictors. In females, only age categories and MetS components showed a statistically significant association with having a BMI of  $\geq 32$ kg/m<sup>2</sup>.

Focusing on the primary predictor variables of interest, (MetS components), the results show that in males the odds of having a BMI 28 kg/m<sup>2</sup> and above are multiplied by 2.4 when a person has high blood pressure, 1.9 with high triglycerides, 1.2 for high fasting blood glucose, and 1.3 for low HDL after adjusting for the selected demographics and dietary covariates. Among females, relative to respondents with normal blood pressure, those with higher blood pressure had significantly higher (150% higher) odds of having a BMI  $\geq 32$  kg/m<sup>2</sup> when adjusting for age categories. It was also noted that relative to participants with normal triglycerides levels, having high triglycerides was associated with a 2.1 times odds of

high BMI. Further, individuals with high fasting blood glucose had significantly higher odds of (3.6) of being in the category of  $\geq 32$  kg/m<sup>2</sup>, while low HDL cholesterol had significantly higher odds (2.3) of BMI  $\geq 32$  kg/m<sup>2</sup> in comparison to participants with normal HDL cholesterol.

### **Correlation and multiple regression**

In males, there was a high correlation between BMI and % body fat mass (.827) and fat free mass (FFM) excluding bone content (.865). In females, the same high correlations were observed as shown in **Table 11**. Under the MetS criteria and BMI correlation, the high relationship was observed with WC for males and females. Other MetS criteria showed positive weak correlation with BMI. Only the low HDL cholesterol had a negative relationship with BMI.

Multiple linear regression analysis was used to investigate the possible influence of lean fat mass, bone content mass, gender and age on the relation between BMI and body fat. BMI was used as the dependent variable. Data for males and females were analyzed separately (**Table 12**). P- values were considered significant at  $p < 0.05$ . Among males, the age and interaction terms (not shown) were not statistically significant and were excluded from the models. The body fat mass explained 88 percent of the variance in BMI. The combination of body fat mass and lean body mass increased the explained percent of variance to 92 percent. No significant additional variance was explained by the addition of bone mass content and age. For females, the largest percent of BMI variance was explained by body fat mass (91.8%). The incorporation of lean body mass, bone mass and age marginally increased the R<sup>2</sup> value to 93 percent.

## Discussion and Conclusion

The existing WHO and NIH cut off values for BMI of 25 and 30 kg/m<sup>2</sup> were established to delineate overweight and obesity based on observed trends in the relationship between the BMI and morbidity and mortality rates (161) in European Americans. The focus of the current study was to assess the unique relationship between BMI and metabolic health risk factors for African Americans, and the health risks that accompany excess adiposity. The optimal cut-off points for BMI were found to correspond to 28 kg/m<sup>2</sup> in males and 32 kg/m<sup>2</sup> in females. These BMI cut-offs which were predicted from the presence of MetS risk factors, are lower in males and higher for females than the currently suggested cut off values of 30 kg/m<sup>2</sup>. This study confirms that African American females experience health issues at high BMI and this is in agreement with a previous study, which observed a small increase in risk of death at BMI 35kg/m<sup>2</sup> or higher among AA females (228). Thus the practice of using a single BMI standard by gender and race is not supported.

Using simple linear regression and ROC analysis, WC corresponding to the newly estimated values of BMI (28 and 32 kg/m<sup>2</sup>) in males and females were 96 cm and 99 cm, respectively. These findings differ from the current NCEP-ATPIII WC values of  $\geq 102$  cm in males and  $\geq 88$  cm in females predicted from the BMI of 30 kg/m<sup>2</sup> (7,8). The lower threshold for WC in African American males compared to European Americans underlines the heterogeneity in WC values associated with metabolic risk factors in different population groups. Using the NCEP-ATPIII definition of central obesity has contributed to the underestimation of the prevalence of MetS among African American males. Further research is needed to compare the



intra-abdominal adipose tissue in relation with to WC and metabolic risk factors in this population.

The relationships between our new BMI calculated cut offs ( $> 28$  and  $32$   $\text{kg/m}^2$ ) and the presence of MetS risk factors confirmed a high prevalence of high blood pressure among African Americans males and females (241). At BMI greater than  $28$   $\text{kg/m}^2$  and  $32$   $\text{kg/m}^2$ , the odds of having a high blood pressure was 140-150% compared to participants with normal blood pressure. Although the risk of having abnormal triglycerides has been estimated to be lower in African Americans compared to European Americans (242, 243), the odds of having high triglycerides levels were  $\sim 2$  times greater among participants with higher BMI for both males and females, after adjusting for lifestyle and socio-economic covariates. This finding however is not in agreement with previous studies which indicate that hypertriglyceridemia ( $\text{TG} \geq 150$   $\text{mg/dL}$ ) tends to be lower at all levels of BMI in African Americans (243). However, the inclusion of covariates (demographics and lifestyle) in our study might explain this discrepancy. Some investigators have suggested the use of  $\geq 130$   $\text{mg/dL}$  as the cut off value for TG (244) but further studies are still needed to determine the appropriate TG threshold for African Americans. Compared to males, the odds of high blood pressure and low HDL were lower in females. There was a 20% and a 30% increase in odds for high fasting blood glucose and low HDL respectively among males with a BMI  $> 28$   $\text{kg/m}^2$  compared to those with lower BMI. The odds were highest for elevated blood glucose and low HDL among African American females (3.6 and 2.3 times)  $> 32$   $\text{kg/m}^2$ . Previous studies have shown a similar significant association between BMI and elevated glucose

levels among African Americans (245). Community based screening for diabetes may enhance the diagnosis of prediabetic and diabetic status among African Americans to insure early intervention.

BMI is considered a proxy for fatness. Of interest to us, this study was also to examine the gender differences in the relationship between BMI and body composition. Multiple regression was run with BMI as the dependent variable while adjusting for age. The present study confirmed a high correlation between BMI and body fat and lean mass. The body fat mass explained a higher percent of the variation in females BMI value (91.8) compared to males (88%). This relationship was significantly influenced by age in females. The addition of lean mass increased the variance to 93%, thereby explaining a small increase but significant variance of BMI in males. These findings confirm a higher fat mass among African American females and are in agreement with previous reports (246). Further studies would be needed to determine BMI that best classifies individuals according to body fat, while taking into consideration the variation in lean body mass.

This study was based on a cross-sectional data set, and further studies are needed to confirm our findings in longitudinally monitored subjects. In summary, the current study results show the need to consider ethnic background in defining the BMI cut-off values that predict the presence of health risk factors. Furthermore, this study confirmed a lower WC in males compared to females. Although body fat mass is a useful measure in predicting BMI status, lean body mass significantly contributed to the variance explained by fat mass.

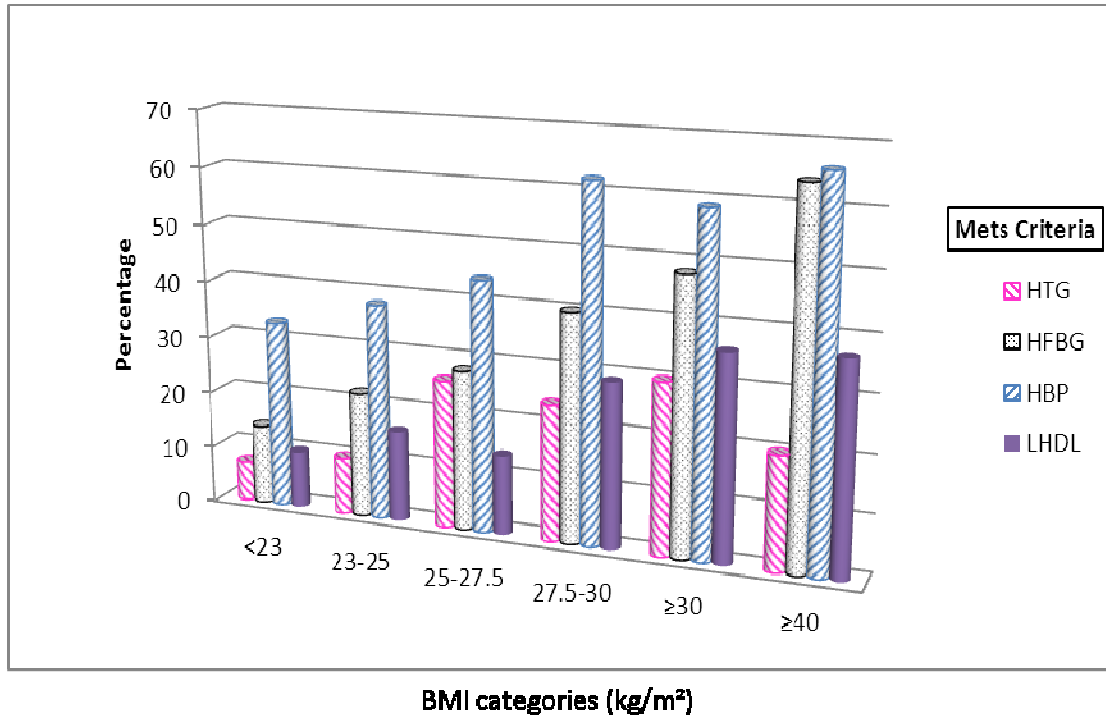
## Appendices

**Table 8. Participant characteristics and body composition by body mass index categories among African American adults. NHANES : 1999-2006**

	<i>BMI ( kg/m<sup>2</sup> )</i>						
	<b>Overall</b>	<b>&lt; 23</b>	<b>23-25</b>	<b>25-27.49</b>	<b>27.5-29.99</b>	<b>≥ 30</b>	<b>≥ 40</b>
<b>Males</b> (n=)	2169	486	358	395	341	495	94
Age ( years)	41.7 ± 0.65	36.7 (±1.52)	40.1 ± 1.99	41.6 ± 1.91	43.2 ± 2.50	44.6 ± 1.32	43.2 ± 2.22
<i>Education</i> (%)							
< high school	5.8 ± 1.29	3.3 ± 1.56	7.3 ± 2.98	5.8 ± 2.18	4.9 ± 2.39	6.9 ± 2.46	11.2 ± 6.46
= high school	49.5 ± 2.98	59.7 ± 5.62	51.7 ± 6.82	37.9 ± 7.07	49.7 ± 5.76	43.7 ± 6.35	61.3 ± 12.68
>high school	44.6 ± 2.76	36.9 ± 5.29	40.9 ± 7.00	56.2 ± 6.96	45.5 ± 5.69	49.3 ± 6.43	27.5 ± 11.11
<i>*PIR</i>							
PIR <1.85	39.7 ± 2.56	49.4 ± 4.82	52.9 ± 7.26	27.9 ± 4.57	39.5 ± 6.53	30.4 ± 6.12	33.3 ± 10.17
PIR 1.85-3.5	27.9 ± 2.18	21.9 ± 4.73	28.9 ± 6.31	35.3 ± 5.52	20.8 ± 5.61	31.5 ± 4.96	31.1 ± 10.92
PIR > 3.5	32.4 ± 2.61	28.7 ± 5.29	18.2 ± 5.69	36.8 ± 5.09	39.6 ± 6.88	38.0 ± 5.86	35.6 ± 11.18
<b>Females</b> (n=)	2246	282	220	275	338	856	275
Age (years)	43.9 ± 0.77	44.7 ± 2.13	48.3 ± 1.44	41.7 ± 3.00	43.9 ± 1.30	40.9 ± 1.85	40.2 ± 1.28
<i>Education</i> (%)							
< high school	5.6 ± 0.92	5.13 ± 2.12	9.6 ± 3.47	7.7 ± 3.34	5.0 ± 2.64	5.2 ± 1.79	2.9 ± 1.84
= high school	47.1 ± 2.63	45.6 ± 7.28	37.2 ± 6.95	43.5 ± 6.55	56.9 ± 6.91	47.8 ± 4.01	46.3 ± 5.53
>high school	47.3 ± 2.59	49.2 ± 7.58	53.1 ± 6.83	48.8 ± 6.58	38.1 ± 6.95	46.9 ± 3.91	50.8 ± 5.36
PIR <1.85	49.2 ± 2.78	44.7 ± 7.87	30.7 ± 7.70	59.9 ± 4.90	43.7 ± 7.65	49.3 ± 3.36	60.4 ± 7.98
PIR 1.85-3.5	24.7 ± 1.66	22.9 ± 5.49	30.5 ± 6.59	18.1 ± 6.21	30.4 ± 5.42	28.0 ± 3.23	14.1 ± 4.47
PIR > 3.5	26.1 ± 2.46	32.3 ± 6.64	38.8 ± 5.55	21.9 ± 5.55	25.8 ± 6.39	22.6 ± 2.79	25.2 ± 6.50

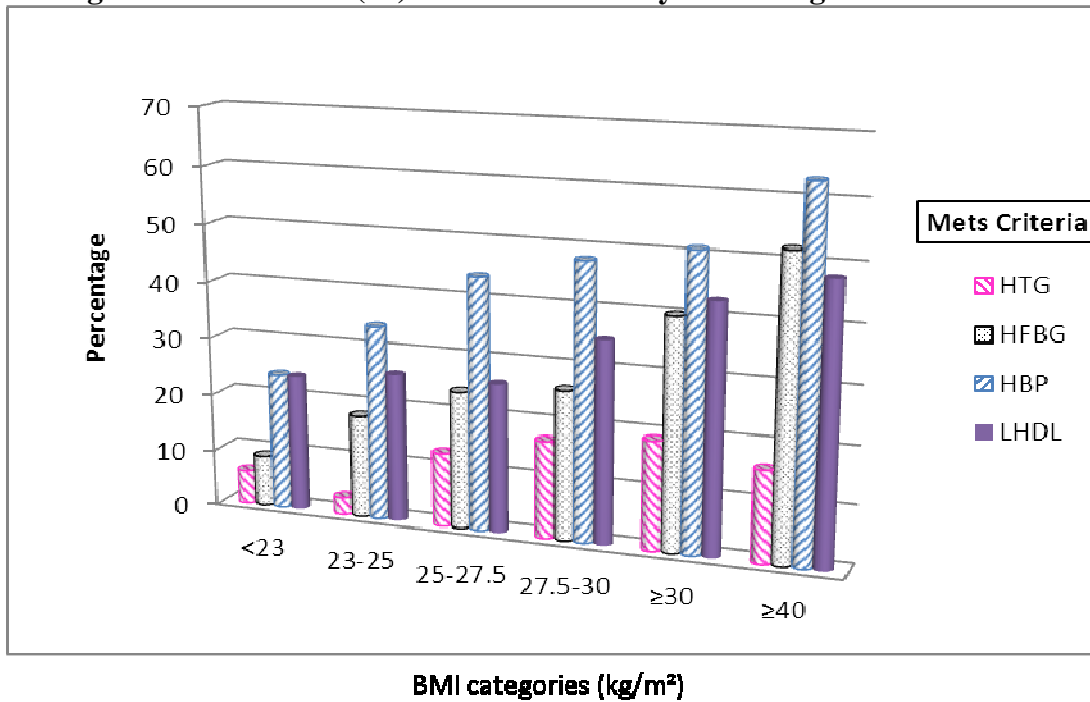
Values are mean ± standard error and percentages. PIR = poverty index ratio  
 SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TG, triglycerides.  
 \*PIR overall p < 0.05 (Wald (Pearson) adjusted F (10, 47) = 2.4358 p = 0.0197)

**Figure 5. Prevalence (%) of MetS criteria by BMI categories in Males**



HBP = high blood pressure; LHD = low high density lipoprotein; HTG= high triglycerides; HFBG = high fasting blood glucose.

**Figure 6. Prevalence (%) of MetS criteria by BMI categories in Women**



HBP = high blood pressure; LHD = low high density lipoprotein; HTG= high triglycerides; HFBG = high fasting blood glucose.

**Table 9. Sensitivity and specificity of BMI cut-offs for metabolic syndrome criteria in females – NHANES 1999-2006**

BMI cut-off (cm)	BP $\geq$ 130/85 MmHG		FBG $\geq$ 100 mg/dL		Triglycerides $\geq$ 150 mg/dL		HDL $\leq$ 40 mg/dL		MetS $\geq$ 2 factors	
	Sens	Spec	Sens	Spec	Sens	Spec	Sens	Spec	Sens	Spec
20	98	4	100	4	98	3	99	4	99	6
21	97	7	100	7	97	6	97	6	98	9
22	95	12	97	11	96	9	94	9	97	13
23	94	15	97	15	95	12	93	13	96	17
24	91	19	95	18	95	16	91	17	94	23
25	89	26	93	25	94	21	87	22	92	29
26	85	29	91	29	93	25	84	25	89	33
27	80	35	87	35	89	31	80	32	85	40
28	75	42	81	42	82	37	77	40	81	46
29	70	46	78	46	76	41	73	43	76	50
30	<u>65</u>	<u>52</u>	73	52	68	46	68	49	70	56
31	58	56	67	58	64	52	61	55	<u>65</u>	<u>62</u>
32	53	61	<u>63</u>	<u>63</u>	<u>60</u>	<u>56</u>	<u>57</u>	<u>59</u>	61	66
33	47	67	56	68	54	62	52	65	52	71
34	43	71	52	72	46	66	46	69	48	74
<b>AUC (95% CI) 0.62 (0.58-0.67) 0.68 (0.64-0.72) 0.60 (0.56-0.65) 0.61 (0.56-0.66) 0.68 (0.64-0.73)</b>										

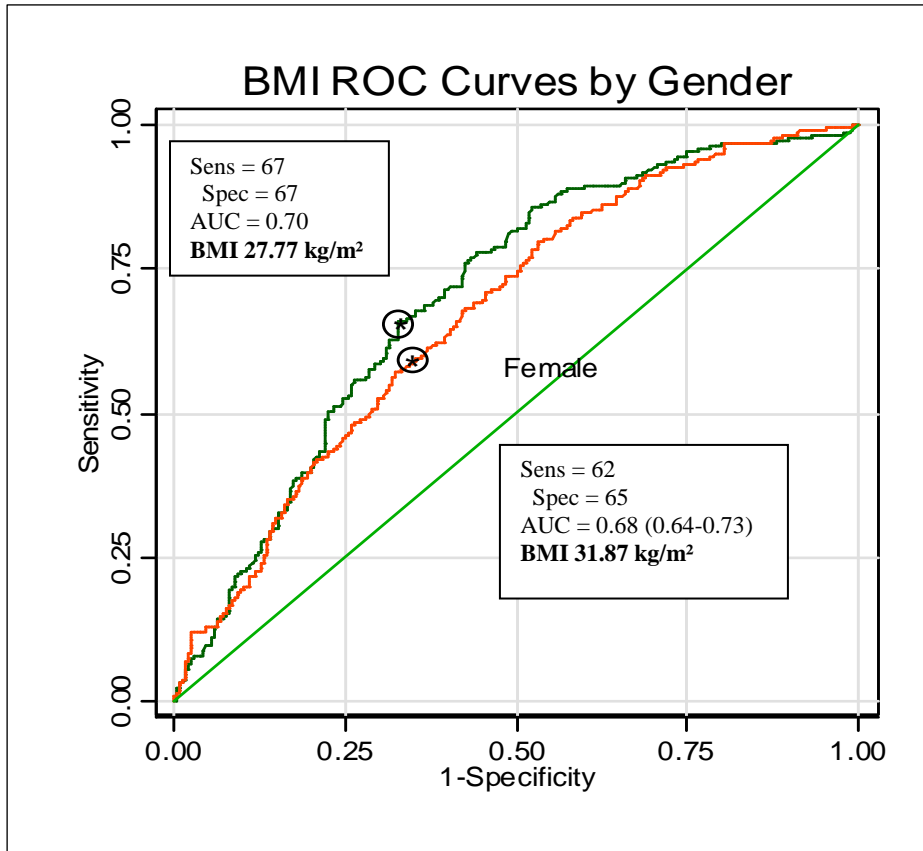
BMI: body mass index; BP: blood pressure; FBG: fasting blood glucose; HDL: High density lipoprotein; MetS: presence of  $\geq$  2 criteria (BP, FBG, low HDL, high triglycerides); Sens: sensitivity; Spec: specificity.

**Table 10. Sensitivity and specificity of BMI cut-offs for metabolic syndrome criteria in males – NHANES 1999-2006**

BMI (kg/m <sup>2</sup> )	BP $\geq$ 130/85 MmHG		FBG $\geq$ 100 mg/dL		Triglycerides $\geq$ 150 mg/dL		HDL $\leq$ 40 mg/dL		MetS $\geq$ 2 factors	
	Sens	Spec	Sens	Spec	Sens	Spec	Sens	Spec	Sens	Spec
20	97	4	97	4	99	4	98	4	98	7
21	94	10	96	10	99	10	97	9	97	15
22	91	17	94	17	98	15	96	14	96	21
23	89	24	92	22	97	21	92	19	94	27
24	84	31	88	29	92	27	89	25	89	35
25	79	41	84	38	88	35	83	33	86	46
26	71	50	79	48	82	43	77	41	78	54
27	<u>62</u>	<u>57</u>	72	56	72	51	74	51	69	61
28	57	64	<u>66</u>	<u>63</u>	<u>63</u>	<u>57</u>	70	57	<u>67</u>	<u>67</u>
29	49	69	58	68	55	63	<u>62</u>	<u>63</u>	63	67
30	41	73	52	74	47	69	56	69	56	73
31	35	77	45	78	41	73	48	74	49	76
32	30	81	38	82	33	78	43	79	39	80
33	26	85	32	85	27	81	39	83	35	83
34	21	88	26	87	23	84	32	86	29	87
<b>AUC (95% CI) 0.62 (0.58-0.67) 0.67 (0.63 -0.71) 0.64 (0.59-0.69) 0.66 (0.60-0.72) 0.70 (0.66-0.74)</b>										

BMI: body mass index; BP: blood pressure; FBG: fasting blood glucose; HDL: High density lipoprotein; MetS: presence of  $\geq$  2 criteria (BP, FBG, low HDL, high triglycerides); Sens: sensitivity; Spec: specificity.

**Figure 7. Receiver operating characteristics curves of the estimated cutoff values for BMI that predict  $\geq 2$  metabolic risk factors in males and females; NHANES 1999-2006**



Sens = sensitivity; Spec: specificity; AUC: Area under the curve; BMI: Body mass index  
 ROC – Receiver Operating Characteristics.

**Table 11. Pearson correlation coefficients between BMI and body composition for males and females measurements adjusted by age\***

<i>Body measures</i>	<i>BMI (kg/cm<sup>2</sup>)</i>		<i>MetS criteria</i>	<i>BMI (kg/cm<sup>2</sup>)</i>	
	<i>MALES</i>	<i>WOMEN</i>		<i>MALES</i>	<i>WOMEN</i>
% body FM	.827	.809	WC	.944	.905
Ln(FM) (g)	.904	.922	Blood glucose	.279	.377
BMC (g)	.449	.531	Systolic BP	.149	.176
BMD (g/cm <sup>2</sup> )	.282	.378	Diastolic BP	.136	.167
FFM(g)	.865	.860	Triglycerides	.295	.208
			HDL-cholesterol	-.345	-.281

lnFM= log of fat mass; BMC = bone mineral content; BMD= bone mineral density; FFM=fat free mass excluding bone mineral content; WC = waist circumference, BP = blood pressure, HDL = high cholesterol lipoprotein. \*All coefficients are significantly greater than zero.

**Table 12. Multiple regression analysis of BMI versus body fat mass, body fat free mass and age. NHANES 1999-2004**

	<b>African Americans</b>	
	Men	Women
	Coefficient ± SE	Coefficient ± SE
Intercept	9.457 ± 0.692	12.434 ± 0.814
Body fat mass (kg)	3.654 ± 0.149*	4.562 ± 0.142*
Lean body mass (kg)	2.278 ± 0.163*	2.223 ± 0.222*
Bone mass content (kg)	-1.503 ± 0.304*	-2.928 ± 0.407*
Age	0.002 ± 0.006	-0.020 ± 0.005*
R <sup>2</sup>	0.92	0.93

\* p < 0.001

**PAPER 3. THE PREVALENCE OF METABOLIC SYNDROME AS INFLUENCED BY MEASURES OF OBESITY & CORRELATES OF THE SYNDROME AMONG AFRICAN AMERICANS.**

**Abstract**

**Background:** African Americans have a lower prevalence of metabolic syndrome (MetS) partly attributable to the use of metabolic criteria that may not be ethnic-specific. Currently used cut offs values for waist circumference might not be appropriate for this group. Our objective was to estimate MetS prevalence using previously developed WC cut-offs and our estimated appropriate WC in a representative sample of adult African Americans. Additionally, the correlates of the syndrome were examined.

**Methods:** A total of 4044 subjects  $\geq 20$  years of age were analyzed, of whom a subsample of 1445 had complete information on metabolic syndrome. Data were derived from the 1999-2006 National Health and Nutrition Examination Survey.

**Results:** Using the National Cholesterol Education Program thresholds of  $\geq 102$  cm for men and  $\geq 88$  cm for women, the age- adjusted prevalence of metabolic syndrome was 25.8% among men and 35.9% among women. Using the newly estimated waist circumference values of  $\geq 95$  cm in men and  $\geq 98$  cm, an increase in age-adjusted prevalence of metabolic syndrome was observed as (30.9%) in men while it decreased to 30.3% for women. The estimated prevalence using the International Diabetes Federation cut offs of  $\geq 94$  cm for men and  $\geq 80$  cm for women was 31.1% and 38.3%, respectively. The latter prevalence was high in women. This was related to the low cut off value of 80 cm, which is too low for African American adult women. Our results also showed that individuals with MetS are impacted by



numerous physiological and biochemical abnormalities, as well as lifestyle choices which negatively affect their health status.

**Conclusion:** The prevalence of metabolic syndrome is underestimated among African American Adults men. The continued increase in obesity and MetS syndrome is of health concern.

### **Introduction**

The concept of metabolic syndrome (MetS) was introduced to characterize a simultaneous occurrence of several cardiovascular risk factors observed in the same subject. The clustering results in markedly high risk of diabetes and heart disease (65,247). In 2001, the National Cholesterol Education Program Expert Panel released the Third Report on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEP/ATPIII), which provided a working definition of the metabolic syndrome (2,32). In 2009, five key organizations reconciled various MetS definitions (29). The condition is diagnosed when any 3 of the 5 metabolic risk factors are present. The risk factors consist of elevated triglycerides  $\geq 150$  mg/dL; glucose  $\geq 100$  mg/dL; systolic blood pressure  $\geq 130$  and/ or diastolic blood pressure  $\geq 85$  mm Hg; reduced high density lipoprotein (men  $< 40$  mg/dL; women  $< 50$  mg/dL); a waist circumference of  $\geq 102$  cm for men and  $\geq 88$  cm for women (29). The MetS definition also includes being treated for dyslipidemia, systemic hypertension and hyperglycemia, excluding use of insulin.

Although the NCEP & IDF definition (30,57) are the most widely used as they provide a relatively simple approach and easily measurable risk factors to diagnose MetS, ongoing research has identified other risk factors associated with the

syndrome. MetS is a proinflammatory condition (2) characterized by high levels of micro-inflammation factors such as C - reactive protein (2,248,249), which is associated with a more deteriorated metabolic risk profile (250). MetS is also linked to a prothrombotic state with increased levels of fibrinogen concentration (251,252). Experimental studies have reported elevated alkaline phosphatase (ALP) with MetS and ALP might promote vascular calcification (253). Moreover, MetS is often associated with hyperuricemia (254, 255). As early as 1923, Kylin recognized that hyperuricemia, hypertension, and hyperglycemia tended to occur together (256). Other risk factors such as microalbuminuria, associated with insulin resistance and central obesity, is also included as an integral component of the MetS by some experts (58,203). Nonalcoholic fatty liver has also recently been recognized as a hepatic manifestation of MetS and obesity (257-260) with elevated liver enzymes. These consist of gamma-glutamyl transferase (GGT) and alanine aminotransferase (ALT) (261-264).

The use of the NCEP/ATPIII criteria to estimate the prevalence of MetS shows it to be a growing problem in the USA. Approximately one-quarter of North Americans (72) are affected by MetS. However, current NCEP criteria have been met with debate in their ability to estimate the prevalence of MetS in different ethnic groups (265,266). For example, in African Americans (AA) who are more prone to high blood pressure, type 2 diabetes (267), and high coronary heart disease mortality (268), a low MetS prevalence is reported. This prevalence is lower in AA men (25.5%) when compared to European Americans (EA) men (38.4%) (32). On the other hand, for women, the MetS prevalence is higher (38.2%) than among EA

women (31.3%). Given that the MetS criteria definition and prevalence for various population remains controversial (165), a review of the limitations of existing MetS definitions is needed. This study estimated the prevalence of MetS in AA based on WC cutoffs the authors estimated to be more appropriate to the AA group and assessed differential characteristics between MetS and non-MetS groups for selected variables. Understanding better the prevalence and correlates of MetS would significantly affect approaches to preventing diabetes and cardiovascular diseases (CVD) among the AA population.

## **Methods**

### **Survey design and study sample**

We analyzed the National Health and Nutrition Examination Survey data collected between 1999 -2006. The data are a representative sample of the non-institutionalized population. The sample was selected based on a multistage, stratified sampling design (270). Due to differential probabilities of participants' selection, sampling weights adjusting for non-response and post stratification were provided. A total of 4044 subjects (men and women)  $\geq 20$  years of age, who were interviewed and underwent medical examination, were included in this study. The exclusion criteria included being pregnant, lactating, using insulin, having cancer and missing values. In order to estimate the prevalence of MetS, only 1445 participants with complete data on NCEP/ATPIII criteria were considered. Detailed information on NHANES dataset design specifications, consent documents, institutional review board approval and survey operations manuals were previously published (183,184,271).

## **Data collection**

The NHANES data included socio-demographic, lifestyle, anthropometrics measurements, dietary intake, medical information, clinical histories, physical examination, blood serum nutrient and biochemical lab values. Demographic and socioeconomic status data, such as poverty income ratio, education (< high school, high school graduate, > high school), marital status and having health insurance were collected using a questionnaire. An electronic scale and a fixed stadiometer were used to measure the weight and height of participants. Dietary intake, based on a 24 hour food intake recall, was collected to estimate intakes of energy, nutrients and other food components. Dietary variables including total Kcal, fat, carbohydrate, protein, fiber, vitamin C, Carotene, vitamin E, selenium, and Iron were estimated using USDA's Food and Nutrient Database for Dietary Studies 3.0 (FNDDS 3.0). Serum concentrations of vitamin C, Carotene, Vitamin E, selenium and iron nutrients were also measured.

The metabolic syndrome was defined comparing the 2009 Joint Scientific Statement for NCEP and IDF and a modified NCEP/ATP III definition to recognize the prevalence of MetS as influenced by the measures of obesity. WC was measured at the high point of the iliac crest to the nearest 0.1 cm during minimal respiration. Up to three blood pressures were recorded using a standard mercury sphygmomanometer. For subjects with three readings, the last two measurements were averaged; for only two readings, the last measurement was taken; and in the case of one reading, that single measurement was considered. Glucose was measured using an hexokinase enzymatic reaction. Serum triglycerides were determined

enzymatically after hydrolyzation to glycerol. HDL-cholesterol was quantified using heparin-manganese chloride mixture.

The diagnosis of MetS was determined for each participant as the presence of at least three of the components of MetS based on three definitions presented in **Table 13**. Participants who reported currently using antihypertensive, antidiabetic, or medications to control triglycerides and cholesterol levels were considered to be positive for MetS (IDF and NCEP/ ATPIII (29). The cut off values used were similar across methods except for WC. Three categories of high waist circumference were defined as  $\geq 102$  cm (40 inches) in men and  $\geq 88$  (35 inches) from NCEP/ATPIII,  $\geq 96$  cm (38 inches) in men and  $\geq 99$  (39 inches) from our previous study, and the IDF values of  $\geq 94$  cm in men and  $\geq 80$  cm in women.

The variables selected to assess some of the characteristics associated with having MetS include urinary albumin measured by a solid-phase fluorescent immunoassay, serum C - reactive protein measured using latex-enhanced nephelometry, plasma levels of fibrinogen determined by the Clauss clotting method using the STA-Compact. Serum alkaline phosphatase was measured using Ostase Immuno Enzymetric Assay (272). Additionally, concentrations of plasma liver function tests alanine aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, and uric acid (273) were considered during the analysis. Other covariates of interest included age, gender, PIR, marital status, and having medical insurance. Detailed descriptions of data collection and analysis methods for NHANES have been previously documented (183,272,273).

### **Definition of variables**

For adults 20 years and older, the level of education completed was categorized as less than 9<sup>th</sup> grade education, 9-11<sup>th</sup> grade, high school/GED, some college or associates degree, and college graduate or higher (274). The marital status variable was defined as married, widowed, divorced, separated, never married, and living with a partner. Poverty income ratio (PIR) values below 1.00 are below the official poverty threshold, whereas PIR values of 1.00 or greater indicate income above the poverty level. The health insurance coverage was defined as being covered by health insurance or some other type of health care plan including governmental programs. Physical activity variable described participants usual daily activities of a typical day. The categories included sitting mainly without much walking, standing or walking a lot without lifting objects, lifting light load or climbing stairs or hills often, and heavy work or carrying heavy loads (275).

C-reactive protein (CRP) was determined and classified based on existing classification of the American Heart Association. A CRP <1.0 mg/L indicates low risk of developing cardiovascular disease, the levels between 1.0 and 3.0 mg/dL is indicative of at average risk for cardiovascular disease, and higher than 3.0 mg/dL represents being at high risk for CVD.

### **Statistical Analysis**

Statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina) and STATA 11 data analysis and statistical software programs (StataCorp LP, College Station, TX). Descriptive analyses were carried out separately in men and women. Data were summarized and displayed as mean and standard error

(SE) for continuous variables and as percentage for categorical variables. T- tests and  $\chi^2$  were used for comparisons between men and women, and for comparisons of subjects with or without MetS. Age adjusted prevalence rates of MetS was calculated to eliminate the confounding effect of age. Age standardization was performed by the direct method using the projected year 2000 US population by NHANES (190). Logistic regression was used to assess the impact of multiple independent variables, presented simultaneously, on the presence/ absence of MetS status. For each type of analysis, statistical significance was considered at  $P < 0.05$ .

## Results

In the study, African American women who have MetS were on average older, had higher BMI and WC compared to men and those who do not have MetS as shown in **Table 14**. Within the African American men group, individuals with MetS were also older and had higher BMI & WC than men without MetS. Distribution of age-specific BMI (**Figure 8 and 9**) revealed consistent high BMI among participants with MetS for both gender. There was a statistically significant ( $p < 0.05$ ) association between PIR and MetS status among men. A high proportion of men with No MetS had a lower PIR, while subjects with a higher PIR showed an increase MetS status. Although education was independent of MetS status, it was observed that men and women with lower education level had a higher percentage of MetS syndrome. Others with higher education had a lower MetS syndrome. For marital status, subjects who had never married had the lowest percentage of MetS while a higher proportion was observed among married men. Among men and women, individuals with health

insurance showed a high proportion of MetS. In terms of lifestyle for both men and women, those who indicated a lower daily average level of physical activity showed higher MetS than the most active. Alcohol intake in both genders did not show any significant correlation with MetS status. Women and men who never smoked had a higher MetS syndrome.

It is noticed in **Table 15** that an assessment of total calorie, fat, protein and carbohydrate intake revealed a higher geo-mean among no MetS than individuals with MetS among men and women. Age specific showed similar findings in addition to a decreased in calorie and macronutrient intake with increasing age. Total protein, carbohydrate, fat intake and fiber intake were higher in men compared to women. Men without MetS significantly consumed higher levels of total carbohydrate, while in women total protein and fat were significantly elevated in no MetS. This observation was reversed within certain age categories. Men with MetS in the 30-39 and 40-49 age groups consumed higher levels of calories, carbohydrate, and total fat compared to those without MetS. In women, higher intake of total kcal was observed in the 40-49 year of age group, and high fat consumption was recorded in the 30-39 and 40-49 age categories. Micronutrients intake including vitamin C, carotene, vitamin E, selenium and iron were lower in MetS compared to individuals without MetS. Only the findings for vitamin E, Selenium and Iron were statistically significant in women. In examining the serum nutrient levels, estimates were omitted for men due to inadequate number of subpopulation members. Among women, except vitamin E, vitamin C, and carotene, iron consumption was statistically significantly lower among those with MetS.



The evaluation of selected laboratory components is summarized in **Table 15**. Hepatic tests show higher laboratory values in men and women with MetS compared to no MetS condition. The differences for ALT, ALP and GGT by MetS status were significant among women, while for men, only the statistical significance was observed for ALP. Other laboratory tests including CRP, fibrinogen, uric acid and microalbuminuria were significantly higher in MetS vs. non MetS respondents in both gender.

**Table 16** summarizes age- adjusted prevalence of metabolic syndrome, which was 30.9% for men and 30.3% for women when the threshold of  $\geq 95$ cm for men and  $\geq 98$  cm for women were used. The prevalence was slightly lower in women compared to men. The prevalence using the IDF threshold of  $\geq 80$  cm was much higher in women. There was no difference in the unadjusted data for men and women using a WC standard of  $\geq 95$ cm/ $98$ cm and  $\geq 94$ cm/ $80$ cm thresholds. However using the WC threshold of  $\geq 102/88$  cm, women had higher MetS prevalence of 34.1% and it was lower in men 23.5%. Considering prevalence by age categories, it increased with age ranges and reached a peak at 60-69 years of age for both gender. Elderly men (70+ years) had similar MetS prevalence of 46.4% when using the  $\geq 95/98$  cm and the IDF thresholds of  $\geq 94/80$  cm. A lower prevalence of 39.2% was observed in the same group when using NCEP/ATPIII thresholds of  $\geq 102/88$  cm. Among women, MetS was higher across age categories when using NCEP/ATPIII thresholds of  $\geq 88$  cm and IDF cut-offs of  $\geq 80$  cm.

Lastly, logistic regression was run for the analysis and prediction of the dichotomous outcome of whether individuals would be classified as having metabolic

syndrome or not. The research hypothesis posed was that the likelihood that individual have MetS is related to presence of biochemical, lifestyle, and dietary predictors. The results showed that according to the model, the log of the odds (coefficients) of having MetS was significantly and negatively related to divorced/separated marital status; stopped smoking; high percent of calorie from carbohydrate and protein; high vitamin E, and Iron intake (  $P < 0.05$ ; **Table 17**). These specified values were associated with the less likelihood of respondents having MetS holding other variables constant. The predictors for which respondents were more likely to have MetS include age, decreased physical activity, high levels of uric acid, and high intake of selenium.

## **Discussion**

This study used the current definition of MetS and suggested WC thresholds to estimate the current metabolic syndrome status among African American adults. The prevalence of metabolic syndrome is higher (30.9%) in men than previously estimated (25.5%) (269) when the criteria for abdominal obesity of  $\geq 102$  cm was used. This WC value was 7 cm higher than our estimated appropriate WC of 95 cm, thus may not capture participants presenting with other metabolic components (276). Our findings also show that the prevalence of MetS in men remains lower than the average national rate of 34.3% (269, 277), which increased from 23.7%, the estimate derived from using the 1988-1994 NHANES III data (72). The prevalence rate from our study 30.9% gave results close to a recent estimate of 32.5% for the MetS using

the IDF WC values of  $\geq 94$  cm. The observed increase of 1.6% was expected as the IDR threshold for WC is smaller.

In women, our observed prevalence of 30.3% was lower than the national average of 32.4% and 38.2% estimated using the  $\geq 88$  cm threshold). Our study suggests the use of a WC of 98 cm, which we determined independently of BMI status and was based on the presence of at least 2 out of the 4 other MetS criteria.

Waist circumference has been shown to be a better criterion in assessing metabolic risk factors than BMI (72) and is the most prevalent component of MetS. The findings in this study support the need for using a WC cutoff point that is not estimated from existing BMI of overweight or obesity values (2). There is still a need for a consensus about which WC threshold to use in the USA. The recent harmonized definition suggests the use of 102 cm for men and 88 cm for women (29), while the 2005 American Heart Association/National Heart, Lung and Blood Institute recommends use of ethnic specific thresholds.

Despite the research and public interest in MetS, the definition and prevalence estimates remain unclear for certain population groups, which may be one of the contributing factors to the low use of metabolic syndrome by health care providers in the diagnosis of the syndrome (278). In order to bridge the gap between the deteriorating health status of the population and tools needed for screening and preventing chronic diseases, further research is needed to advance the conceptualization and formulation of group specific thresholds for different population groups. Among African Americans, the triglycerides and HDL cholesterol levels still require determination of thresholds that are specific to this group and these

may also affect the current estimates of MetS prevalence. Considering that in this study a large percent (83%) of participants with MetS have health insurance, a clear definition of MetS can enhance the diagnosis of this condition in order to implement therapeutic lifestyles and treatments that would improve the health status and reverse the high rate of death related to heart disease and diabetes (2,267).

Our findings of the demographic, anthropometrics, biochemical, and lifestyle characteristics of individuals who have MetS are consistent with previous studies (269). Older age, low education, decreased physical activity, hepatic test abnormalities, chronic inflammatory indicators, microalbuminuria, high uric acid and high fibrinogen status are abnormalities found among individuals with MetS compared to those without MetS. This underscores the need for effective assessment and health care plans to treat the syndrome. However, our logistic regression results only showed age, low physical activity, and uric acid level as significant predictors of positive MetS status. The inclusion of high selenium consumption among the predictors of MetS cannot be explained by this study and require further investigation. In general, higher intake of micronutrients and increased physical activity were confirmed to predict the non-MetS status. However, dietary information provided unreliable results on the lower consumption of macronutrients by individual with MetS. This could be related to the underestimation of food intake by subjects with MetS and use of 24 hour recalls which might not represent an individual regular diet.

## Conclusion

In summary, our results indicate that the prevalence of metabolic syndrome among African American men is higher than current rates when the WC (95cm) that predicts the presence of MetS criteria was used. It was observed that 5.4% of individuals with MetS cannot be diagnosed with this condition when the NCEP-ATPIII WC of 102 cm is considered. Among women, the prevalence of MetS slightly decreased but remained high (~31%) when a WC of 98 cm was applied. The current NCEP-ATPIII WC of 88 cm in women is too low and captures a percentage of subjects without MetS. The use of WC determined based on presence of multiple metabolic risk factors provides a better assessment of MetS than WC based on BMI. The stunning increase in the MetS prevalence in the USA and among various ethnic groups coupled with the increase in obesity (269) calls for population specific assessment criteria and strategies to reduce obesity, excess food intake, and decreased physical activity.

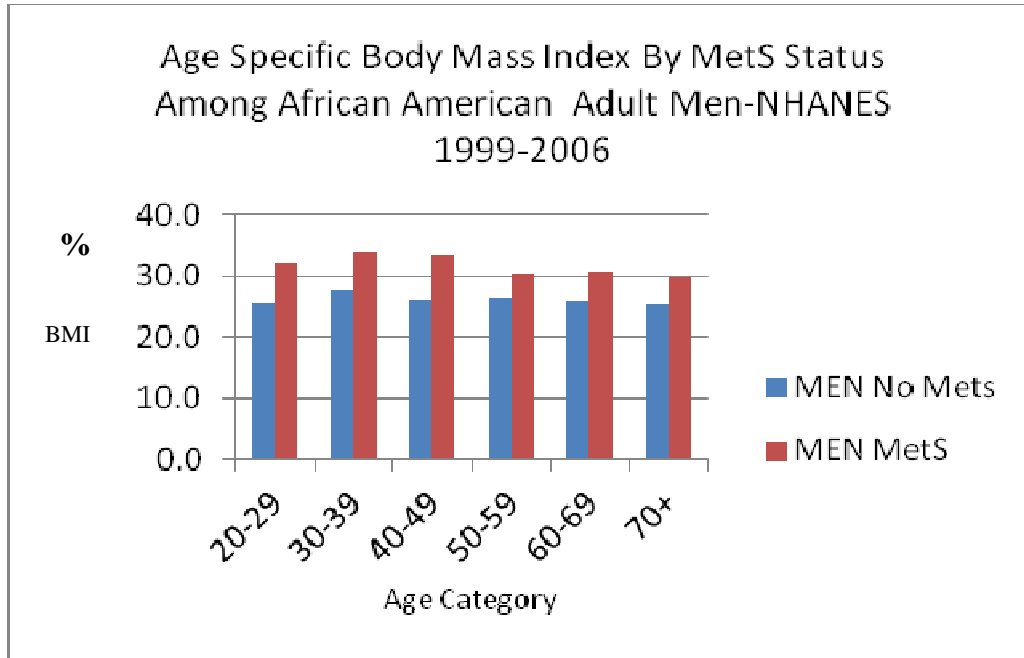
## Appendices

**Table 13. Diagnostic criteria of the metabolic syndrome**

CRITERIA	Rev. ATP III	Modified ATPIII*	IDF
	3 or > Components	3 or > Components	3 or > Components
<b>Waist circumference</b>			
<b>Men (cm)</b>	≥ 102	≥ 95	≥ 94
<b>Women (cm)</b>	≥ 88	≥ 99	≥ 80
<b>HDL Cholesterol mg/Dl</b>			
<b>Men</b>	< 40	< 40	< 40
<b>Women</b>	< 50	≥ 50	≥ 50
<b>Blood Pressure mmHg</b>	≥ 130/85	≥ 130/85	≥ 130/85
<b>Glucose (mg/dL)</b>	≥ 100	≥ 100	≥ 100
<b>Triglycerides (mg/dL)</b>	≥ 150	≥ 150	≥ 150

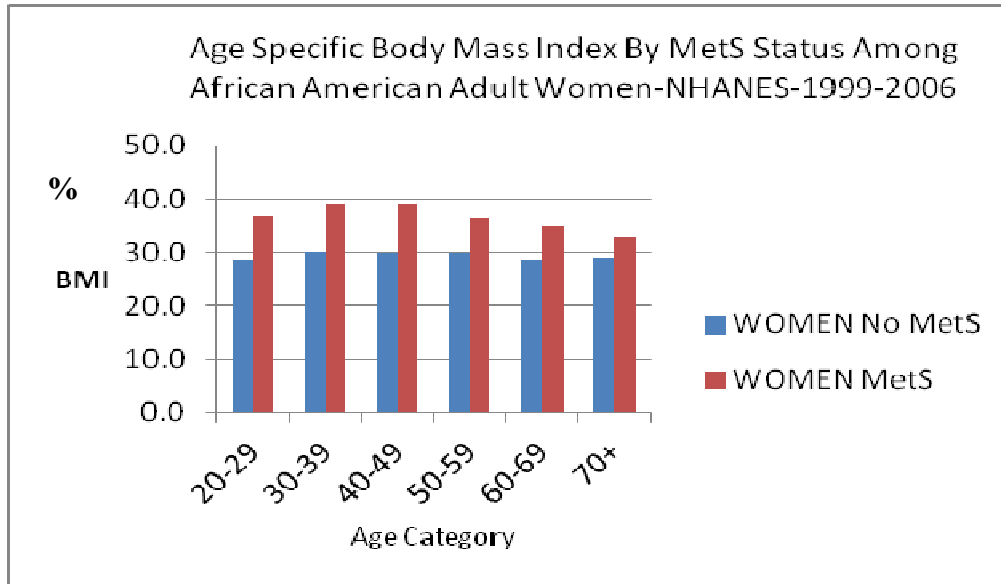
ATPIII- Diagnostic Criteria of the Adult Treatment Panel III Revised by the American Heart Association and the National Heart, Lung, and Blood Institute; Modified ATPIII\* - Diagnostic Criteria of the Adult Treatment Panel III Revised by the American Heart Association and the National Heart, Lung, and Blood Institute –WC adjusted to 95 cm for men and 99 cm for women; IDF – Diagnostic Criteria of the International Diabetes Federation.

**Figure 8 . Age Specific BMI Index by MetS-African American Adult Men-NHANES 1999-2006**



Values: distribution of age group specific BMI; BMI: body mass index; No MetS: no metabolic syndrome; MetS: 3 or more metabolic syndrome criteria are present

**Figure 9. Age Specific BMI Index by MetS-African American Adult Women-NHANES 1999-2006**



Values: distribution of age specific BMI; BMI: body mass index; MetS: presence of 3 or > metabolic syndrome criteria; No MetS: absence of metabolic syndrome.

**Table 14. Characteristics of African Americans Adults by Metabolic Syndrome Status, NHANES 1999-2006**

	Men				P value	Women				P value
	No MetS		MetS			No MetS		MetS		
	N	Mean (SE)	N	Mean (SE)		N	Mean (SE)	n	Mean (SE)	
Age ( years)	431	39.0 (0.58)	213	50.2 (0.93)		469	41.0 (0.71)	216	51.3 (1.1)	
BMI (kg/m <sup>2</sup> )	419	26.4 (0.29)	209	32.0 (0.37)		457	29.6 (0.32)	214	36.7 (0.49)	
Waist (cm)	410	91.0 (0.77)	205	109.5 (0.92)		440	94.0 (0.69)	213	112.3 (0.78)	
<b>PIR</b> < 1.85	179	40.9(2.4)	80	34.2(3.5)	0.045	240	51.1(1.8)	103	46.9(3.8)	0.057
1.85 - ≤3.5	137	31.4(1.9)	62	29.4(3.9)		105	22.1(1.8)	67	31.4(3.1)	
> 3.5	122	27.7(2.1)	73	36.4(3.3)		121	26.7(2.0)	46	21.6(3.8)	
<b>Education</b>					0.93					0.13
< 12 years	160	32.1(2.7)	87	34.1(4.0)		137	24.5(2.2)	83	32.8(3.4)	
= 12yr/GED	113	25.3(2.0)	54	24.3(2.8)		112	22.6(1.9)	62	23.9(3.1)	
Some college	137	30.2(2.1)	61	28.4(3.2)		180	36.0(2.3)	69	30.8(3.7)	
Graduate+	59	12.4(1.7)	28	13.1(2.6)		83	16.8(2.0)	28	12.4(2.3)	
<b>Marital Status</b>					<0.001					<0.001
Married	172	36.5(2.7)	123	51.1(3.3)		146	29.4(2.1)	78	32.7(2.9)	
Widowed	23	2.7(0.4)	21	7.0(1.7)		47	6.8(1.0)	53	17.9(2.5)	
divorced/separated	52	10.5(1.4)	31	14.2(2.2)		117	23.2(1.6)	61	26.2(3.2)	
with partner	164	38.9(2.7)	32	15.5(2.6)		147	30.9(2.1)	35	17.6(2.9)	
never married	45	11.2(1.6)	22	12.1(2.3)		46	9.6(1.4)	11	5.5(1.6)	
<b>Health Insurance</b>										
Yes	323	67.4(2.7)	195	83.1(2.4)	<0.001	405	79.5(2.4)	202	84.1(2.9)	0.188
No	139	32.6(2.7)	34	16.9(2.4)		102	20.5(2.4)	38	15.8(2.9)	
<b>Physical Activity</b>					<0.001					0.072
mainly seats	94	18.2(1.6)	76	29.1(2.4)		140	26.6(1.8)	92	37.5(3.9)	
stand or walk	234	49.9(2.4)	118	53.9(3.1)		297	57.6(2.4)	121	49.6(3.9)	
light load, stairs, hills	96	21.3(1.9)	24	11.1(2.2)		64	12.6(1.8)	22	9.9(2.1)	
heavy load	46	10.5(2.1)	10	5.8(1.9)		14	3.1(1.0)	7	2.9(1.3)	
<b>Alcohol Intake</b>					0.07					0.512
<30 drinks/month	303	84.4(2.2)	156	91.1(2.3)		405	95.6(0.9)	193	96.1(1.4)	
≥ 30 - ≤ 60 /month	34	10.8(1.8)	11	7.7(2.2)		12	2.9(0.9)	4	1.6(0.9)	
≥ 61 drinks/month	16	4.7(1.2)	2	1.2(0.8)		6	1.4(0.4)	3	2.3(1.4)	
<b>Cigarette Smoking</b>					<0.001					0.037
Daily	163	35.5(2.6)	63	28.6(3.3)		94	18.4(1.8)	46	21.7(3.0)	
Stopped	73	12.7(1.2)	66	23.3(2.6)		65	11.7(1.4)	52	17.8(2.3)	
Never	233	51.8(2.6)	108	48.1(3.5)		354	69.9(2.6)	144	60.5(3.2)	

Mean (SE) : mean and standard error; No MetS = absence of metabolic syndrome ; MetS= Presence of 3 or > metabolic syndrome criteria; BMI: body mass index; PIR : Poverty income ratio.



**Table 15. Comparison of dietary intake, nutrient serum levels and biochemical characteristics by metabolic syndrome status among African American Adults, NHANES 1999-2006\***

Dietary	Men					Women				
	N	No MetS	N	MetS	pvalue	N	No MetS	N	MetS	Pvalue
		Mean (SE)		Mean (SE)			Mean (SE)		Mean (SE)	
Total Kcal	207	2347 (61.3)	406	2079 (65.3)	0.001	214	1706 (39.4)	437	1553 (43.6)	0.023
Total Prot. (gm)	207	82 (2.6)	406	78 (2.5)	0.109	214	61 (1.7)	437	56 (1.7)	0.044
Total CHO (gm)	207	276 (7.1)	406	242 (8.6)	0.001	214	205 (5.4)	437	194 (5.6)	0.203
Total Fat (gm)	207	80 (2.9)	405	76 (3.1)	0.191	214	62 (1.4)	437	55 (2.1)	0.005
Fiber (gm)	207	11.3 (0.9)	406	8.9 (1.3)	0.09	214	8.9 (0.4)	437	8.4 (0.6)	0.524
Vitamin C (mg)	207	65.9 (11.3)	402	44.4 (11.6)	0.197	214	39.3 (4.8)	437	53.2 (10.3)	0.249
Carotene (RE)	31	139.2 (31.6)	57	79.2 (32.8)	0.141	37	130.2 (16.9)	84	162.1 (37.7)	0.418
Vitamin E (mg)	207	7.5 (0.8)	405	6.1 (0.6)	0.09	214	6.6 (0.3)	437	5.3 (0.4)	0.014
Selenium (mcg)	207	114.1 (5.7)	406	117.3 (6.9)	0.736	214	98.9 (4.1)	437	67.8 (4.5)	0.000
Iron (mg)	207	14.1 (0.4)	406	14.1 (0.5)	0.96	214	11.0 (0.3)	437	9.0 (0.3)	0.009
<b>SERUM</b>										
VitaminC mg/dl	124	(-)	239	(-)	(-)	120	0.87 (0.02)	250	0.61 (0.05)	0.001
Carotene ug/dL	178	(-)	360	(-)	(-)	176	2.4 (0.19)	370	1.5 (0.17)	0.004
Vitamin E ug/dL	211	(-)	422	(-)	(-)	213	996.8 (17.1)	455	997.1 (38.8)	0.997
Iron ug/dL	87	(-)	187	(-)	(-)	154	67.0 (2.6)	417	67.1 (2.7)	0.979

Means - geo-mean & standard error. Total Kcal Energy (kcal); Total Prot.: Total Protein (gm); total CHO: carbohydrate (gm); Total fat (gm); \*p value based on log results. (-) omitted due to inadequate number of subpopulation members.

**Biochemical Laboratory Characteristics by Metabolic Syndrome Status among African American adults , NHANES 1999-2006\***

HEPATIC TEST	Men					Women				
	n	No MetS	N	MetS	Pvalue	n	No MetS	n	MetS	Pvalue
		Mean (SE)		Mean (SE)			Mean (SE)		Mean (SE)	
ALT (U/L)	210	27.3 (0.9)	421	28.2 (1.0)	0.502	213	18.9 (0.6)	452	21.3 (0.8)	0.015
ALP (U/L)	177	66.5 (1.2)	360	72.7 (1.9)	0.01	176	67.8 (1.4)	367	76.1 (1.7)	0.001
GGT (U/L)	210	37.3 (3.03)	422	41.5 (3.4)	0.341	213	22.7 (1.1)	452	33.1 (3.3)	0.004
<b>OTHERS</b>										
CRP (mg/dL)	211	0.13(0.01)	426	0.29 (0.03)	0.001	214	0.23 (0.02)	462	0.62 (0.05)	0.001
Fibr. mg/dL	70	361.7 (9.3)	104	396.3 (12.2)	0.03	73	386.8 (7.4)	123	439.7 (11.9)	0.002
uric acid mg/dL	210	6.1 (0.16)	422	7.0 (0.21)	0.001	213	4.8 (0.15)	452	5.7 (0.14)	0.001
Micralb. mg/dL	209	10.3 (0.6)	423	18.6 (2.0)	0.001	215	10.8 (0.5)	452	18.6 (1.9)	0.001

Means - geo-mean & standard error; ALT - Alanine aminotransferase ALT (U/L) ; ALP Alkaline phosphatase (U/L); GGT (U/L); CRP C-reactive protein(mg/dL); Fibr. Fibrinogen; Micralb. Microalbuminuria(mg/L) \*p value based on log results.

**Table 16. Age -adjusted and age-specific prevalence of metabolic syndrome among African Americans adults, NHANES 1999-2006**

	<b>N</b>	<b>Mets* Syndrome</b>	<b>Mets** NCEP Syndrome</b>	<b>Mets ***IDF Syndrome</b>
Adjusted	<b>1457</b>	<b>30.6 (1.2)</b>	<b>31.5 (1.1)</b>	<b>35.2 (0.9)</b>
Men	<b>700</b>	<b>30.9 (1.8)</b>	<b>25.8 (1.7)</b>	<b>31.1 (1.7)</b>
Women	<b>757</b>	<b>30.3 (1.3)</b>	<b>35.9 (1.2)</b>	<b>38.3 (1.1)</b>
Unadjusted	1329	28.3 (0.6)	29.3 (1.1)	28.7 (1.1)
Men	644	28.4 (1.9)	23.5 (1.8)	28.6 (1.9)
Women	685	28.8 (1.4)	34.1 (1.5)	28.8 (1.3)
<b>Men</b>				
20-29	126	8.6 (2.2)	5.3 (1.9)	8.6 (2.2)
30-39	126	21.9 ( 3.8)	19.6 ( 3.4)	21.9 (3.8)
40-49	137	29.1 (3.8)	23.7 (3.5)	29.9 ( 3.7)
50-59	65	43.7 (5.3)	35.5 (5.0)	43.7 (5.3)
60-69	110	60.5 (3.8)	52.6 (4.1)	60.5 (3.8)
70+	80	46.4 (4.1)	39.2 (4.7)	46.4 (4.1)
<b>Women</b>				
20-29	114	10.2 ( 2.8)	12.4 (3.3)	14.5 (3.2)
30-39	131	19.8 (3.4)	20.8 (3.2)	20.8 (3.2)
40-49	160	28.8 (4.1)	36.5 (4.1)	40.4 (4.2)
50-59	85	38.7 (5.2)	51.9 (5.2)	51.9 (5.3)
60-69	110	59.7 (3.6)	60.4 (3.6)	64.7 (3.4)
70+	85	43.4 (5.2)	51.9 (5.5)	54.5 (5.0)

\* MetS- Metabolic Syndrome defined using Waist Circumference (WC)  $\geq$  95cm in men and  $\geq$  98 cm in women

\*\* MetS- Metabolic Syndrome defined using WC  $\geq$ 102 cm in men and  $\geq$  88 cm in women (NCEP/ATP)

\*\*\* MetS- Metabolic Syndrome defined using WC  $\geq$  94 cm in men and  $\geq$  80 cm in women (IDF)

**Table 17. Predictors of metabolic syndrome status by selected factors among African American adults, NHANES 1999-2006**

Variables		DF	Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square
Intercept		1	-24.1426	3.7234	42.0425	<.0001
<b>Age</b>	60 + yrs	1	2.1953	0.7721	8.0833	0.0045
<b>physical activity</b>	seat	1	16.0856	2.3241	47.9025	<.0001
	stairs, hill light load	1	14.1954	3.0035	22.3379	<.0001
	Walk stand	1	13.7886	2.3165	35.431	<.0001
<b>Marital status</b>	divorced separated	1	-1.5027	0.6159	5.9524	0.0147
	never married	1	0.7731	1.3116	0.3474	0.5556
	Partner	1	-0.2395	1.6663	0.0207	0.8857
	Widowed	1	0.746	0.8449	0.7796	0.3773
<b>smoking</b>	daily/ sometimes	1	-0.7349	1.2137	0.3666	0.5448
	Stopped	1	-2.5249	0.4944	26.0849	<.0001
<b>PCALCHO</b>	percent of CHO	1	-0.0305	0.0165	3.4275	0.0641
<b>PCALPROT</b>	percent of Prot	1	-0.2427	0.0742	10.7081	0.0011
<b>LBXSUA</b>	Uric acid	1	0.599	0.2435	6.0496	0.0139
<b>LOGVITE</b>	log vit E	1	-0.8379	0.4268	3.8549	0.0496
<b>LOGSEL</b>	log sel	1	3.2573	1.1398	8.1668	0.0043
<b>LOGIRN</b>	Log Iron	1	-1.3628	0.6666	4.1803	0.0409

Pcalcho = percent of calories from carbohydrate; Pcalprot: percent of calories from protein;  
Likelihood ratio  $\chi^2= 1503264.77$  (df=27), P <0.0001.

## Chapter 5: SUMMARY AND IMPLICATIONS

The study examined the waist circumference and body mass index cut-offs for African Americans according to the clustering of metabolic syndrome risk factors. It also assessed the prevalence of MetS as influenced by measures of obesity and correlates of the syndrome. Using NHANES 1999-2006 data, the major findings suggest that current NCEP/ATP III waist circumference of 102 cm fails to identify individuals with multiple metabolic risk factors among males, while for female, the 88 cm threshold include individuals without MetS resulting in the estimation of a high prevalence of MetS in women. The thresholds with relative high sensitivity and specificity are 95 cm in men and 98 cm in women. Findings on the relationship between BMI and metabolic health risk factors, that accompany excess adiposity, show that African American females experience health issues at high BMI 32kg/m<sup>2</sup> compared to males at 28kg/m<sup>2</sup>. Corresponding waist circumference values using simple linear regression or ROC analysis were 96 cm and 99 cm, respectively, for males and females. Thus the findings support the need to review existing WC cut off values. The evaluation of MetS prevalence using the newly estimated WC values revealed a higher age-adjusted MetS prevalence of 30.9% than current estimated of 25.5% and a decrease in MetS rate among women (30.3%) compared to the national average of 32.4% among women.

### Implications

African American females have high obesity rates compared to men. In general, MetS prevalence and obesity continue to rise in the USA. With increase health costs, reduced quality of life, and the need to lower health disparities, successful prevention

and management of increasing metabolic abnormalities and related cardiovascular and type 2 diabetes illnesses require accurate identification of high-risk individuals. Defining population based MetS criteria will enhance its diagnosis, as well as the prevention and control of non-communicable diseases. This implies using simplified screening tools to identify high risk individuals that would yield effective intervention and costs. Within the African American population group, further research is still needed to conceptualize this MetS. This would provide appropriate cut off values for other MetS criteria such as triglycerides and HDL Cholesterol.

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