

ABSTRACT

Title of Document: **APPROPRIATE WAIST CIRCUMFERENCE
CUTOFF VALUES FOR THE DIAGNOSIS OF
METABOLIC SYNDROME IN MEXICAN
AMERICAN ADULTS**

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Metabolic syndrome increases the risk of cardiovascular disease and diabetes. The International Diabetes Federation (IDF) recently proposed new criteria for the diagnosis of metabolic syndrome, which requires the presence of central obesity as measured by ethnic specific waist circumference (WC) cutoff values. Currently, no specific WC thresholds for diagnosis of central obesity in Hispanics are available. The objectives were to determine the appropriate gender specific WC thresholds for diagnosis of central obesity in Mexican American adults and to estimate the prevalence of metabolic syndrome using IDF definition with and without the modified WC in this population. Data from 3265 Mexican American adults aged 20-80 years who participated in the National Health and Nutrition Examination Survey 1999-2006 were used. The prevalence of metabolic syndrome was compared using IDF criteria with and without the modified waist circumference. Receiver operating characteristic curve analysis suggested that yielding at least 80% sensitivity, the WC value of 90 cm in both genders was more appropriate in predicting the presence of two or more metabolic syndrome risk factors in

this population. Based on this cutoff, there was 34% reduction in the prevalence of central obesity in women (82.5% to 54.2%). The age adjusted prevalence of metabolic syndrome decreased from 58.4 to 48.2%. The metabolic syndrome was more common among Mexican American men than women (55.8% in men versus 37.8% in women, $P = 0.0003$). Our findings provided a practical guidance in the assessment and screening of central obesity and metabolic syndrome in Mexican Americans.

APPROPRIATE WAIST CIRCUMFERENCE CUTOFF VALUES FOR THE
DIAGNOSIS OF METABOLIC SYNDROME IN MEXICAN AMERICAN
ADULTS

By

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Dedication

To my devoted mother Afifeh, who inspired me to develop a deep awareness of love, human values, wisdom and knowledge. Her lifetime love and support has encouraged me to achieve my goals.

To my loving husband Mohsen, whose incredible love, patience and support gave our family enormous joy, happiness and pride.

To my loving children Ilia, Ariana and Arya, whose affection and compassion have enriched and enlightened my being.

To my dearest uncle Davood, whose integrity, strength and courage will remain as invaluable sources of truth and guidance.

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Table of Contents

Dedication	i
Aknowledgment.....	ii
Table of Content.....	iii
List of Tables.....	v
List of Graphs.....	vi
Chapter 1. Introduction.....	1
Objectives.....	6
Research Questions.....	7
Literature Review.....	8
Metabolic Syndrome.....	8
Characteristics of Metabolic Syndrome.....	14
Prevalence of metabolic syndrome.....	17
Pathogenesis of Metabolic Syndrome.....	18
Hispanic/Latino Population.....	24
Metabolic syndrome in Hispanics.....	29
Diabetes in Hispanics.....	30
Cardiovascular Disease in Hispanics.....	31
Overweight and Obesity in Hispanics.....	32
Hypertension in Hispanics.....	33
Dyslipidemia in Hispanics.....	35
Dietary Pattern and Lifestlye in Hispanics.....	37
Elevated C-reactive Protein in Hispanics.....	41
Chapter 2: Methods.....	42
Survey Description and Sample Design.....	42
Data Prepration and Use of Sample Weight.....	43
Statistical Software.....	44
Study Population.....	45
Variables of Interest.....	45
Metabolic syndrome Risk Factors.....	49
Assessment of Covariates.....	49
Statistical Analysis.....	49
Chapter 3: Appropriate Waist Circumference Cutoff Values for the Diagnosis of Metabolic Syndrome in Mexican American Adults	53
Abstract	53
Introduction.....	55
Subjects and Methods.....	57
Statistical Analysis.....	60
Results.....	61
Discussion.....	64
References.....	67
Appendices 1.....	72

Chapter 4: Abdominal Adiposity, Overall Obesity and Metabolic Syndrome in Mexican American Adults	79
Abstract.....	79
Introduction.....	81
Subjects and methods.....	82
Statistical Analysis.....	86
Results.....	87
Discussion.....	89
References.....	93
Appendices 2.....	98
Chapter 5: Metabolic Syndrome and C - reactive protein Levels among Mexican American Adults	102
Abstract.....	102
Introduction.....	104
Subjects and methods.....	105
Statistical Analysis.....	109
Results.....	110
Discussion.....	113
References.....	117
Appendices 3.....	123
Chapter 6: Conclusion.....	133
Bibliography.....	140

List of Tables

- 1.1. Criteria for Clinical Diagnosis of Metabolic Syndrome
- 3.1. Basic characteristics and metabolic risk indicators among Mexican American adults aged 20-80 years, NHANES 1999-2006
- 3.2. Socio-economic and behavioral characteristics of the study population, NHANES 1999-2006
- 3.3. The age adjusted prevalence of the metabolic syndrome among Mexican American adults aged 20-80 years by cardiovascular risk factors, NHANES 1999-2006
- 3.4. Sensitivity, specificity and distance in the receiving operating characteristic (ROC) curve for waist circumference cutoff values in Mexican American adults
- 3.5. The age adjusted prevalence of the metabolic syndrome and central obesity among Mexican American adults aged 20-80 years by gender, NHANES 1999-2006
- 4.1. Basic characteristics and metabolic risk indicators among Mexican American adults aged 20-80 years, NHANES 1999-2006
- 4.2. Socio-economic and behavioral characteristics of the study population, NHANES 1999-2006
- 4.3. Correlation coefficients of waist circumference or body mass index with metabolic syndrome risk factors
- 4.4. Odds ratios and 95% confidence interval for metabolic syndrome risk factors according to quartiles of waist circumference in Mexican American adults
- 5.1. Basic characteristics and metabolic risk factors among Mexican American adults aged 20-80 years, NHANES 1999-2006
- 5.2. Socio-economic and behavioral characteristics of the study population, NHANES 1999-2006
- 5.3. Geometric mean concentrations and the age adjusted prevalence of elevated CRP (mg/l) concentrations by presence and absence of metabolic syndrome or its components among Mexican American adults, NHANES 1999-2006
- 5.4. The age adjusted prevalence of metabolic syndrome according to quartiles of CRP among Mexican American adults, NHANES 1999-2006
- 5.5. Correlation coefficients of log transformed CRP and the components of metabolic syndrome among Mexican American adults, NHANES 1999-2006
- 5.6. Odds ratios and 95% confidence interval for metabolic syndrome and its components according to quartiles of CRP among Mexican American adults, NHANES 1999-2006
- 5.7. Association between elevated CRP and elements of metabolic syndrome among Mexican American adults

List of Graphs

- 3.1. Prevalence of the metabolic abnormalities among Mexican American adults aged 20-80 years, NHANES 1999-2006.
- 3.2. The ROC curves for waist circumference to predict the presence of two or more metabolic syndrome risk factors based on IDF definition in men and women
- 5.1. Geometric mean CRP concentrations by the number of components of metabolic syndrome in Mexican American men and women, NHANES 1999-2006

Chapter 1: Introduction

Metabolic syndrome, the clustering of metabolic risk factors including central obesity, insulin resistance, atherogenic dyslipidemia, hyperglycemia, hypertension, prothrombotic and a proinflammatory condition is associated with increased risk of cardiovascular disease and type 2 diabetes mellitus (1). This syndrome is one of the major medical and public health problems in the United States (2, 3) and worldwide (4-6). An estimated 47 million U.S. residents have metabolic syndrome and the age adjusted prevalence of syndrome is 23.7 percent (2). The prevalence ranges from 6.7 percent among people ages 20–29 to 43.5 percent for ages 60–69 and 42.0 percent for those age 70 and older. Mexican Americans have the highest age adjusted prevalence of metabolic syndrome (31.9 percent). The lowest prevalence is among whites (23.8 percent), African Americans (21.6 percent) and people reporting as “other” race or ethnicity (20.3 percent) (7).

Subjects with metabolic syndrome have twice greater risk to die from and three times greater risk of having a heart attack or stroke, compared with people without the syndrome. Furthermore, people with metabolic syndrome have five fold larger risk of developing type 2 diabetes (1). Coronary Heart Disease (CHD) is a major public health problem and the leading cause of death in the United States and worldwide (8). In 2004, more than 15 million adults age 20 and older had CHD and each year, more than half a million Americans die from this condition (7). Diabetes is one of the most common chronic diseases worldwide affecting almost 200 million people and is the fourth leading cause of death in the developed countries (8).

In the effort of introducing the metabolic syndrome into clinical practice and identifying individuals with this condition, several sets of criteria have been proposed by different organizations. World Health Organization (WHO), the European Group for the Study of Insulin

Resistance (EGIR), the American Association of Clinical Endocrinologists (AACE) and the National Cholesterol Education Program- Adult Treatment Panel III (NECP ATP III) have suggested some of the most accepted definitions (9-13). All of these definitions agree on the key elements of the metabolic syndrome including obesity, insulin resistance, hypertension and dyslipidemia; however they provide different criteria and cut points to define this cluster. The existence of several definitions was the main reason for proposing single unifying criteria by the International Diabetes Federation (IDF) in 2005, as a simple diagnostic tool for use in clinical practice and research worldwide. The IDF definition requires the presence of central obesity for diagnosis of metabolic syndrome. Central obesity is most easily measured by waist circumference (WC) with gender-ethnic specific thresholds (9). The current recommendations for defining central obesity in MAs (waist circumference ≥ 90 cm in men and ≥ 80 cm in women) are based on data from South Asia population and may not correctly estimate the prevalence of obesity in Hispanics due to ethnic differences in overall adiposity, abdominal adiposity and visceral fat accumulation (14-16). Studies on Asians have shown that for a given BMI or waist circumference, Asians had higher percentage of body fat when compared to Caucasians (17-19). Findings from prospective study of 110 Hispanic and non-Hispanic white women revealed higher levels of adiposity and lower fat free mass in trunk region in Hispanic women (20).

Previous studies have shown a disproportionately high prevalence of diabetes in Hispanics compared to non-Hispanic whites. Hispanics are twice as likely to have diabetes as non-Hispanic whites of similar age. The prevalence of cardiovascular disease is also high in this population and is comparable to non-Hispanic whites (7). Hispanic population is the largest, fastest growing minority group in the United States, representing 14% of the total population (21). Combining

the number of U.S. born Hispanics with legal residents, temporary workers and those without proper documentation would increase the total U.S. Hispanic population to 75 million (22). Recently Ford et al. (2002) reported that metabolic syndrome risk factors are very frequent in Hispanic men and women. Obesity is epidemic among this population and abdominal obesity is present in nearly 46% of Mexican Americans. MA also have a high incidence of other components of metabolic syndrome including: hypertriglyceridemia (37.7%), low levels of HDL cholesterol (39.6%), hypertension or being treated for blood pressure (36.6%) and hyperglycemia or taking medication for diabetes (20%)(2).

Central obesity is one of the main features in identifying individuals with metabolic syndrome. The association between obesity and the components of metabolic syndrome has been investigated by anthropometric measurements such as body mass index (BMI), waist to hip ratio (WHR) and waist circumference (23-26). Body mass index in Kg/m^2 , is a measure of overall obesity and provides estimation of total body fat with no further information on the distribution of excess fat storage. Waist to hip ratio measures abdominal fat accumulation, and has less power in predicting health risk factors when compared to waist circumference. Waist circumference reflects the amount of abdominal adipose tissue storage as well as total fat mass, providing a measure of body fat distribution. It also complements BMI in predicting obesity related diseases and health risks (24-26). Several studies have shown that waist circumference is a better predictor of metabolic abnormalities and cardiovascular disease risk factors than BMI (14, 15 and 26).

A proinflammatory state is frequently present in patients with metabolic syndrome and is recognized by elevated inflammatory markers such as interleukin-1, interleukin-6, tumor necrosis factor- α , intercellular adhesion molecule-1, C- reactive protein (CRP) and elevated

leukocyte count (27-29). CRP, an acute phase reactant produced by liver is the most studied biomarker of low grade inflammation and increases in response to infection, injury and chronic inflammation. Physical activity, smoking, alcohol consumption, estrogen use, lipid lowering statin and anti-inflammatory medications have been documented to alter the CRP concentrations (29, 30). CRP distributions vary by gender and ethnicity (31-34). Previous studies have shown higher levels of CRP among women than men. Mexican American and Black individuals also have higher CRP concentrations when compared to Caucasians (35, 36). Several studies have found associations between higher levels of CRP and metabolic syndrome risk factors (37-39), cardiovascular disease (40-42) and diabetes mellitus (27, 43 and 44).

Considering the high incidence of metabolic syndrome, diabetes and CVD in Hispanic population, there is an urgent medical, ethical and economical need to identify individuals with this syndrome early, so that lifestyle interferences and treatment may prevent the development of diabetes and/or cardiovascular disease in this population. Few studies have investigated the association of abdominal adiposity, overall obesity and the components of metabolic syndrome in Mexican Americans (45) and little information is available on the CRP distribution and its relation with metabolic syndrome in this population. Most of the previous studies have focused on non Hispanic Whites or non representative population samples (23-27, 34, 37 and 47).

Therefore, using data from the National Health and Nutrition Examination Survey (NHANES) 1999-2006, I focused primarily on determining the appropriate waist circumference cutoff values for diagnosis of central obesity in Mexican American adults and compared the prevalence of metabolic syndrome based on IDF definition with and without the modified waist circumference in Mexican Americans. I also examined the association between abdominal adiposity, measured by waist circumference and overall obesity, measured by body mass index with the components

of metabolic syndrome including, triglyceride, blood pressure, fasting plasma glucose and HDL cholesterol in Mexican American adults and investigated the odds for developing metabolic syndrome risk factors according to quartiles of waist circumference in this population. To study the final objectives of the dissertation, I investigated the distribution of CRP and its association with metabolic syndrome in Mexican Americans and estimated the odds ratios for developing metabolic syndrome or its components (central obesity, hypertriglyceridemia, hyperglycemia, hypertension and low HDL cholesterol) according to quartiles of CRP in this population.

To my knowledge, this is the first study to investigate the appropriate waist circumference cutoff values for diagnosis of central obesity and metabolic syndrome in Mexican American adults. In addition, it is the first study to examine the association between abdominal adiposity, overall obesity and CRP with the components of metabolic syndrome in Mexican American adults using 8 years of continuous NHANES 1999-2006 data. The findings of the present study are derived from a representative sample of Mexican American adults in the United States and are applicable to this population. The results from this study will provide practical guidance in identifying individuals with metabolic syndrome and contribute in understanding the association between waist circumference, CRP and metabolic risk factors in this population.

Objectives

1. To determine the appropriate gender specific waist circumference cutoff values for the diagnosis of central obesity in Mexican American adults to predict increased risk of elevated triacylglycerol, reduced HDL cholesterol, elevated fasting plasma glucose, elevated blood pressure, or two or more of these factors.
2. To compare the prevalence of metabolic syndrome in Mexican American adults using current IDF waist circumference and new WC determined in question 1.
3. To investigate the relationship between CRP and the components of metabolic syndrome, in Mexican American adults.
4. To estimate the odds ratios for developing metabolic syndrome and its components (central obesity, hypertriglyceridemia, low HDLc, hyperglycemia and hypertension) in subjects with elevated CRP concentration.
5. To examine the associations of overall obesity (measured by BMI) and abdominal adiposity (estimated by WC) in subjects with metabolic syndrome.
6. To estimate the odds ratios for the development of metabolic syndrome and its components (central obesity, hypertriglyceridemia, low HDLc, hyperglycemia and hypertension) in subjects with elevated WC.

Research Questions

1. What are the appropriate gender specific waist circumference cutoffs for diagnosing central obesity in Mexican American adults?
2. What is the prevalence of metabolic syndrome in Mexican American adults using current IDF waist circumference and new WC determined in question 1?
3. What is the association between plasma CRP concentration and the components of metabolic syndrome in this population?
4. What are the odds ratios for the development of metabolic syndrome and its components (central obesity, hypertriglyceridemia, low HDLc, hyperglycemia and hypertension) in subjects with elevated CRP concentration?
5. What is the association between overall obesity (measured by BMI) and abdominal adiposity (measured by waist circumference) with the components of metabolic syndrome including, triglyceride, blood pressure, fasting plasma glucose and HDL cholesterol in Mexican Americans?
6. What are the odds ratios for the development of metabolic syndrome and its components (hypertriglyceridemia, low HDLc, hyperglycemia and hypertension) in subjects with elevated WC?

Literature Review

Metabolic Syndrome

The combination of metabolic abnormalities now known as metabolic syndrome was first described by Kylin in 1923 as the clustering of gout, hypertension, and hyperglycemia (47). In 1988 Reaven used the term syndrome X and established the clinical importance of this condition as concurrence of hypertension, hyperglycemia, glucose intolerance, elevated triglycerides, and low HDL cholesterol (48). This syndrome has also been termed as the deadly quartet, dysmetabolic syndrome X and insulin resistance syndrome by other scientists (49, 50).

Metabolic syndrome (MetS) is the constellation of metabolic risk factors including central obesity, atherogenic dyslipidemia, elevated plasma glucose, elevated blood pressure, prothrombotic and a proinflammatory state that increases the development of cardiovascular disease and is associated with type 2 diabetes mellitus (1).

In the effort of introducing the metabolic syndrome into clinical practice, several different sets of criteria have been proposed by different organizations for identifying patients with MetS. The more accepted of these definitions has been proposed by World Health Organization (WHO), the European Group for the Study of Insulin Resistance (EGIR), the American Association of Clinical Endocrinologists (AACE) and the National Cholesterol Education Program- Adult Treatment Panel III (NECP ATP III) (9-13).

The World Health Organization (WHO) definition for MetS emphasizes insulin resistance as the major underlying risk factor and requires its evidence for diagnosis. The presence of one of the several markers of insulin resistance and at least two risk factors among obesity, hypertension, high triglycerides, reduced HDL cholesterol and microalbuminuria constitutes a diagnosis of metabolic syndrome. Insulin resistance is difficult to measure directly in clinical

setting and field studies, therefore different markers of indirect evidence were accepted, i.e., impaired glucose tolerance (IGT), impaired fasting glucose (IFG), type 2 diabetes mellitus, or impaired disposal of glucose under hyperinsulinemic, euglycemic conditions. The WHO group allows the term metabolic syndrome to be used in patients with type 2 diabetes who met the requirements for this syndrome. They justified that patients with type 2 diabetes mellitus are at higher risk for cardiovascular disease (10).

In 1999 the European Group for the Study of Insulin Resistance (EGIR) defined the syndrome in non-diabetic individuals who have hyperinsulinemia, which is simpler to use in epidemiological studies, since it does not require measurement of insulin sensitivity. EGIR proposed to use fasting insulin levels to estimate insulin resistance and impaired fasting glucose as a surrogate for IGT. By their criteria, plasma insulin levels in the upper quartile of the population will define insulin resistance. Elevated fasting plasma insulin plus 2 other factors including abdominal obesity, hypertension, increased triglycerides, decreased HDL cholesterol and increased fasting plasma glucose will define metabolic syndrome. They also modified the threshold for triglycerides, hypertension, and HDL cholesterol and used waist circumference as a measure of central obesity. Further, if subjects were receiving treatment for hypertension or dyslipidemia they were considered to have the risk factor (11).

In 2001 the National Cholesterol Education Program (NCEP), Adult Treatment Panel III (ATP III) proposed alternative clinical criteria for defining metabolic syndrome. The definition is based on WHO criteria and requires the presence of at least three of five components including elevated triglycerides, reduced HDL cholesterol, hypertension, elevated fasting glucose and central obesity (highly correlated with insulin resistance). It does not include any measure of insulin resistance, which makes it more practical to use in epidemiological studies and clinical

practice. The criteria do not emphasize a single cause and includes waist circumference as the measure of obesity (12). The cut points for central obesity adopted from 1998 National Institute of Health obesity clinical guideline were waist circumference ≥ 102 cm (≥ 40 inch) for men and ≥ 88 cm (≥ 35 inch) for women (51). These cut points represent the upper quartile of the US population. As some individuals of other ethnic groups i.e., South Asians and Chinese are susceptible to develop metabolic syndrome at lower waist circumference, The ATP III noted that individuals who have only 2 metabolic criteria can manifest characteristics of metabolic syndrome even when the waist circumference is marginally elevated, for example 94-101 cm in men or 80-87 cm in women. If so, they should be treated similarly to those who have higher waist circumference plus two other risk factors. ATP III, like WHO allows the term metabolic syndrome to be used in patients with type 2 diabetes because of higher risk of cardiovascular disease among these patients (12). Few years later, the ATP III announced some clarifications in metabolic syndrome definition including using lower waist circumference thresholds for ethnic groups who are susceptible for insulin resistant, counting the medication use for high triglyceride, low HDL and high blood pressure as the risk factor for these conditions even when their values are normal, and reducing the blood glucose thresholds for hyperglycemia from 110 mg/dl to 100 mg/dl (1).

In 2003 the American Association of Clinical Endocrinologists (AACE) released a position statement on insulin resistance syndrome. Major factors for identifying the syndrome are elevated triglycerides, reduced HDL cholesterol, elevated blood pressure, obesity and elevated fasting and post load glucose. The AACE statement does not provide a specific number of factors for definition of syndrome and allows the diagnosis to rely on clinical judgment. Other factors used to inform clinical judgment are family history of CVD or type 2 diabetes mellitus,

polycystic ovary syndrome and hyperuricemia. By this definition the term “insulin resistance syndrome” can be applied until the person is diagnosed with type 2 diabetes (13).

In 2005, the International Diabetes Federation (IDF) proposed new criteria that modify ATP III definition. This definition requires the presence of abdominal obesity for diagnosis of syndrome. The rationale for this requirement is that abdominal obesity is highly correlated with insulin resistance and other components of the syndrome. They introduced a simple diagnostic tool for use in clinical practice and research worldwide. The definition would allow comparison of the prevalence of the syndrome in different populations and its association with various health consequences. “According to IDF definition, for a person to be defined as having the metabolic syndrome, they must have the central obesity plus any two of the four additional factors. These factors are:

- Elevated triglycerides level: ≥ 150 mg/dl (1.7 mmol/l) or specific treatment for this lipid abnormality
- Reduced HDL cholesterol level: < 40 mg/dl (1.03 mmol/l) in men and < 50 mg/dl (1.29 mmol/l) in females or specific treatment for this lipid abnormality
- Elevated blood pressure: systolic BP ≥ 130 or diastolic BP ≥ 85 mmHg or treatment of previously diagnosed hypertension
- Elevated fasting plasma glucose: FPG ≥ 100 mg/dl (5.6 mmol/l) or previously diagnosed type 2 diabetes” (9).

IDF emphasized the use of gender-ethnic specific values for waist circumference when measuring central obesity, as there are clear differences across ethnic populations between overall adiposity, abdominal adiposity and visceral fat accumulation (14, 15). For Euroids the specified cut points for abdominal obesity is the waist circumference ≥ 94 cm in men and ≥ 80 cm

in women. These thresholds are based on cross sectional studies in European countries and are the best values for identifying overweight people, defined as BMI of $\geq 25 \text{ kg/m}^2$ or WHR ≥ 0.90 for men and ≥ 0.85 for women (52). For Asian populations, the cut points are $\geq 90 \text{ cm}$ in men and $\geq 80 \text{ cm}$ in women (22, 53-57).

All definitions agree on the key elements of the MetS including obesity, insulin resistance, hypertension and dyslipidemia. However they provide different criteria and cut points to define this condition. The different criteria proposed for clinical diagnosis of metabolic syndrome are summarized in Table 1.1.

Table 1.1. Criteria for Clinical Diagnosis of Metabolic Syndrome

Characteristics	WHO (1998)	EGIR (1999)	NCEP ATP III (2001)*	AACE (2003)	IDF (2005)
Insulin resistance	IGT, IFG, T2DM and/or insulin resistance Plus 2 or more of the following	Fasting plasma insulin > 75 percentile for non-diabetic individuals Plus 2 or more of the following	None Any of the 3 following	IGT or IFG Plus any of the following based on clinical judgment	None
Central obesity	Men: WHR >0.90 Women: WHR >0.85 and/or BMI >30 kg/m ²	Men: WC ≥94 cm Women: WC ≥80 cm	Men: WC ≥102 cm Women: WC ≥88 cm	BMI ≥25 kg/m ²	Central obesity defined as WC with ethnic specific cutoffs plus 2 or more of the following
Triglycerides	TG ≥150 mg/dl	TG >180 mg/dl and/or medication use for dyslipidemia	TG ≥150 mg/dl	TG ≥150 mg/dl	TG ≥150 mg/dl or specific treatment for dyslipidemia
HDLc	Men: <35 mg/dl Women: <39 mg/dl	HDLc <39 mg/dl and/or medication use for dyslipidemia	Men: <40 mg/dl Women: <50 mg/dl	Men: <40 mg/dl Women: <50 mg/dl	Men: <40 mg/dl Women: <50 mg/dl or specific treatment for dyslipidemia
Fasting glucose	IGT, IFG or T2DM	≥ 110 mg/dl	≥ 110 mg/dl	IGT or IFG (Not diabetes)	≥ 110 mg/dl or previously diagnosed T2DM
Blood pressure	≥ 140/90 mmHg	≥ 140/90 mmHg and/or medication use for hypertension	≥ 130/85 mmHg	≥ 130/85 mmHg	≥ 130/85 mmHg or treatment for hypertension
Other	Microalbuminuria			Family history of CVD or T2DM, poly cystic Ovary syndrome and hyperuricemia	

BMI, body mass index; CVD, cardiovascular disease; HDLc, high density lipoprotein cholesterol; IGT, impaired glucose tolerance; IFG, impaired fasting glucose; T2DM, type 2 diabetes mellitus; WHR, waist to hip ratio; WC, waist circumference.

*In 2004, the NCEP ATP III definition had some clarifications including using lower WC cutoffs for ethnic groups who are susceptible for insulin resistance, counting the medication use for lipid abnormalities and hypertension as the risk factor for these conditions and reducing the blood glucose cutoff from 110 to 100 mg/dl (1).

Characteristics of Metabolic Syndrome

General features of metabolic syndrome are summarized as:

Abnormal body fat distribution

Central or abdominal obesity is one of the main features of metabolic syndrome and is independently correlated with all other components of the syndrome. Central obesity contributes to insulin resistance, hypertension, dyslipidemia and hyperglycemia and is associated with increased risk of cardiovascular disease and type 2 diabetes mellitus independent of overall adiposity (58-62). Waist circumference reflects the amount of abdominal adipose tissue deposits as well as total fat mass, providing a measure of body fat distribution. It also complements body mass index in evaluation of obesity related health risk (24-26). Several studies have shown that in assessment of abdominal adiposity waist circumference is complementary or superior to body mass index (14, 15 and 26). When measuring central obesity, gender-ethnic specific values for waist circumference should be used, since there are clear differences in overall adiposity, abdominal adiposity and visceral fat accumulation among ethnic populations (14, 15).

Insulin resistance

Insulin resistance is the condition in which liver, skeletal muscle and adipose tissue cells become less sensitive and eventually resistant to insulin. Insulin resistance in fat cells results in hydrolysis of stored triglycerides and increases of free fatty acids in the blood. In muscle, insulin resistance reduces glucose uptake whereas in liver it reduces glucose storage, both would cause an increase in blood glucose. Insulin resistance is present in most people with metabolic syndrome. It is strongly associated with some metabolic risk factors; however its association with hypertension is weak (9). An abnormal fat distribution (upper body fat obesity) is

commonly seen in individuals with metabolic syndrome (63) and studies have shown that upper body adiposity is strongly associated with insulin resistance. Excess upper body fat can be accumulated as intraperitoneal (visceral) or subcutaneous (truncal) fat. Results from several studies suggest that excess visceral fat is more strongly correlated with insulin resistance than any other adipose tissue compartment (64-66); other researchers claim that excess subcutaneous abdominal fat has a significant association with insulin resistance (67-69). In general the pattern of upper body adiposity (abdominal obesity) correlates more strongly with insulin resistance and the components of metabolic syndrome than lower body obesity (1). Elevated circulating free fatty acids are important factor which links upper body adiposity and insulin resistance (70, 71).

Atherogenic Dyslipidemia

The dyslipidemia found in individuals with metabolic syndrome is multi-factorial, and is associated with a cluster of interrelated cardiovascular disease risk factors. Lipoprotein abnormalities including increased triglycerides and apo lipoprotein B, reduced HDL cholesterol, increased small dense LDL particles and increased small HDL particles are main features of atherogenic dyslipidemia. Variations in the pattern and magnitude of the dyslipidemia are due to the interaction of genetic factors with environmental influences including diet, physical activity and stress. All of these lipid abnormalities are independently atherogenic (1, 9). The lipid abnormalities in metabolic syndrome are related to insulin resistance and some mediators like lipoprotein lipase, hepatic lipase and cholesterol ester transfer protein (72-74).

Hypertension

Elevated blood pressure is a medical condition in which the blood pressure is chronically increased. Persistent hypertension is one of the risk factors for strokes, heart attacks, heart failure and can cause chronic renal failure. Hypertension can be classified as essential or secondary. In

essential hypertension, no specific medical cause can explain a patient's condition. In secondary hypertension the high blood pressure is caused by another condition, such as kidney disease or adrenal gland tumor (75). Elevated blood pressure is associated with obesity and glucose intolerance and insulin resistance. The strength of this relation varies in different populations (9, 76).

Proinflammatory State

A proinflammatory state is frequently present in patients with metabolic syndrome and is recognized by elevated inflammatory markers (27, 28). In general a proinflammatory state can be characterized by determining proinflammatory risk factors such as oxidized LDL cholesterol, proinflammatory cytokines (e.g., interleukin-1, tumor necrosis factor- α), adhesion molecules (e.g., intercellular adhesion molecule-1, selectins), inflammatory stimuli with hepatic effects (e.g., interleukin-6) or the products of the hepatic stimulation, such as serum amyloid A (SAA), C-reactive protein (CRP), and other inflammation factors, such as elevated leukocyte count (29). According to American Heart Association (AHA) and Centers for Disease Control and Prevention (CDC) scientific statement on “Markers of Inflammation and Cardiovascular Disease”, C-reactive protein (hs-CRP) is the first choice if inflammatory markers need to be measured. Recent studies have shown that elevated CRP level is strongly associated with components of metabolic syndrome. CRP is an acute phase reactant produced by liver and will increase dramatically in response to infection, injury and inflammation (31). CRP should be measured in metabolically stable patients without known inflammatory or infectious conditions to decrease intra individual variability, and the assessment should be repeated in 2 weeks and the average of the 2 measurements should be used. Serum hs-CRP levels <1.0 mg/L are defined as low risk, 1.0 – 3.0 mg/L as average risk, and >3.0 mg/L as high risk for cardiovascular disease and

cardiac events, corresponding approximately to tertiles of the adult population. Serum CRP level greater than 10 mg/L is an indicator of ongoing infection, acute illness or injury (29).

Prothrombotic State

A prothrombotic state is a feature of metabolic syndrome and is characterized by an increase in plasminogen activator inhibitor-1(PAI-1), fibrinogen, tissue factor and factor VII and a decrease in tissue plasminogen activator activity. PAI-1 is a marker of reduced fibrinolytic capacity and is strongly associated with components of metabolic syndrome (9, 38 and 77).

Prevalence of Metabolic Syndrome

Metabolic syndrome is one of the major medical and public health problems in the United States (2, 3) and worldwide (4-6). An estimated 47 million U.S. residents have metabolic syndrome (7). The age-adjusted prevalence of this syndrome for adults is 23.7 percent (2). The prevalence of syndrome rises with age. Analysis of data on 8814 nationally representative non-institutionalized US population aged 20 years or older from Third National Health and Nutrition Examination Survey revealed that metabolic syndrome prevalence is highly correlated with age, increasing from 6.7% in individuals aged 20-29 years to over 40% in individuals aged ≥ 60 years (2). Another study showed that metabolic syndrome reaches its peak levels in the 60s for men and 70s for women (78). The prevalence of the syndrome increases significantly with increasing BMI. Results from NHANES III revealed that metabolic syndrome was evident in 4.6% of normal weight, 22.4% of overweight and 59.6% of obese men. A comparable distribution was observed in women (77, 78). Metabolic syndrome prevalence varies by sex and ethnicity (2, 78). In the analysis of NHANES III, Park et al. (78) found the lowest prevalence in black men (13.9%) and the highest in Mexican American women (27.2%). Ford et al. reported the highest prevalence among Mexican Americans (31.9%) and lowest among whites (23.8%), African

Americans (21.6%) and individuals from “other” ethnicity. The prevalence of metabolic syndrome was similar in men and women among whites and people from “other” ethnicity. African American women had about 57% higher prevalence than men and Mexican American women had about 26% higher prevalence compared to men (3).

Pathogenesis of Metabolic Syndrome

The pathogenesis of metabolic syndrome and its components is multifaceted and continues to challenge the professionals. The underlying risk factors for developing this syndrome appear to be abdominal obesity (63, 78) and insulin resistance (48, 79). Other related risk factors are genetic profile (1, 80), aging (2), physical inactivity (78, 81) and hormonal imbalance (82).

The hypotheses relating central obesity to metabolic syndrome focus on adipose tissue (particularly visceral adipose tissue) hormonal role and secretion of adipokines (cytokines) and other bioactive substances such as free fatty acids. Adipose tissue actively secretes large numbers of hormones and adipokines including leptin, adiponectin, tumor necrosis factor α (TNF α), interleukin 6 (IL-6), monocyte chemotactic protein 1, inducible nitric oxide synthase (iNOS), transforming growth factor β 1, plasminogen activator inhibitor 1 (PAI-1) and resistin. These adipokines have autocrine, paracrine and endocrine actions for controlling different metabolic functions (37, 38 and 83). The expanding adipose tissue also discharges high levels of FFA into the portal and systemic circulation (71, 84 and 85); this may result in accumulation of lipid in areas other than adipose tissue or ectopic fat storage syndrome. In muscles and liver, increased FFA will promote insulin resistance (86, 87) and dyslipidemia (88). FFAs decrease insulin sensitivity in muscle by inhibiting insulin signaling, glucose phosphorylation, glycogen synthase and pyruvate dehydrogenase (89, 90). In the liver, FFAs promote glucose production (due to stimulation of gluconeogenesis and hepatic insulin resistance) and increase secretion of very low

density lipoproteins (VLDL) since high amounts of glucose and FFA are available. Other lipid abnormalities include a decrease in high density lipoprotein (HDL), an increase in intermediate density lipoprotein (IDL), low density lipoprotein (LDL), and production of small dense LDL (90).

Obesity is correlated with an inflammatory response which is characterized by abnormal adipokines production and activation of some proinflammatory pathways resulting in overproducing of several inflammatory markers (38, 83). Recent data indicate that obese adipose tissue is infiltrated by macrophages, which are responsible for the most part of the locally produced **TNF α** and large amounts of IL-6 and inducible nitric oxide synthase expression (91, 92). Adipose tissue TNF α increases adipocyte lipolysis, partly through its effects on perilipin (86, 87). “Perilins are phosphoproteins found in adipocytes on the surface of triacylglycerol droplets that act as gatekeepers, preventing lipases from hydrolyzing triacylglycerol to facilitate the release of FFAs.”(37). Therefore, TNF α may increase insulin resistance by promoting the fatty acid release from adipose tissue into the portal and systemic circulation (93, 94).

IL-6 production by adipose tissue is also increased in obesity (95, 96). In obese individuals the IL-6 expression is 10 fold than in lean individuals when normalizing for the number of current adipocytes. IL-6 increases lipolysis and fat oxidation in humans (97), it rises plasma concentration of fibrinogen, PAI-1 and CRP (98) and recently has been suggested to play an important role in the link between obesity, inflammation and coronary heart disease. Overproduction of IL-6 by adipose tissue could directly alter liver metabolism by inducing VLDL secretion and hypertriglyceridemia, since visceral adipose tissue (VAT) is closely connected to liver by the venous portal system (99).

Plasminogen activating inhibitor-1 is an important factor in the maintenance of vascular homeostasis, regulating thrombus formation by inhibiting the activation of plasminogen and impairing fibrinolysis (100-102). PAI-1 is synthesized in liver and adipose tissue. The serum concentrations of PAI-1 is increased in visceral adiposity and decreased in caloric restriction, change in dietary composition, weight loss, physical training and use of oral antidiabetic medications such as metformin (102-104). Visceral fat tissue secretes significantly more PAI-1 than subcutaneous abdominal or femoral fat tissue (105, 106). The mechanisms connecting PAI-1 to metabolic syndrome are complex and interrelated. Several inducers including ectopic fat depot, TNF α , cortisol, renin angiotensin system and the oxidative and hypoxic stress may function together at different sites of synthesis (107-111).

Leptin, the first adipocyte hormone identified, is involved in regulating food intake and energy expenditure through a direct effect on hypothalamus. The relation between leptin and the low grade inflammatory state in obesity has been suggested by many studies (37, 99), implying that leptin can exert peripheral biological effects due to its cytokine like structure (112). It also can modulate TNF α production and macrophages activation. However, the underlying mechanisms have not been clearly determined (113).

Adiponectin or adipose most abundant gene transcript 1 (APM1) is an adipose tissue collagen like protein and has anti-atherogenic and anti-inflammatory effects (114). This hormone increases insulin sensitivity in muscles and liver, enhances FFA oxidation in different tissues, including skeletal muscle, promotes glucose utilization in muscles and reduces serum FFA, glucose and triglyceride level (37, 101 and 115). Additionally adiponectin may control the TNF α -induced inflammatory response by reducing TNF α secretion of macrophages; this may

partly explain its anti-inflammatory and anti-atherogenic effect (116). The levels of circulating adiponectin are decreased in obesity, diabetes and insulin resistance (117-119).

Resistin, a 114 amino acid polypeptide hormone, was first discovered in 2000 by Steppan and colleagues (120). It is also called FIZZ3 (found in inflammatory zones) and originally proposed as a link between adipose tissue, obesity and insulin resistance. This hormone is primarily secreted by adipocytes in rodents and in humans is mainly derived from immune competent cells such as monocyte and macrophages (121). Review of the literature on physiological role of resistin in rodent and human models has shown several discrepancies (122-125). In rodents resistin has an important role in development of liver insulin resistance; however in humans its role as an insulin resistance inducing factor is less determined and is more involved in the regulation of inflammation. Recently, Lehrke et al. reported that resistin may have a role as a pro-inflammatory factor in healthy humans (126).

Many studies indicate that **insulin resistance** is an important factor in the development of obesity, metabolic syndrome and diabetes; however the mechanisms linking insulin resistance and other components of metabolic syndrome is not well understood (1, 9). Elevated level of circulating free fatty acids is an important factor that links obesity, dyslipidemia and insulin resistance (90, 127). The expanding adipose tissue discharges high levels of FFA into the portal and systemic circulation (71, 84 and 85); this will result in accumulation of lipid in areas other than adipose tissue and the ectopic fat storage syndrome could occur. In muscles and liver, increased FFA will promote insulin resistance (86, 87) and dyslipidemia (88). These FFAs decrease insulin sensitivity in muscle by inhibiting insulin signaling, glucose phosphorylation, glycogen synthase and pyruvate dehydrogenase (89, 90). Increased cytokine production in obesity might be a link between inflammation and insulin sensitivity. Many studies have shown

that cytokines such as TNF α and IL-6 are involved in insulin resistance and its complications (128-130). Although the mechanisms have not been clearly determined, it could be related to tyrosine phosphatase activation (99) or an interaction between suppressor of cytokine signaling (SOCS) proteins and the insulin receptor (128, 129).

Several researches have suggested that **genetic background** is an important factor in developing metabolic syndrome and its components (131, 132). Findings from twin and family studies confirm this genetic contribution (133- 136). Carmelli et al. in study of 2508 male twin pairs in the U.S. reported that clustering of hypertension, diabetes and obesity was found in 31.6% of monozygotic pairs and only in 6.3% of dizygotic pairs (137). Comparable results for heritable factors were found in a female twin study (133). Candidate genes have been identified for key components of metabolic syndrome with single or multiple effects on syndrome components. For example variation in ADIPOQ that encodes adiponectin, has been associated with visceral obesity, diabetes, hypertension and dyslipidemia (138-140). The AGT variation which encodes angiotensinogen has been associated with blood pressure (141) and blood lipid concentrations have been related to variations in the APOE and APOC3 genes encoding apolipoproteins E and CIII, respectively (142, 143). In addition, variations in genes encoding FOXC2 and SREBP1 have been associated with insulin sensitivity and plasma triglycerides (144, 145). More research is needed to identify the genomic DNA markers that can be used clinically in the diagnosis and /or treatment of metabolic syndrome (132).

Aging has an important role in pathogenesis of metabolic syndrome since most of the metabolic syndrome components including obesity, hypertension and glucose intolerance are associated with aging. Many studies have shown an increase in prevalence of metabolic syndrome in elderly (1, 146 and 147). In the analysis of 8814 men and women aged 20 or older

from Third National Health and Nutrition Examination Survey, Ford et al. observed that metabolic syndrome was prevalent in 6.7% of individuals aged 20-29 years, 43.5% of individuals aged 60–69 years and 42.0% of those age 70 and older (2, 146). Recent studies have shown psychosocial risk factors such as depression, anxiety, inadequate emotional support and negative life events are associated with a higher prevalence of metabolic syndrome in older people (148). Furthermore, a decrease in circulating androgen levels including lower total testosterone and low sex hormone binding globulin (SHBG) level can predict the development of metabolic syndrome and type 2 diabetes mellitus in middle aged and older men (146, 149).

Physical inactivity is another important factor in pathogenesis of metabolic syndrome. Numerous studies have examined the link between physical activity, fitness and metabolic abnormalities (150-154). Almost all studies reported that the levels of physical activity are inversely associated with the prevalence of this syndrome. Findings from epidemiological and intervention studies suggest that exercise training can reduce body weight and visceral fat accumulation (154, 156), improve insulin sensitivity (155-157), promote HDL cholesterol, decrease triglyceride and blood pressure levels (158, 159). The favorable effect of physical exercise on insulin sensitivity can be linked to changes in insulin signaling pathway in response to muscle contraction, for example increase in GLUT4 glucose transporters to the cell surface (160, 161). This effect is short term and will last 48-72 hours. Thus to maximize the benefits of physical training on insulin sensitivity, a daily activity is recommended (159).

Hormonal imbalances including hypercortisolemia, sex steroids and growth hormone deficiencies are important in pathogenesis of metabolic syndrome (1, 82 and 162). In 1992, Björntorp proposed that these hormonal insufficiencies may promote triglyceride deposition in adipose tissue, intensify visceral fat accumulation, dyslipidemia and insulin resistance (162).

Many studies have shown the high prevalence of metabolic syndrome in women and adolescent girls with polycystic ovary syndrome (PCOS). The PCOS is the most common cause of women infertility due to anovulation in the United States and around one-third to one-half of all women and adolescent girls with PCOS has the metabolic syndrome and increased risk of CVD and/or diabetes (82, 163 and 164).

The Hispanic or Latino Population (Hispanic versus Latino)

The terms Hispanic and Latino have often been used interchangeably in the literature, but in fact are not corresponding to the same population. The term “Hispanic” comes from the Latin word for “Hispania” or “Spain”. It refers to people who were born in of the Latin America countries and Spanish is their primary language (except Brazil which Portuguese is the primary language). The word “Latino” is a broader term and refers to people who were born in a country where a Latin language is spoken. This term applies to individuals coming from countries in Latin America and even some in Europe such as France, Portugal, Spain, Italy, Albania and Romania (21). According to CDC “Hispanics or Latinos are persons of Cuban, Mexican, Puerto Rican, South or Central-American, or other Spanish culture or origin, regardless of race” (165). In this research term Hispanic/Latino will be used, trying to be consistent with CDC definition.

Hispanics/Latinos in the United States

Demographics: The Hispanic/Latino population is the largest, fastest growing minority group in the United States, representing 14% of the total population. According to the 2006 U.S. Census Bureau population estimate, there are nearly 42.6 million Hispanics living in the United States (166). This population’s growth rate is four times that of the total population and it is estimated by the year 2050, Hispanics will number 102.6 million and 24% of the U.S. population.

Hispanics are a diverse population. In 2004, the largest Hispanic subgroups in the country were Mexicans (66%), followed by Central and South Americans (13%), Puerto Ricans (9.4%), Cubans (3.9%) and people of other Hispanic Origins (7.5%). The 10 states with the largest Hispanic/ Latino populations are California (12.5 million), Texas (7.8 million), Florida (3.4 million), New York (3 million), Illinois (1.8 million), Arizona (1.6 million), New Jersey (1.3 million), Colorado (0.89 million), New Mexico (0.82 million) and Georgia (0.62 million)(167-169).

Unfortunately, these figures do not reflect the total number of Hispanics in the country as they are not accounting for an estimated 11.5 to 12 million unauthorized immigrants who live in the United States. According to Jeffrey S. Passel, Senior Research Associate of the Pew Hispanic Center, “the number of unauthorized migrants living in the United States has continued to increase steadily for several years, reaching an estimated 11.1 million based on the March 2005 compared to an estimate of 8.4 million based on Census 2000”. In 2005, Mexicans were the largest unauthorized immigrants entering the country at 6.2 million (56%), while 2.5 million undocumented immigrants (24%) were from the rest of Latin America countries, mainly from Central America (170).

According to American Community Survey for Hispanics (171), the average **age** of Latinos in U.S. is about 13 years younger than the non-Hispanic White population (26.9 vs. 40.1 years). The average age for Latinos is also younger than that of the total U.S. population for men (26 vs. 34 years) and women (27 vs. 36 years)(165).The Hispanic population has a larger percentage of young people and a smaller percentage of older people when compared to non- Hispanic Whites. About 80% of Latinos are 24 years or younger and 1 in 3 Hispanics are 18 years old or younger, compared with 1 in 5 non-Hispanic Whites and around 5 percent of Hispanics are 65 and older,

compared with about 15 percent of non-Hispanic Whites. Among the Hispanic-origin subgroups, Mexicans have the lowest median age, 25.3 years, and Cubans have the highest, 40.6 years (171). The **gender distribution** for Latinos is 50% males and 50% females, which is similar to the gender distribution for the total U.S. population (51% and 49%, respectively).

Latinos as a group tend to be married. In 2000, 52% of Latinos were married compared to 33% never married, 4% widowed and 11% separated or divorced. They comprise 12% of households in the U.S. Fifty-one percent of Latinos live in households that consist of 3 to 5 people. Eighteen percent live in households that include non-relatives compared with 11% of the total U.S. population.

Socioeconomic status can be defined as a function of different variables such as income, occupation and education. The U.S. Census Bureau has set a poverty threshold, which is defined as a function of the family size. Since Latinos have larger households compared to the total U.S. population, different thresholds should be set for them to make comparisons. Only 29% of Latinos earn \$50,000 or more compared with 49% for the total U.S. population. The percentage of Latinos whose annual income is less than \$10,000 is also larger than that for the total population. The average income when measured by the number of family members is \$26,641 for U.S. population and \$15,415 for Latinos. According to U.S. Census, the percentage of Latinos below the poverty level was 27% in 2000, which is a larger figure compared to the total population (172).

According to 2000 U.S. Census, 60% of the total U.S. population was employed in managerial and technical, sales, and/or administrative jobs, comparing to 61% of Latinos who are mainly engaged in service, industrial and agricultural jobs. There are some differences within Latino subgroups too, for instance Mexicans have lower employment in professional and/or

managerial, technical, sales, and administrative support jobs than do other groups such as Puerto Ricans and Cubans, though they have higher employment in labor and farm occupations.

There are significant gaps in **educational attainment** rates when comparing Latinos and the total U.S. population. In 2000, the proportion of Hispanics with only a fifth grade education was 17 times larger than that of non-Hispanic Whites (0.6% for NHW). According to 2004 U.S. Census, 58.4% of Hispanics in comparison to 85.8% NHW had a high school diploma and 12.1% of Hispanics in comparison to 28.2% of NHW have a bachelor's degree (166). When looking at educational attainment by gender, more women have an advantage of having high school diploma and college level education compared to men. The school drop-out rate is significantly higher for Latinos who were born outside of the United States. In 1997, the drop-out rate for this group was much higher compared to individuals who were born in the United States but whose parents were born outside the United States (39% vs. 15%)(172).

Hispanic/Latino **health status** is affected by different factors such as language/cultural barriers, lifestyle behaviors, access to preventive health care services and health insurance coverage. When compared with other ethnic groups, Latinos have the second lowest death rates in the United States (601 per 100,000 deaths). According to the Centers for Disease Control and Prevention the 10 leading causes of death among Hispanics in 2001 were: heart disease, cancer, unintentional injuries (accidents), stroke, diabetes, chronic liver disease and cirrhosis, homicide, chronic lower respiratory disease, pneumonia & influenza and birth defects (173). There are clear differences in leading causes of death among Latinos and the total U.S. population as well as non-Hispanic Whites. These differences are in accident rates, liver diseases, homicides, and birth defects. Accidents are the third cause of death for Latinos and fifth for the total U.S. population and for non-Hispanic Whites. Homicides, liver disease, and birth defects are not

considered the leading cause of death for the total U.S. population or for non-Hispanic Whites. Some of these differences may be related to the different number of younger and older population among Latinos when compared with the total U.S. population. Also, recent immigrants can be at increased risk for chronic disease and injury, particularly if they are not fluent in English, familiar with U.S. health care system or have different cultural attitudes like preferring traditional medicine to conventional medicine (172, 173).

Over one third of Hispanic adults does not have **health insurance** coverage and 59% of those, personally know someone who is uninsured (174). Despite the fact that Hispanics are the largest ethnic minority population in the country, they are underserved by the health care system. Hispanics are less likely to seek and receive health care services, especially preventive services, which might contribute to their poorer health status and higher rates of morbidity and mortality. In the analysis of Behavioral Risk Factor Surveillance System (BRFSS) surveys 2001-2002 data, considerable differences in prevalence of health care coverage were documented among Hispanics compared with non-Hispanics. These differences remained significant even after adjusting for health status and socioeconomic factors (175).

In this country access to health care is related to insurance coverage, the type of insurance, and whether a person has a regular source of care (176). The lower prevalence of health care access among Hispanics might be explained by disparities in receiving preventive services. Hispanic adults in the BRFSS were less likely than non-Hispanic adults to receive blood cholesterol and cancer screenings. Hispanics' effort to obtain health insurance and health care services have been compromised by Language barriers, cultural practices, beliefs and the administrative complexity of health plans (175, 177).

Associations between mortality and socioeconomic factors including education, occupation and employment, health insurance and poverty have been reported. Despite higher poverty rates, less education attainment and worse access to health care, for most Hispanic groups living in the United States, health and mortality outcomes are equal to or better than non Hispanic whites (178, 179). This phenomenon is known as “Epidemiological Paradox” or “**Hispanic Health Paradox**”. Some potential explanations for this multifactor paradox are: under-reporting and/or misclassification of Hispanic deaths, Salmon bias and healthy migrant effects. The Salmon bias hypothesis suggests that Hispanics are returning to their origin country after they retire or became seriously ill. The healthy migrant effect hypothesis is “based on the notion that the strongest and healthiest members of a population migrate”. The paradox does not hold equally for all Hispanic subgroups. Morales et al. in the review of social, economic and behavioral determinants of health for Hispanics in the United States observed that, the health paradox exists most strongly in Mexicans but does not appear to hold for Puerto Ricans (178, 179).

Metabolic Syndrome in Hispanics

Mexican Americans have the highest age-adjusted prevalence of metabolic syndrome (31.9%), when compared to whites (23.8%), African Americans (21.6%) and individuals from “other” ethnicity (20.3%). In Mexican Americans the syndrome is more prevalent among women (26% higher) than men (7). In 2003, Meigs et al. (180) compared the prevalence and characteristics of metabolic syndrome among non Hispanic White (NHW) and Mexican American (MA) subjects participating in San Antonio Heart Study (SAHS) phase II follow up exam (1992-1996) and Framingham Offspring Studies (FOS) exam 5 (1991-1995). They analyzed data on 1081 NHW and 1656 MA from SAHS and 3224 white subjects from FOS, and classified them based on NCEP ATP III and WHO criteria. The age and sex-adjusted prevalence

of metabolic syndrome was 24% (by ATP III and WHO criteria) in subjects from FOS; 23 and 21% in NHW individuals and 31 and 30% in MA subjects from SAHS. The rates were highest among MA women 31% (ATP III) and 30% (WHO) and lowest among NHW women (21% ATP III). This study confirmed that metabolic syndrome was most prevalent among Mexican Americans.

Analysis of data on 3601 nationally representative non-institutionalized US population aged 20 years or older from National Health and Nutrition Examination Survey 1999-2002 confirmed that Mexican American men and women (according to IDF criteria) have the highest age adjusted prevalence of metabolic syndrome, 50.6% and 46.2%; respectively. The prevalence was lowest among White men and women (41.9% and 34.4%) and African American men and women (27.1% and 34.4%) (3).

Diabetes in Hispanics

Diabetes is one of the most common chronic diseases worldwide. It affects nearly 200 million people (about 5 percent of the total adult population). In USA an estimated 20.8 million people (7% of the population) have diabetes and about 30% are unaware of the diagnosis (7, 181).

Diabetes disproportionately affects Hispanics in the United States. According to National Institute of Health, National Diabetes Education Program, about 2.5 million or 9.5% of Hispanic or Latino Americans aged 20 years or older have been diagnosed with diabetes. Mexican Americans adults are 2 times more likely than non-Hispanic white adults to be diagnosed with diabetes by a physician. In 2002, Hispanics were 1.5 times as likely to start treatment for end-stage renal disease related to diabetes, when compared to non-Hispanic white men and in 2003 Hispanics were 1.5 times as likely as non-Hispanic Whites to die from diabetes (182, 183).

Cowie et al. research on the prevalence of diagnosed and undiagnosed diabetes, and impaired

fasting glucose in U.S. adults confirmed the information on the existence of health disparities among minorities. They analyzed data on 4761 adults from NHANES 1999-2002. The age and sex adjusted prevalence of diagnosed diabetes was 10.4% among Mexican Americans and 5.2% in NHW (184).

According to Institute of Medicine (IOM), clear health care disparities exist when comparing diabetes care between White population and Minority groups (185). Recently, the diabetes care quality in Hispanics and non-Hispanic White adults was investigated by Mainous et al. They analyzed 2004 Behavioral Risk Factor Surveillance System (BRFSS) data on 18,510 NHW and 2,078 Hispanics and observed less appropriate diabetes quality of care in Hispanics when compared to NHW. Hispanics were also less likely to self monitor their disease. Ethnic disparities for receiving HbA1c tests and foot exams remained even after controlling for confounders including access to care, socioeconomic status and demographics (186). Multifaceted strategies for prevention and treatment of diabetes and improving diabetes care in Hispanics may help to eliminate disparities in this population.

Cardiovascular Disease in Hispanics

Research has shown that Hispanics have a higher prevalence of CVD risk factors than non-Hispanic Whites, including type 2 diabetes, obesity, lipid abnormalities and lower levels of physical activity, but lower cardiovascular disease and coronary heart disease mortality when compared to NHW individuals (187). In 2004, Hispanics were 10% less likely to have heart disease, as compared to NHWs. Less nonfatal CHD in Hispanics versus NHW has also been observed, especially among men and individuals with type 2 diabetes. However, findings from other studies like Corpus Christi Heart Project showed a higher incidence of myocardial infarction (MI) and greater fatality after acute MI in Mexican Americans compared to NHWs.

Therefore, the actual cardiovascular disease pattern in this population is not well clear (166, 187).

Swenson et al. in 2002 compared the all cause and CVD mortality in Hispanic and non Hispanic White participants of San Luis Valley Diabetes Study. Using medical records they investigated 310 deaths that occurred in 15 years follow-up from 1984-1998 among 1,862 Hispanic and NHW individuals. The results revealed that among non-diabetics, there was no significant ethnic difference in risk for CVD or CHD death. Among individuals with type 2 diabetes the risk of CVD and CHD were significantly lower in Hispanics than NHWs, particularly in men (187). Conversely, Hunt et al. in the analysis of San Antonio Heart Study have observed different results. They found excess risk of all-cause, CVD and CHD mortality is associated with being Mexican American. They present evidence against the “Hispanic Paradox”, which refers to the widely spread credence that Hispanics have lower all-cause and CVD mortality rates than NHW, despite their higher rates of diabetes and obesity, lower socioeconomic status and barriers to health care. The authors argue that such observations are predominantly due to misclassification of ethnicity and causes of death for Hispanics (188, 189).

Overweight and Obesity in Hispanics

Overweight and obesity elevate the risk of developing variety of chronic diseases, including cardiovascular disease, type 2 diabetes, stroke, hypertension, dyslipidemia, osteoarthritis, breathing problems, some cancers and depression (190, 191). The prevalence of overweight and obesity is increasing rapidly in United States among all ages, races, ethnicities, socioeconomic status and geographic regions. Based on data from National Health and Nutrition Examination Survey, the combined prevalence of overweight and obesity (BMI of 25 or higher) increased from 46% in 1976-1980 to 64.5% in 1999-2000 (about 40% raise). During the same period the

prevalence of obesity (BMI of 30 or higher) increased from 14.5% to 30.5% (nearly 110% raise). According to NHANES 2001-2002, racial disparities in weight exist among women, but not in men; among black women 68.6% are overweight or obese compared to 56.0% of white women and 54.5% of Hispanic women. Racial differences are more evident when obesity rates are compared; 41.5% of black women compared to 19.3% of white women and 26.2% of Hispanic women (7). In the analysis of NHANES 1999-2000, the prevalence of obesity was reported 29% and 40% in MA men and women, 27% and 30% in NHW men and women and 28% and 50% in NHB men and women, respectively (192). Although, poor diet and physical inactivity are major contributors to overweight and obesity, other factors such as aging, genetics, low socioeconomic status (low education, unemployment, poverty), acculturation and number of children for women have been related to overweight and obesity among some ethnic groups. Lack of health insurance, less access to health care services including services for prevention, treatment and management of overweight, obesity and their complications have been associated to Hispanics excess weight status (191, 193).

Hypertension in Hispanics

Hypertension is a chief risk factor for heart disease and stroke, peripheral vascular and end-stage renal disease, and a strong predictor of premature death and adult disability. Although effective therapy has been available for more than 50 years, hypertension remains as a major public health problem in United States (194). In 2004, the overall estimated prevalence of hypertension was 72,000,000 and it was higher for females (39,000,000) than for males (33,000,000) (7).

According to AHA, hypertension is defined as untreated systolic pressure of 140 mm Hg or higher, or diastolic pressure of 90 mm Hg or higher or taking antihypertensive medicine; or

being told at least twice by a physician or other health professional that you have HBP. The pre-hypertension is untreated systolic pressure of 120–139 mm Hg, or untreated diastolic pressure of 80–89 mm Hg, and not being told on two occasions by a doctor or other health professionals that you have hypertension. An estimated 37.4 % of the U.S. population age 20 and older (41,900,000 men and 27,800,000 women) has pre-hypertension (7).

Several recent studies have reported that the prevalence of individuals with high blood pressure is increasing in the United States. The prevalence of hypertension increased from 25% in 1991-1994 to 31.3% in 1999-2000 (195-197). Analysis of NHANES 1999-2002 showed an age adjusted prevalence of 28.6% for hypertension (198), some part of these inconsistencies may be related to redefining the cutoffs and criteria in defining high blood pressure (199).

In United States, ethnic/racial disparities in hypertension prevalence, awareness, treatment and control exist. Hypertension is more common in African Americans than in Whites, and Mexican Americans have the lowest prevalence when compared with Whites and African Americans. The lowest awareness, treatment and control rates of high blood pressure is also exist among Mexican Americans (195, 197). Consistent with these findings, analysis of NHANES1999-2002 data demonstrate that the age-adjusted prevalence of hypertension was 40.5% among NHB, 27.4% among NHW, and 25.1% in Mexican Americans. Among individuals with hypertension 70.3% of NHB, 62.9% of NHW and 49.8% of Mexican Americans were aware of their condition. The age-adjusted proportion who received antihypertensive medication was 55.4% among NHB, 48.6% among NHW and 34.9% among Mexican Americans. Only 29% of U.S. adults with hypertension had controlled blood pressure levels (<140/90 mm Hg). The proportion with controlled blood pressure was comparable in NHB and NHW (29%) but considerably lower among Mexican American (17.3%).

Eliminating racial/ethnic disparities in hypertension awareness, prevention and control is an important public health issue and one of the Healthy People 2010 goals (200). Effective interventions are needed to prevent hypertension and /or improve blood pressure diagnosis and control in all populations, particularly among African Americans and Mexican Americans.

Dyslipidemia in Hispanics

Among adults 20 years and older, the 2004 estimated prevalence of high LDL cholesterol (LDLc >130 mg/dL) was 79,300,000 (40,800,000 males; 38,600,000 females). The mean level of LDLc for American adults, age 20 and older, is 123 mg/dL, which is close to the borderline high level. According to AHA classification, levels of 130-159 mg/dL are considered borderline high; levels of 160-189 mg/dL are classified as high and LDLc >190mg/dL is considered very high (7). Analysis of NHANES data 1999-2002 found, among NHW, the mean LDLc level was 126 mg/dL for men and 121 mg/dL for women. Among NHB, the mean LDLc was 121 mg/dL for both men and women. Among Mexican Americans, the mean LDLc level was 125 mg/dL in men and 117 mg/dL in women (7). In 2007, the trends in the prevalence, awareness, treatment and control of LDLc were investigated by Hyre et al. (201). They compared data from 6497 participants of NHANES III conducted in 1988-1994 and 5626 participants of NHANES 1999-2004. High LDLc was defined based on NECP ATP III criteria.

The age adjusted prevalence of high LDLc among U.S. adults was 26.6% in 1988-1994 and 25.3% in 1999-2004 (P = 0.28). During the periods of 1988-1994 and 1999-2004, awareness was increased significantly from 39.2% to 63.0%, use of pharmacologic lipid lowering medications increased significantly from 11.7% to 40.8% and among individuals with high LDLc levels, LDLc control increased significantly from 4.0% to 25.1%. In 1999-2004, NHB and MA had

lower LDLc control rates compared with NHW (17.2% and 16.5% vs. 26.9%, respectively; $p = 0.05$ and $p = 0.008$).

In adults age 20 and older, the 2004 estimated prevalence of HDLc <40mg/dL was 44,100,000 (31,700,000 males; 12,300,000 females). The mean level of HDLc for American adults age 20 and older is 51.3 mg/dL. Findings from NHANES 1999-2002 revealed that mean HDLc was 45.5 and 52.9 mg/dL among NHW men and women, 51.0 mg/dL and 57.3 mg/dL among NHB men and women and 45.0 and 52.9 mg/dL among MA men and women, respectively (7). In the analysis of NHANES III, Ford et al. observed the highest age adjusted prevalence of decreased HDLc levels in Mexican Americans (39.6%), followed by NHW(37.9%) and NHB (28.8%)(2).

According to NHANES 1999-2002, the mean adult triglyceride levels for NHW, NHB and Mexican Americans were 140, 99 and 144 mg/dL, respectively (202). Reports from NHANES III documented that Mexican Americans (37.7%), have the highest age adjusted prevalence of hypertriglyceridemia (TG >150 mg/dL), followed by NHW (31.1%) and NHB (17.7%).

The National Cholesterol Education Program advises to self monitor plasma lipid levels as a good motivator for improving the management of hypercholesterolemia. Clinical trials suggest that informing patients of their plasma lipid condition may help to improve lipid control and dietary habits (203). Comparing to other ethnicities, Hispanics tend to have lower knowledge of hyperlipidemia and its associations with CVD and lipid lowering therapy. Consistent with these findings, Kaplan et al. observed the same trend in the patients' knowledge on elevated plasma cholesterol and lipid lowering medications. Their study showed, Hispanic subjects, particularly non-English speaking speakers, were significantly less likely to know about CVD risks and its association with hypercholesterolemia. Continued efforts are needed to prevent hyperlipidemia

and /or improve hyperlipidemia control in all populations especially among African Americans, Mexican Americans and older people.

Dietary Patterns and Lifestyle in Hispanics

Latinos are a highly diverse group with a great variety in dietary traditions and food preferences. Hispanics dietary patterns like in any other ethnic group, account for cumulative and interactive effects of nutrients in food and reflect the interactions of biology, food availability, customs, beliefs, education and lifestyle of this population. Several studies have reported that acculturation among Hispanics is positively correlated with poorer dietary choices including low intake of fruits and vegetables and high consumption of discretionary fat and soft drinks with added sugar (193, 204 and 205).

Sharma et al. examined the adherence to the food guide pyramid recommendations among 5 different ethnic groups including African Americans and Latinos who participated in Multiethnic Cohort Study in Hawaii and Los Angeles. Subjects were 45-75 years and completed a self administered quantitative food frequency questionnaire at baseline in 1993 and after 3 years of follow up in 1996. The results revealed the lowest adherence among African Americans, Hawaiians and Latinos and the highest among Japanese American females and white females. They also found that non-U.S. born Latinos consumed 0.96 and 1.25 more servings of fruits and vegetables, respectively than their U.S. born counterparts. The author concluded that birthplace as one of the main components of acculturation, has a remarkable influence on fruits and vegetables intake in Latinos (204, 206). Nuehouser et al. investigated the associations of dietary patterns and acculturation among Hispanic immigrants from Mexico to Washington State. Dietary intake data on fat, fruit and vegetable intake were collected on 1,689 adults by using the Fat-Related Diet Habits questionnaire and the National 5-A-Day for Better Health Program

dietary assessment instruments. After adjusting for age, gender and socioeconomic factors, Latinos with higher acculturation scores had a significantly lower intake of fruits and vegetables (4.69 vs. 5.10 servings per day) compared to their less acculturated counterparts. Highly acculturated Latinos had vaguely higher scores on the Fat Related Diet Habit questionnaire. Adding fat to breads and potatoes was one of the early dietary changes through acculturation (207).

Findings on the fat intake and its association with acculturation are inconsistent among Hispanic subgroups. Some studies on Mexican Americans suggest that those born in Mexico or those with less acculturation, have lower dietary fat intake (208, 209) and other studies show the opposite results (210). The association between dietary fat intake and acculturation vary among Hispanics with different origins. Many studies have reported higher fat consumption in Puerto Ricans compared to other Latino groups (193, 211).

Findings on sugar consumption in Hispanics and its association with acculturation are more consistent. Several studies have found a positive association between sugar intake and acculturation among this population. Himmelgreen et al. (212) investigated the association of food consumption and acculturation among 174 low income Puerto Rican women in Connecticut. Acculturation was measured by length of time living in U.S., language use and birthplace. They observed a significantly higher consumption of soft drinks and other artificial drinks such as sodas and fruit drinks in Puerto Rican women who lived longer in U.S. ($P=0.048$). Consistent with these findings, Bermudez et al. documented a higher frequency consumption of foods with simple sugar in older Hispanics who resided longer in USA (213).

According to American Heart Association report based on National Health Interview Survey in 2004, only 45% of Hispanic adults compared to 49.3% of NHB and 65.7% of NHW were

engaged in at least some leisure-time **physical activity**. Adults with higher education (graduate degree) and income (four times the poverty level and more) were more likely to be engaged in any regular physical activity. Trend studies show the prevalence of engaging in a regular physical activity is increasing in United States, although racial/ethnic disparities persist (7). In 2005 only NHW men (52.3%) and NHW women (49.6%) had reached the Healthy People 2010 goal of 50% of adults engaging in a regular physical activity (214). Cultural barriers, education and poverty are major risk factors for a sedentary lifestyle and increasing obesity in Hispanics (193). Some of these factors might be modifiable through acculturation process.

Abradio-Lanza et al. analyzed data from 1991 National Health interview Survey, to examine the health behavior (including smoking, alcohol use, leisure-time physical activity and BMI) and acculturation hypotheses among Latinos. Acculturation was assessed by nativity status and length of stay in the U.S. After adjusting for age, education and income, acculturation was positively associated with higher likelihood of recent exercise performance (215).

Using data from NHANES III, Crespo et al. (216) investigated the association between acculturation (as measured by language preferences at home, birth place and number of years lived in the U.S.) and leisure-time physical activity among Mexican American adults. Mexican American women had a higher age adjusted prevalence of physical inactivity than men. In both men and women, inactivity was lower among those who spoke mostly English than among those who spoke Spanish or both English and Spanish. Inactivity patterns were less likely to be seen in subjects who were born in U.S. and those who lived longer in the country. In a recent study Slattery et al. examined the associations between physical activity and language acculturation (using Spanish or English written and oral fluency) and their effect on obesity. They analyzed data on 2039 participant of 4-Corner's Breast Cancer Study and compared the activity patterns in

Hispanics and non-Hispanic whites. The majority of women (25% Latinos vs. 35% whites, $p < 0.01$) were not engaged in leisure-time physical activity at least 5 times per week for a minimum of 30 minutes. Variation in activity patterns (type and intensity) were noticed among Latino and non-Latino women. Latino women reported more housework, dependent care giving, dancing and work activity. Differences in activity patterns were observed by the level of acculturation. Latino women with low, intermediate and high levels of acculturation met 13.6%, 26.2% and 28.4% of the leisure-time physical activity recommendations (217). According to CDC, implementing culturally appropriate, community based physical activity interventions including walking clubs, free exercise classes and other culturally relevant activities can help to increase leisure-time physical activity in this population and other minority groups.

Cigarette smoking is the leading cause of preventable death in the United States, resulting in approximately 438,000 deaths annually. According to CDC in 2005, the direct medical and productivity lost associated with smoking was \$167 billion (7). Reports from 2006 National Health Interview Survey (NHIS) revealed that around 20.8% of U.S. adults are current cigarette smokers (218). The prevalence of current cigarette smoking varies significantly by gender, education, income and population subgroups. It is higher among men (23.9%) than women (18.0%), among subjects with 9-11 years of education (35.4%) than those with more than 16 years of education (6.6%) and among adults living below poverty levels (30.6%) than those at or above poverty level (20.4%). The prevalence is significantly lower in Hispanics (15.2%) than non-Hispanic blacks (23%) and non-Hispanic whites (21.9%).

Recently Bethel and Schenker reviewed published articles on acculturation and smoking patterns in Hispanic men and women in the United States (1985-2003). They found a gender-specific association between acculturation and smoking in Hispanics. This positive association

was observed just in women but not among men. The authors concluded increasing cigarette smoking in women could be related to the customs and practices' influence of the dominant population (219).

Elevated CRP in Hispanics

Reports on inflammatory markers distribution comparing different ethnic groups are far and few. Lin et al. (147) analyzed NHANES 1999-2002 to investigate the prevalence of metabolic syndrome and inflammation markers among White, Black and Mexican American adults aged 40 years or older with and without diabetes. Among diabetes, the highest prevalence of elevated CRP was noticed among Blacks (24.5%), followed by Whites (17.7%) and Mexican Americans (17.3%). These differences were not statistically significant. Comparing CRP distribution among non-diabetes individuals showed, Blacks have substantially higher prevalence (17.4%) of elevated CRP than Mexican Americans (11.4%) and Whites (9.7%). More research is needed to investigate CRP status in Hispanics with metabolic syndrome.

Chapter 2: Methods

Survey Description and Sample Design

The National Health and Nutrition Examination Surveys (NHANES) are a series of national studies that the National Center for Health Statistics, Center for Disease Control and Prevention (CDC) has been conducting since 1966 to assess the health and nutritional status of the U.S. population.

In the past (from 1971 to 1994), the NHANES were conducted on a periodic basis and the data were released as single, multiyear data sets. For example, NHANES III was conducted 1988-1994 and can be analyzed as one, 6-year survey. In 1999, the survey became a continuous program that has a changing focus on different health and nutritional measurements to meet emerging public health issues. NHANES data are now released in two year cycles. Every year, the survey examines a nationally representative sample of about 5000 individuals. Participants are interviewed in their homes to obtain demographic, socioeconomic, dietary and health related information. Medical examinations, physiological measurements and laboratory tests are administered in mobile examination centers (MEC) by highly trained medical staff. Informed consent is obtained from all participants, and the institutional review board of the National Center for Health Statistics has approved the protocol.

The NHANES surveys use complex, stratified, multi-stage, clustered sampling of civilian, non-institutionalized U.S. population. A detailed description of design, procedures to select the sample and content of each survey can be obtained from NHANES Analytic and Reporting Guidelines (220).

The sample design and weighting methodology for NHANES 1999-2006 is very similar to past NHANES data releases. The stages of sample selection can be summarized as below:

1. Selection of Primary Sampling Units (PSUs), which are generally single counties; sometimes small counties are combined to meet a minimum population size.
2. Selection of Segments within PSUs; segment is a block or group of blocks containing a cluster of households.
3. Selection of households within segments.
4. Selection of one or more participants within households.

A total of 15 PSUs was visited in 12 months period. For NHANES 1999-2000, there were 12,160 individuals selected for the sample, 9,965 of those were interviewed (81.9 %) and 9,282 (76.3 %) were examined in the MEC. For NHANES 2001-2002, there were 13,156 individuals selected for the sample, 11,039 of those were interviewed (83.9 %), and 10,477 (79.6 %) were examined in the MEC. For NHANES 2003-2004, there were 12,761 individuals selected for the sample, 10,122 of those were interviewed (79.3 %) and 9,643 (75.6 %) were examined in the MEC. The NHANES 2005-2006 contains data for 10,348 individuals of all ages (220, 221).

Data Preparation and Use of Sample Weights

The continuous NHANES 1999-2006 data files from National Center for Health Statistics website is available for public use and will serve as the source of data for this study (222-225). These NHANES files consist of four separate data files including Demographic, Examination, Laboratory and Questionnaire. The multi-level data collection, information on specimen collection and processing and instructions on quality control systems are discussed in the Laboratory Procedures Manual of the NHANES 1999-2006 (226). All interview, laboratory, and examination data are sent to NCHS for final processing.

Since the data sets for NHANES 1999-2006 are in a SAS format, data preparation (sorting, appending, merging and recoding) were performed using Statistical Analysis Software (SAS)

version 9.1 (SAS Institute Inc, Cary, NC). Identification number or sequence was used to sort the subjects and merge variables from different data files into one data set for each NHANES cycle and combine the cycles to form the final data set.

The appropriate sample weights, stratum variable (SDMVSTRA) and primary sampling unit (PSU) variable (SDMVPSU) were included in all analyses to account for the complex survey design, unequal probabilities of selection, non-response and over-sampling of selected population subgroups. By weighting the sample data, we produced estimates of statistics that would have been obtained if the entire sampling population (for NHANES the entire sampling population is the United States) had been surveyed. The continuous NHANES 1999-2006 has over-sampled low income people, adolescents 10-12 years, elderly 60+ years, African Americans and Mexican Americans. The sample weight used in this study is calculated based on the recommendation from the National Center for Health Statistics and is the appropriate sample weight when data from combined cycles are analyzed (220, 228).

Statistical Software

According to NHANES 2005-2006 Analytic and Reporting Guidelines, “software for survey data, such as SUDAAN or software that has specific survey procedures, such as STATA and SAS, can be used to estimate sampling errors by the Taylor series (linearization) method” (220). Therefore, data preparation was performed using the Statistical Analysis Software (SAS) version 9.1 (SAS Institute Inc, Cary, NC). SAS Callable SUDAAN (Software for the Statistical Analysis of Correlated Data) version 10.0 (Research Triangle Institute, Research Triangle Park, NC) was used to estimate descriptive and inferential statistics of interest and the associated variances. SUDAAN has the capability to analyze data from stratified, cluster or multistage sample designs and does not need the assumption of sampling with replacement.

Study Population

This study analyzed data on 3265 Mexican American adults aged 20-80 years who participated in the National Health and Nutrition Examination Survey (NHANES) 1999-2006. Subjects who were fasted less than 8 hours before venipuncture, pregnant and lactating women and participants with type 1 diabetes mellitus were excluded from the analysis. The study was approved by the Institutional Review Board at the University of Maryland.

Variables of Interest

The variables of interest are grouped together and placed into one of the following categories: Socio-demographic, Anthropometric, Biochemical and Clinical variables.

Socio-demographic variables including age, gender, marital status, language spoken at home, smoking, drinking alcohol, physical activity, income and education levels were assessed using the Sample Person and Family Demographic questionnaires (227).

Marital status was divided into two categories as married including living as married, and unmarried including being widowed, divorced, separated, never married or living with a partner.

Language spoken at home was classified into five categories as only Spanish, more Spanish than English, both equally, more English than Spanish and only English.

Cigarette smoking was categorized as never smoked (if they had smoked <100 cigarettes in their lifetime), former smoker (≥ 100 lifetime cigarettes, not currently smoking), and current smoker (≥ 100 lifetime cigarettes, currently smoking) (154).

Alcohol intake levels were determined from number and frequency of alcoholic beverages consumed such as liquor, beer, wine and wine coolers in the past 30 days. The total number of

alcoholic drinks consumed per month was then calculated and divided into 4 categories: <1, 1 to 4, 5 to 7 and >7 drinks per month (147, 154).

Physical activity was defined based on frequency and duration of moderate or vigorous intensity leisure time activities and moderate tasks around the home or yard. Total minutes per week spent performing these activities were computed and divided into 3 categories: 0 min/week, < 150 and \geq 150 min/week of moderate or vigorous physical activity (154, 230 and 231).

Income status was defined based on Poverty Income Ratio (PIR) and divided into three levels (<1.85, 1.85-3.50 and >3.50) to represent low, middle and high income level, respectively (232). Poverty Income Ratio (PIR), the ratio of family income to poverty threshold, is an income criterion that varies by family size and composition. The U.S. Census Bureau uses PIR to define poverty status. PIR is also used as an eligibility criterion for participation in federal and state assistance programs and as an index of relative socioeconomic status in National Health and Nutritional Examination Surveys. PIR values less than 1.00 are below the official poverty threshold while PIR values of 1.00 or greater indicate income above the poverty level (229).

Education was measured as the highest grade completed or the highest degree received by the respondent and was further categorized to less than high school, high school diploma and more than high school.

Anthropometric variables including weight, height, BMI and waist circumference (WC) were determined using Examination data files. Detailed information on descriptions of the NHANES protocol, survey equipment and quality control procedures can be obtained from Anthropometry and Physical Activity Monitor Procedures Manual (233).

The participant's weight was measured on a Toledo digital scale with subjects wearing light clothing (underwear, disposable paper gowns and foam slippers). Weight was measured in pounds and was converted to kilograms in the automated system. Height was measured barefoot with a fixed stadiometer with a vertical backboard and a movable headboard. Subjects should move or remove hair ornaments, jewelry, buns and braids from the top of the head in order to measure stature properly. Body Mass Index (BMI) was calculated by dividing weight by squared height (Kg/m^2) and categorized as; underweight ($\text{BMI} < 18.5$), normal ($18.5 \leq \text{BMI} < 25$), overweight ($25 \leq \text{BMI} < 30$), obese ($\text{BMI} \geq 30$). Waist circumference was measured with a steel measuring tape at the high point of the iliac crest in a horizontal plane at minimal respiration to the nearest 0.1 cm.

The following **biochemical variables** were included in the analysis: triglyceride (TG), total cholesterol (TC), HDL cholesterol (HDLc), LDL cholesterol (LDLc), fasting plasma glucose (FPG) and C-reactive protein (CRP). Detailed description on laboratory methods is available on NHANES website in the Laboratory Procedures Manual (234). Serum triglyceride (TG) concentration was measured enzymatically after hydrolyzing to glycerol. Serum total cholesterol (TC) was also measured enzymatically after hydrolyzing cholesteryl esters to free cholesterol and fatty acids. HDL cholesterol concentration was measured on a Roche Hitachi Analyzer after the precipitation of other lipoproteins with a heparin-manganese chloride mixture. Low Density Lipoprotein cholesterol (LDLC) was calculated according to Friedewald formula: $[\text{LDLc}] = [\text{TC}] - [\text{HDLc}] - [\text{TG}/5]$. All the values in formula are expressed in mg/dl. This calculation is only valid for triglyceride less than 400 mg/dl. Fasting plasma glucose concentration was measured using an enzymatic reaction (enzyme hexokinase method) by the Diabetic Diagnostic Laboratory at the University of Missouri on participants aged 12 years and older and only in the

morning examination session. C - reactive protein (CRP) was quantified by particle-enhanced assay (latex enhanced nephelometry). Particle-enhanced assays are based on the reaction between a soluble analyte and the corresponding antigen or antibody bound to polystyrene particles.

In this study, blood pressure, medication use, presence of inflammation, family history of diabetes or stroke, menopausal status and estrogen use in women were categorized as **clinical variables**. Blood pressure was determined in mobile examination center using mercury sphygmomanometer in a sitting position after 5 minutes rest. Up to four blood pressure readings were obtained. Participants who had three or four blood pressure readings, the average of the last two measurements were used in the analysis. Those who had two blood pressure readings, the last measurement and participants who only had one reading, that measurement was considered as their blood pressure value. Information on blood pressure measurement procedures may be obtained from Physician Examination Procedures Manual (235, 236). Information on medication use including prescribed medicine for high blood pressure and hypercholesterolemia, lipid lowering statin medications, nonsteroidal anti-inflammatory and estrogen containing medications was obtained from questionnaire files (225, 237-239).

Chronic inflammation was determined if participant has been diagnosed with arthritis (240). Family history of diabetes, stroke/hypertension and angina were defined based on the presence of diabetes, stroke/hypertension and angina in biological relatives. Information on family history of hypertension/stroke was only available for 1999-2004 NHANES (240). Postmenopausal status was determined if there had been complete menses cessation ≥ 12 month (240, 241).

Metabolic Syndrome risk factors

Metabolic syndrome risk factors were defined based on International Diabetes Federation criteria. According to this definition, subjects have metabolic syndrome if they have central obesity plus any two of the following factors: 1) Elevated triglycerides level: ≥ 150 mg/dl or specific treatment for this lipid abnormality; 2) Reduced high density lipoprotein cholesterol (HDLc) level: < 40 mg/dl in men and < 50 mg/dl in women or specific treatment for this lipid abnormality; 3) Elevated blood pressure: systolic blood pressure ≥ 130 or diastolic blood pressure ≥ 85 mmHg or treatment of previously diagnosed hypertension; 4) Elevated fasting plasma glucose: ≥ 100 mg/dl or previously diagnosed type 2 diabetes and a combination of two or more of these risk factors (9).

Assessment of Covariates

The information on covariates and potential confounders such as age (y), BMI (Kg/m^2), marital status (married, unmarried), language spoken at home (only Spanish, more Spanish than English, both equally, more English than Spanish and only English), smoking habit (current, former and never), drinking alcohol, physical activity, economic status, education ($<$ high school, high school diploma or general equivalency diploma and $>$ high school), menopausal status (yes or no), current estrogen use (yes or no), medication use (yes or no), presence of arthritis (yes or no) and family history of diabetes (yes or no), family history of angina (yes or no) and family history of stroke (yes or no) were included in the analysis.

Statistical Analysis

Descriptive statistics was applied for all variables, including mean and standard error of the mean (SEM) for continuous variables and relative frequencies for categorical variables.

SUDAAN's t-test and Chi square test were applied to compare the means of continuous variables

and frequencies of categorical variables in male and female subjects, respectively. The estimates were considered unstable if the relative standard error for means or frequencies were greater than 30%.

The distribution of all continuous variables including waist circumference, height, weight, BMI, fasting plasma glucose, triglycerides, HDL and LDL cholesterol, systolic and diastolic blood pressure and CRP were examined graphically to check for normality. Since CRP values were not normally distributed, the log transformed CRP were used in all analyses. The results were back transformed and reported as geometric mean of CRP. Multicollinearity among independent variables and also between confounders was tested in regression model by checking variance inflation factor (VIF). Any variable with VIF greater than 4 was excluded from the model (no variable with VIF greater than 4 was detected). We also checked for outliers by plotting predicted and observed standardized residuals. The outliers at the 0.01 level (standardized residuals > 2.58) were removed from the analysis.

The appropriate sample weights, stratum variable (SDMVSTRA) and primary sampling unit (PSU) variable (SDMVPSU) were included in all analyses to account for the complex survey design, unequal probabilities of selection, non-response and over-sampling of selected population subgroups (228).

Receiver Operating Characteristic (ROC) curve analysis was used to determine the appropriate gender specific waist circumference cutoffs that predict the presence of two or more risk factors of metabolic syndrome including, hypertriglyceridemia, hyperglycemia, hypertension and low HDL cholesterol. Using logistic regression analysis and plotting sensitivity vs. 1-specificity, we investigated how accurately waist circumference (continuous predictor) could predict the presence of two or more metabolic syndrome risk factors. If waist circumference is a

perfect predictor will have a point on ROC curve with 100% sensitivity and 100% specificity. The distance on ROC curve for WC values from perfect predictor was calculated as the square root of $[(1-\text{sensitivity})^2 + (1-\text{specificity})^2]$. The waist circumference value with the shortest distance on the ROC curve and maximum sensitivity and specificity was selected as the appropriate cutoff (53, 242).

Regression analysis was used to address the associations between WC and BMI with triglycerides, fasting plasma glucose, HDL cholesterol, systolic and diastolic blood pressure (all continuous variables), in each gender after adjusting for age, income, alcohol intake, physical activity and the levels of education, smoking, marital status, language spoken at home, family history of diabetes, angina and stroke and menopausal status for women. Logistic regression was used to estimate the odds ratios (ORs) of developing metabolic syndrome components (hypertriglyceridemia, hyperglycemia, hypertension and low HDL cholesterol) according to quartiles of waist circumference after controlling for potential confounders including age, income, alcohol intake, physical activity and the levels of education, smoking, marital status, language spoken at home, family history of diabetes, angina and stroke. The reference point was set at 25 percentile for waist circumference.

Regression analysis was used to address the associations between log transformed CRP with triglycerides, fasting plasma glucose, HDL cholesterol, systolic and diastolic blood pressure (all continuous variables), in each gender after adjusting for age, income, alcohol intake, physical activity and the levels of education, smoking, marital status, language spoken at home, chronic inflammation, family history of diabetes, angina and stroke, medication use, menopausal status and estrogen use in women. Logistic regression was used to estimate the odds ratios (ORs) of developing metabolic syndrome and its components (central obesity, hypertriglyceridemia,

hyperglycemia, hypertension and low HDL cholesterol) according to quartiles of CRP after controlling for potential confounders mentioned above. The reference point was set at 25 percentile for CRP.

Data preparation (sorting, appending, merging and recoding) and ROC curve analysis were performed using Statistical Analysis Software (SAS) version 9.1 (SAS Institute Inc, Cary, NC). SUDAAN (Software for the Statistical Analysis of Correlated Data) version 9.0 (Research Triangle Institute, Research Triangle Park, NC) was used for all other analyses. Statistical significance was set at $P < 0.05$ for both t-test and χ^2 test.

Chapter 3: Appropriate Waist Circumference Cutoff Values for the Diagnosis of Metabolic Syndrome in Mexican American Adults

ABSTRACT

Background: Metabolic syndrome increases the risk of cardiovascular disease and diabetes.

The International Diabetes Federation (IDF) recently proposed new criteria for the diagnosis of metabolic syndrome, which requires the presence of central obesity as measured by ethnic specific waist circumference (WC) cutoff values. Currently, no specific WC thresholds for diagnosis of central obesity in Hispanics are available.

Objective: The objectives were to determine the appropriate gender specific WC thresholds for diagnosis of central obesity in Mexican American adults and to estimate the prevalence of metabolic syndrome using IDF definition with and without the modified WC in this population.

Design: Data from 3265 Mexican American adults aged 20-80 years who participated in the National Health and Nutrition Examination Survey 1999-2006 were used. The prevalence of metabolic syndrome was compared using IDF criteria with and without the modified waist circumference.

Results: Receiver operating characteristic curve analysis suggested that yielding at least 80% sensitivity, the WC value of 90 cm in both genders was more appropriate in predicting the presence of two or more metabolic syndrome risk factors in this population. Based on this cutoff, there was 34% reduction in the prevalence of central obesity in women (82.5% to 54.2%). The age adjusted prevalence of metabolic syndrome decreased from 58.4 to 48.2%. The metabolic syndrome was more common among Mexican American men than women (55.8% in men versus 37.8% in women, $P = 0.0003$).

Conclusion: Our findings provided a practical guidance in the assessment and screening of central obesity and metabolic syndrome in Mexican Americans.

KEY WORDS Metabolic syndrome, waist circumference, cutoff points, central obesity, NHANES, Mexican American

INTRODUCTION

Metabolic syndrome, the clustering of metabolic risk factors including central obesity, insulin resistance, atherogenic dyslipidemia, hyperglycemia and hypertension is associated with increased risk of cardiovascular disease (CVD) and type 2 diabetes mellitus (1). This syndrome is one of the major medical and public health problems in the United States and worldwide (3-6). An estimated 47 million U.S. residents have metabolic syndrome and the age adjusted prevalence of syndrome is 23.7 percent (2, 7).

In the effort of introducing the metabolic syndrome into clinical practice and identifying individuals with this condition, several sets of criteria have been proposed by different organizations. World Health Organization (WHO), the European Group for the Study of Insulin Resistance (EGIR), the American Association of Clinical Endocrinologists (AACE) and the National Cholesterol Education Program- Adult Treatment Panel III (NECP ATP III) have suggested some of the most accepted definitions (8-12). All of these definitions agree on the key elements of the metabolic syndrome including obesity, insulin resistance, hypertension and dyslipidemia; however they provide different criteria and cut points to define this cluster. The existence of several definitions was the main reason for proposing single unifying criteria by the International Diabetes Federation (IDF) in 2005, as a simple diagnostic tool for use in clinical practice and research worldwide. The IDF definition requires the presence of central obesity for diagnosis of metabolic syndrome. Central obesity is most easily measured by waist circumference (WC) with gender-ethnic specific thresholds (8). The current recommendations for defining central obesity in MAs (waist circumference ≥ 90 cm in men and ≥ 80 cm in women) are based on data from South Asia population and may not correctly estimate the prevalence of obesity in Hispanics due to ethnic differences in overall adiposity, abdominal

adiposity and visceral fat accumulation (13-15). Studies on Asians have shown that for a given BMI or waist circumference, Asians had higher percentage of body fat when compared to Caucasians (16-18). Findings from prospective study of 110 Hispanic and non-Hispanic white women revealed higher levels of adiposity and lower fat free mass in trunk region in Hispanic women (19).

Previous studies have shown a disproportionately high prevalence of metabolic syndrome, diabetes and CVD in Hispanics compared to non-Hispanic whites. Metabolic syndrome is more prevalent among Mexican Americans (MA) than non-Hispanic whites (31.9% vs. 23.8%). Hispanics are twice as likely to have diabetes as non-Hispanic whites of similar age. The prevalence of CVD is also high in this population and is comparable to non-Hispanic whites (7). Recently Ford et al. (2) reported that metabolic syndrome risk factors are very frequent in MA men and women. Obesity is epidemic among this population and abdominal obesity is present in nearly 46% of Mexican Americans. They also have a high incidence of other components of metabolic syndrome including: hypertriglyceridemia (37.7%), low levels of HDL cholesterol (39.6%), hypertension or being treated for blood pressure (36.6%) and hyperglycemia or taking medication for diabetes (20%). Considering the high incidence of metabolic syndrome, diabetes and CVD in the Hispanic population, there is an urgent medical, ethical and economical need to identify individuals with syndrome early, so that lifestyle interventions and treatment may prevent or delay the development of diabetes and/or CVD in this population.

In this study we investigated the appropriate waist circumference cutoff values for diagnosis of central obesity in Mexican American adults. We also compared the prevalence of metabolic syndrome based on IDF definition with and without the modified waist circumference in the same population.

SUBJECTS and METHODS

Study population

This study analyzed data on 3265 Mexican American adults aged 20-80 years who participated in the National Health and Nutrition Examination Survey (NHANES) 1999-2006. The survey used complex, multi-stage, stratified, clustered sampling to access the health and nutritional status of the civilian, non-institutionalized U.S. population. Participants were interviewed in their homes to obtain demographic, socioeconomic, dietary and health related information and were asked to attend the mobile examination center (MEC) to undergo medical examinations and laboratory tests. Detailed information on study design and sample selection may be found elsewhere (20). Subjects who were fasted less than 8 hours before venipuncture, pregnant and lactating women and participants with type 1 diabetes mellitus were excluded from the analysis. The study was approved by the Institutional Review Board at the University of Maryland.

Metabolic risk factors

Metabolic syndrome was defined based on IDF criteria. According to this definition, subjects have metabolic syndrome if they have central obesity plus any two of the following factors: 1) Elevated triglycerides level: ≥ 150 mg/dl or specific treatment for this lipid abnormality; 2) Reduced high density lipoprotein cholesterol (HDLc) level: < 40 mg/dl in men and < 50 mg/dl in women or specific treatment for this lipid abnormality; 3) Elevated blood pressure: systolic blood pressure ≥ 130 or diastolic blood pressure ≥ 85 mmHg or treatment of previously diagnosed hypertension; 4) Elevated fasting plasma glucose: ≥ 100 mg/dl or previously diagnosed type 2 diabetes (8).

The IDF emphasizes the use of gender-ethnic specific thresholds for waist circumference when measuring central obesity. For Europid, Sub-Saharan African, Eastern Mediterranean and

Middle East (Arab) men, the specified cut point is $WC \geq 94$ cm; for South Asian, Chinese, Japanese and ethnic South and Central American men, $WC \geq 90$ cm; and in Women $WC \geq 80$ cm is defined as central obesity(21). In this analysis, the cut off values of 90 and 80 cm were used as original cutoffs to define central obesity in Mexican American men and women, respectively.

Waist circumference was measured with a steel measuring tape at the high point of the iliac crest in a horizontal plane at minimal respiration to the nearest 0.1 cm (22). Serum triglyceride (TG) concentration was measured enzymatically after hydrolyzing to glycerol. Serum total cholesterol (TC) was also measured enzymatically after hydrolyzing cholesteryl esters to free cholesterol and fatty acids. HDL cholesterol concentration was measured on a Roche Hitachi Analyzer after the precipitation of other lipoproteins with a heparin-manganese chloride mixture. Hypercholesterolemia was defined as $TC \geq 200$ mg/dl or using cholesterol lowering medications. Low Density Lipoprotein cholesterol (LDLC) was calculated according to Friedewald formula: $[LDLc] = [TC] - [HDLc] - [TG/5]$. Fasting plasma glucose concentration was measured using an enzymatic reaction (enzyme hexokinase method) by the Diabetic Diagnostic Laboratory at the University of Missouri. C - reactive protein (CRP) was quantified by particle-enhanced assay (latex enhanced nephelometry). Detailed description of laboratory methods is available on NHANES website in the Laboratory Procedures Manual (23). Blood pressure was determined in mobile examination center using mercury sphygmomanometer in a sitting position after 5 minutes rest. Up to four blood pressure readings were obtained. Participants who had three or four blood pressure readings, the average of the last two measurements were used in the analysis. Those who had two blood pressure readings, the last measurement and participants who only had one reading, that measurement was considered as their blood pressure value (24, 25).

Information on age, Body Mass Index (BMI), education and income levels, smoking and drinking habits, physical activity, marital status, language spoken at home, family history of diabetes, angina and stroke were also included in the analysis. BMI was calculated from weight and height values and classified according to standard definitions (26) as; underweight ($\text{BMI} < 18.5 \text{ kg/m}^2$), normal weight ($\text{BMI} = 18.5\text{-}24.9 \text{ kg/m}^2$), overweight ($\text{BMI} = 25.0\text{-}29.9 \text{ kg/m}^2$) and obesity ($\text{BMI} \geq 30 \text{ kg/m}^2$). Education was measured as the highest grade completed or the highest degree received by the respondent and was further categorized to less than high school, high school diploma and more than high school. Income status was defined based on Poverty Income Ratio (PIR) and divided into three levels (<1.85 , $1.85\text{-}3.50$ and >3.50) to represent low, middle and high income level, respectively (27). Cigarette smoking was categorized as never smoked (if they had smoked <100 cigarettes in their lifetime), former smoker (≥ 100 lifetime cigarettes, not currently smoking), and current smoker (≥ 100 lifetime cigarettes, currently smoking). Alcohol intake levels were determined from number and frequency of alcoholic beverages consumed such as liquor, beer, wine and wine coolers in the past 30 days. The total number of alcoholic drinks consumed per month was then calculated and divided into 4 categories: <1 , 1 to 4, 5 to 7 and >7 drinks per month (28, 29). Physical activity categories were defined based on frequency and duration of moderate or vigorous intensity leisure time activities and moderate tasks around the home or yard. Total minutes per week spent performing these activities were computed and divided into 3 categories: 0 min/week, < 150 and ≥ 150 min/week of moderate or vigorous physical activity (28, 30 and 31). Marital status was classified into two categories as married including living as married, and unmarried including being widowed, divorced, separated, never married or living with a partner. Language spoken at home was divided into five categories as only Spanish, more Spanish than English, both equally, more

English than Spanish and only English. Family history of diabetes, angina and stroke/hypertension were defined based on the presence of diabetes, angina and stroke/hypertension in biological relatives. Information on family history of hypertension/stroke was only available for 1999-2004 NHANES (32). Postmenopausal status was determined if there had been complete menses cessation ≥ 12 month (33).

Statistical analysis

Descriptive statistics were applied for all variables, including mean and standard error of the mean (SEM) for continuous variables and relative frequencies for categorical variables. SUDAAN's t-test and Chi square test were applied to compare the means of continuous variables and frequencies of categorical variables in male and female subjects, respectively. The estimates were considered unstable if the relative standard error for means or frequencies were greater than 30%. The appropriate sample weights, stratum variable (SDMVSTRA) and primary sampling unit (PSU) variable (SDMVPSU) were included in all analyses to account for the complex survey design, unequal probabilities of selection, non-response and over-sampling of selected population subgroups (34). Receiver Operating Characteristic (ROC) curve analysis was used to determine the appropriate gender specific waist circumference cutoffs that predict the presence of two or more risk factors of metabolic syndrome including, hypertriglyceridemia, hyperglycemia, hypertension and low HDL cholesterol. The distance on ROC curve for WC values was calculated by as the square root of $[(1-\text{sensitivity})^2 + (1-\text{specificity})^2]$. The waist circumference value with the shortest distance on the ROC curve and maximum sensitivity and specificity was selected as the appropriate cutoff (35, 36). We checked for outliers by plotting

predicted and observed standardized residuals. The outliers at the 0.01 level (standardized residuals > 2.58) were removed from the analysis.

Data preparation (sorting, appending, merging and recoding) and ROC curve analysis were performed using Statistical Analysis Software (SAS) version 9.1 (SAS Institute Inc, Cary, NC). SAS callable SUDAAN (Software for the Statistical Analysis of Correlated Data) version 9.0 (Research Triangle Institute, Research Triangle Park, NC) was used for all other analyses. Statistical significance was set at $P < 0.05$ for both t-test and χ^2 test.

Results

The basic characteristics of the study population and the prevalence of metabolic risk factors are summarized in **Table 3.1**. The mean age was 37.1 ± 0.4 years for men and 39.5 ± 0.6 years for women ($P = 0.0001$). Men were significantly taller and heavier and had larger WC than women. Significant differences in triglyceride, total cholesterol, LDL and HDL cholesterol, systolic and diastolic blood pressure and CRP values were found between genders. Family history of diabetes mellitus, angina and hypertension/stroke were more prevalent in women ($P = 0.0001$). All metabolic risk factors were found to be significantly different between men and women. Generally, men were more likely to be married, speak Spanish at home, be current smokers, less educated and drink more alcohol as compared to women. Except for the middle income category, there were no significant differences in the values of income and physical activity in men and women (**Table 3.2**).

According to the IDF definition, the overall age adjusted prevalence of metabolic syndrome was 58.4% (55.8% in men and 64.8% in women, $P = 0.06$). Metabolic syndrome was significantly more prevalent in women in the 1st and 2nd quartile of waist circumference, hypercholesterolemic, hypertriglyceridemic and hyperglycemic women with CRP levels greater

than 3 mg/l and no moderate or vigorous physical activity. Current smokers and women who had less than one drink per month also were found to have higher prevalence of the metabolic syndrome ($P < 0.05$ for all). However the metabolic syndrome was significantly higher in men with family history of angina and men who had more than 7 drinks per month ($P = 0.002$ and $P = 0.05$, respectively). There was a significant increase in the prevalence of metabolic syndrome across the levels of waist circumference and C-reactive protein (P for trend < 0.001 for both). In addition, subjects with hypertension, reduced HDL cholesterol, hypertriglyceridemia and hyperglycemia had higher prevalence of metabolic syndrome compared to those who did not have these metabolic abnormalities ($P = 0.0001$ for all). Metabolic syndrome was also more prevalent in participants who reported having family history of angina or stroke than those who did not have the family history of angina or stroke ($P < 0.05$ for both). Former smokers had higher prevalence of metabolic syndrome compared to never smokers ($P < 0.01$). However, the prevalence did not vary by family history of diabetes, drinking and physical activity status (**Table 3.3**).

The prevalence of having metabolic abnormalities including hypertriglyceridemia, hyperglycemia, hypertension, reduced HDL cholesterol or central obesity is presented in **Figure 3.1**. Overall 89% of the population had one or more metabolic abnormality. Mexican American women were more likely to have one or more metabolic abnormalities than men (92% vs. 87%, $P = 0.001$). There were no significant differences in prevalence of two or more or three or more metabolic abnormalities among genders.

According to ROC curve analysis, the optimal waist circumference cutoff values with maximum sensitivity and specificity for predicting the presence of two or more metabolic risk factors and the shortest distance on the ROC curve from perfect predictor was 95 cm for both

men and women (**Figure 3.2**). The sensitivity and specificity of this cutoff were 66.7% and 60.4% in both genders, respectively (**Table 3.4**). Since IDF criteria requires the presence of central obesity for the diagnosis of metabolic syndrome, we justified to choose a cutoff point that obtains at least 80% sensitivity even if it causes a significant decrease in specificity. Therefore, the appropriate waist circumference to predict two or more metabolic risk factors in Mexican Americans with 80% sensitivity was 90 cm in men and women, with a corresponding specificity of 45.6% in men and 45.8% in women. After applying the modified waist circumference of 90 cm, we noticed 34% reduction in the prevalence of central obesity in women (82.5% to 54.2%). In addition, the prevalence of central obesity was significantly lower among women compared to men (54.2% vs. 69.8%, $P=0.0001$). The age adjusted prevalence of metabolic syndrome in women also decreased from 64.8% to 37.8%. With the original cutoff value of 80 cm, the syndrome was more prevalent in women (64.8% vs. 55.8%), while the reverse pattern was observed with the modified cutoff value of 90 cm and more men had metabolic syndrome (55.8% vs. 37.8%, $P=0.0003$) compared to women (**Table 3.5**).

Discussion

Our findings suggest that waist circumference of 90 cm for both men and women is more appropriate in predicting the presence of two or more metabolic risk factors and defining central obesity in Mexican American adults aged 20-80 years old. The WC value of 90 cm in men is smaller than the recommended obesity cutoff for Americans (102 cm) and Europeans (94 cm) and has been recommended by the joint World Health Organization (WHO)/ International Association for the Study of Obesity (IASO)/ International Obesity Task Force (IOTF) committee for defining central obesity in Asian populations (8, 37 and 38). The same cutoff value of 90 cm has been proposed by IDF for defining central obesity in South Asian, Chinese,

Japanese and South and Central American men (21). Our finding on WC cut point in men is consistent with the results from previous studies who examined the appropriate waist circumference for central obesity in different ethnic populations. Analysis of data on 4723 Chinese, Malay and Asian-Indian men and women from 1998 Singapore National Health Survey suggested that WC of 90 cm was more appropriate in defining central obesity in this population (14). Using data from Korean Health and Nutritional Examination Survey 1998, Lee and colleagues also reported that the WC of 90 cm was more appropriate in determining metabolic syndrome risk factors in Korean men (39).

We suggest that the WC value of 90 cm would be more appropriate for defining central obesity and predicting the presence of two or more metabolic risk factors in Mexican American women. This value differs from recommended thresholds for American (88 cm) and European (80 cm) women by 2 and 10 cm, respectively. There is a 10 cm gap between our cutoff for women (90 cm) and the value recommended by WHO/ IASO/IOTF committee for defining obesity in Asian women and the IDF proposed cutoff for central obesity and defining metabolic syndrome in South Asian, Chinese and South and Central American women (80 cm). However, this finding follows the results from a previous study on determining the optimal waist circumference cutoff for obesity in Japanese women (40). Consistent with this finding, Zhu et al. (33) in analyzing data from NHANES III found the WC value of 94 cm as a more appropriate threshold in determining cardiovascular disease risk factors in Mexican American women.

According to the waist circumference cutoff identified in the present study, the prevalence of central obesity among men and women were 69.8% and 54.2%, respectively. In contrast to our result, Ford et al. (2) in the analysis of data from NHANES III reported that central obesity as defined by $WC \geq 102$ cm in men and $WC \geq 88$ cm in women was more prevalent in Mexican

American women compared to men (62.7% vs. 30.6%). Using data from NHANES 1999-2000, Flegal and colleagues also found obesity to be more prevalent among Mexican American women than men (40% vs. 29%). However, they used different criteria in defining the central obesity (41).

Based on IDF definition and the waist circumference cutoff proposed by our study the age adjusted prevalence of metabolic syndrome was 55.8% and 37.8% in men and women, respectively. Consistent with this finding, Ford and colleagues in the study of data from NHANES 1999-2002, reported higher prevalence of metabolic syndrome among men than women (50.6% vs. 46.2%)(3). Some of the differences in the estimates of prevalence in these studies might be explained by applying different waist circumference cutoff points in defining central obesity and metabolic syndrome. In the Ford et al. study they used the thresholds of 90 cm for men and 80 cm for women (3). However, in both studies the IDF criteria for metabolic syndrome were used.

Our results are not applicable to all Hispanics as only Mexican Americans were over sampled in NHANES and the small number of 'other Hispanics' in data set were not sufficient to be analyzed as a separate group. To our knowledge, this is the first study to investigate the appropriate waist circumference cutoff for diagnosis of central obesity and metabolic syndrome in Mexican Americans adults, using 8 years of continuous NHANES 1999-2006 data. The findings of the present study are derived from a representative sample of Mexican American adults in the United States and are applicable to this population.

In summary, our results indicated that the appropriate waist circumference to predict two or more metabolic risk factors in Mexican Americans is 90 cm in men and women. According to this cutoff the central obesity and metabolic syndrome are both more prevalent among Mexican

American men than women. The current study will contribute not only to the understanding of the importance of appropriate assessment of central obesity in screening metabolic syndrome but also to provide practical guidance in identifying individuals with metabolic syndrome and taking proper procedures to prevent or delay the development of diabetes and /or cardiovascular disease.

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Appendices 1

Table 3.1. Basic characteristics and metabolic risk indicators among Mexican American adults aged 20-80 years, NHANES 1999-2006*

Variables	Total		Men		Women	
	n	Mean or % (SEM) [†]	n	Mean or % (SEM)	n	Mean or % (SEM)
Age (y)	3265	38.07 (0.52)	1794	37.08 (0.46)	1471	39.50 (0.67) [§]
Height (cm)	3223	165.05 (0.18)	1780	169.97 (0.25)	1443	157.88 (0.23) [§]
Weight (kg)	3203	76.56 (0.41)	1764	80.69 (0.59)	1439	70.57 (0.58) [§]
Body mass index (kg/m ²)	3196	28.04 (0.15)	1761	27.85 (0.18)	1435	28.32 (0.24)
< 18.5 (%)	24	0.81 (0.21)	6	0.35 (0.15) [¶]	18	1.47 (0.48) [¶]
≥ 18.5 to < 25 (%)	856	28.99 (1.36)	458	27.91 (1.67)	398	30.55 (1.70)
≥ 25 to < 30 (%)	1327	40.48 (0.92)	824	44.86 (1.09)	503	34.15 (1.42) [§]
≥ 30 (%)	987	29.71 (1.16)	472	26.87 (1.48)	515	33.83 (1.85) [§]
Waist Circumference (cm)	3139	95.02 (0.41)	1726	96.69 (0.55)	1413	92.62 (0.58) [§]
Fasting plasma glucose (mg/dl)	1421	104.16 (1.07)	789	104.91 (1.31)	632	103.08 (1.77)
Total cholesterol (mg/dl)	1407	196.37 (1.47)	783	199.90 (1.91)	624	191.22 (2.00) [§]
HDL cholesterol (mg/dl)	1408	49.20 (0.48)	784	46.33 (0.50)	624	53.39 (0.69) [§]
LDL cholesterol (mg/dl)	1343	117.82 (1.21)	737	123.03 (1.54)	606	110.51 (1.57) [§]
Triglycerides (mg/dl)	1407	155.65 (6.12)	783	166.00 (8.70)	624	140.55 (6.86) [§]
SBP (mmHg)	2939	119.20 (0.51)	1631	120.56 (0.60)	1308	117.19 (0.66) [§]
DBP (mmHg)	2939	70.33 (0.31)	1631	70.97 (0.41)	1308	69.38 (0.37) [§]
C-reactive protein (mg/l)	1415	2.65 (0.10)	786	2.17 (0.10)	629	3.35 (0.13) [§]
Family history (%)						
Diabetes mellitus	1584	50.12 (1.37)	830	46.61 (1.66)	754	55.21 (1.62) [§]
Angina	267	8.16 (0.63)	103	5.52 (0.74)	164	12.01 (0.98) [§]
Hypertension/Stroke	562	24.45 (1.27)	268	20.91 (1.20)	294	29.46 (2.04) [§]
Metabolic risk factors (%) [‡]						
Elevated triglyceride	640	38.27 (1.94)	370	42.44 (2.48)	270	32.18 (2.09) [§]
Reduced HDL cholesterol	604	38.28 (1.71)	280	30.63 (2.20)	324	49.46 (2.01) [§]
Elevated blood pressure	1175	24.59 (1.22)	669	27.33 (1.37)	506	20.77 (1.63) [§]
Elevated fasting plasma glucose	669	39.65 (1.99)	411	44.91 (2.03)	258	32.04 (3.25) [§]
Central obesity	2509	75.00 (1.25)	1299	69.81 (1.82)	1210	82.48 (1.43) [§]
Menopausal status (%)						
Pre	□	□	□	□	559	70.42 (1.83)
post	□	□	□	□	590	29.58 (1.83)

* HDL, high density lipoprotein; LDL, low density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure. The means of all continuous variables and frequencies of all categorical variables were compared in men and women using SUDAAN's *t* test and χ^2 test, respectively. Statistical significance was set at $P < 0.05$.

[†] Values are means (SEM) for continuous variables and percentages (SEM) for categorical variables.

[‡] Metabolic risk factors were defined according to IDF definition (21): elevated triglyceride, ≥ 150 mg/dl or specific treatment for hypertriglyceridemia; reduced HDL cholesterol, < 40 mg/dl for men and < 50 mg/dl for women or specific treatment for this lipid abnormality; elevated blood pressure, systolic blood pressure ≥ 130 mmHg, diastolic blood pressure ≥ 85 mmHg or treatment for previously diagnosed hypertension; elevated fasting plasma glucose ≥ 100 mg/dl or previously diagnosed type 2 diabetes; central obesity, waist circumference ≥ 90 cm for men and ≥ 80 cm for women.

[§] Significant difference between men and women. [¶] Unstable estimates.

Table 3.2. Socio-economic and behavioral characteristics of the study population, NHANES 1999-2006

Characteristics	Total		Men		Women	
	n	% (SEM)	n	% (SEM)	n	% (SEM)
Education (y)						
<12	2000	55.14 (1.25)	1124	56.82 (1.70)	876	52.71 (1.56)
12	563	20.69 (0.89)	306	20.76 (1.23)	257	20.59 (1.37)
>12	699	24.12 (1.25)	362	22.35 (1.59)	337	26.68 (1.47) [§]
Marital status						
Married	2015	60.41 (1.38)	1186	61.63 (1.78)	829	58.64 (1.39)
Unmarried	1159	39.59 (1.38)	565	38.37 (1.78)	594	41.36 (1.39)
Language spoken at home						
Only Spanish	1582	47.98 (2.33)	900	50.08 (2.81)	682	44.96 (2.12) [§]
Spanish > English	338	10.35 (0.81)	198	10.74 (1.01)	140	9.79 (1.07)
Spanish = English	433	12.12 (1.20)	207	10.68 (1.33)	226	14.20 (1.45) [§]
English > Spanish	356	11.54 (1.17)	192	11.33 (1.30)	164	11.84 (1.43)
Only English	548	18.01 (1.25)	293	17.17 (1.50)	255	19.23 (1.73)
Income						
Low	1739	57.83 (1.91)	936	56.37 (2.20)	801	60.02 (2.02)
Middle	734	25.48 (1.60)	443	27.37 (1.84)	291	22.64 (1.52) [§]
High	485	16.69 (1.09)	267	16.26 (1.28)	218	17.34 (1.37)
Smoking status						
Never	1815	57.40 (0.99)	758	46.39 (1.27)	1057	73.34 (1.31) [§]
Former	782	19.45 (0.83)	560	24.24 (1.03)	222	12.51 (1.09) [§]
Current	665	23.15 (0.82)	476	29.37 (1.15)	189	14.15 (0.87) [§]
Alcohol intake (drink/mon)						
<1	1565	53.11 (1.35)	626	38.65 (2.04)	939	73.67 (1.16) [§]
1-4	719	31.39 (1.23)	526	40.49 (1.92)	193	18.46 (1.10) [§]
5-7	100	4.34 (0.42)	67	5.01 (0.72)	33	3.39 (0.56) [§]
>7	219	11.16 (0.87)	180	15.85 (1.37)	39	4.48 (0.61) [§]
Physical activity (min/wk)						
0	1112	33.11 (1.58)	589	33.30 (1.88)	523	32.85 (1.76)
≤ 150	809	26.71 (1.07)	449	27.06 (1.46)	360	26.19 (1.23)
> 150	1220	40.18 (1.73)	697	39.64 (1.99)	523	40.96 (1.94)

[§] The frequencies of categorical variables were compared in men and women using SUDAAN's χ^2 test. Statistical significance was set at $P < 0.05$.

Table 3.3. The age adjusted prevalence of the metabolic syndrome among Mexican American adults aged 20-80 years by cardiovascular risk factors, NHANES 1999-2006*

Characteristics	Total		Men		Women	
	n	% (SEM)	n	% (SEM)	n	% (SEM)
Waist circumference (cm)						
<86	211	8.08 (1.27) [‡]	114	0	97	13.50 (2.22) [¶]
86-94.1	198	54.25 (4.00)	117	39.85 (4.73)	81	100.0 (0.00) [¶]
94.2-103.2	227	100.0 (0.00)	139	100.0 (0.00)	88	100.0 (0.00)
>103.2	281	100.0 (0.00)	179	100.0 (0.00)	102	100.0 (0.00)
Hypertension						
Yes	461	75.74 (4.27) [§]	255	78.21 (4.17)	206	66.04 (12.98)
No	460	53.11 (2.70)	286	48.58 (3.40)	174	63.31 (3.74) [¶]
Hypercholesterolemia[†]						
Yes	548	66.01 (2.99) [§]	312	62.28 (3.74)	236	80.10 (5.28) [¶]
No	5	100 (0.00)	2	100 (0.00)	3	100 (0.00)
Reduced HDL cholesterol						
Yes	504	84.94 (2.48) [§]	255	82.93 (3.79)	249	87.63 (2.51)
No	432	38.02 (2.36)	304	39.94 (2.60)	128	29.38 (4.99) [¶]
Hypertriglyceridemia						
Yes	582	83.84 (2.35) [§]	334	80.21 (3.05)	248	94.56 (2.34) [¶]
No	354	31.92 (2.90)	225	27.97 (3.38)	129	41.41 (5.68)
Hyperglycemia						
Yes	575	71.56 (3.47) [§]	350	68.26 (4.05)	225	87.64 (3.92) [¶]
No	366	45.24 (2.69)	209	41.17 (3.78)	157	53.24 (4.64) [¶]
Family history of diabetes						
Yes	503	62.42 (2.92)	281	62.01 (4.06)	222	63.65 (3.97)
No	422	54.53 (3.00)	271	50.59 (3.33)	151	66.98 (5.29) [¶]
Family history of angina						
Yes	87	73.66 (6.46) [§]	29	96.24 (2.17)	58	68.73 (8.58) [¶]
No	833	57.53 (2.46)	520	54.74 (2.93)	313	65.94 (3.96) [¶]
Family history of stroke or hypertension						
Yes	166	68.57 (5.15) [§]	84	65.20 (7.82)	82	73.74 (5.59)
No	572	56.14 (2.58)	342	53.07 (3.25)	230	64.68 (3.83) [¶]
Physical activity (min/wk)						
0	313	58.15 (3.46)	181	54.05 (3.96)	132	69.34 (6.33) [¶]
≤ 150	229	61.28 (4.10)	140	59.48 (5.15)	89	66.52 (4.87)
> 150	363	57.38 (3.46)	220	56.42 (5.08)	143	59.07 (5.67)
C-reactive protein (mg/l)						
<1	241	36.71 (3.06) [‡]	184	38.21 (3.74)	57	31.42 (6.18)
1-3	335	64.97 (3.41)	214	64.75 (4.30)	121	64.79 (5.25)
>3	351	77.99 (3.52)	155	72.71 (4.81)	196	85.13 (3.40) [¶]
Smoking status						
Never	495	54.97 (2.32) [§]	235	52.49 (3.50)	260	59.72 (4.34)
Former	251	66.71 (4.38)	183	65.16 (5.12)	68	71.43 (6.84)
Current	193	57.93 (3.32)	141	53.86 (3.26)	52	70.79 (7.58) [¶]
Alcohol (drink/mon)						
<1	457	57.47 (2.75)	201	48.32 (3.79)	256	71.09 (3.25) [¶]
1-4	195	60.95 (4.00)	150	60.13 (4.26)	45	65.05 (7.12)
5-7	32	59.96 (9.08)	22	51.76 (11.53)	10	68.86 (16.24)
>7	69	61.19 (6.29)	60	61.22 (6.65)	9	47.85 (0.00) [¶]
Menopausal status (%)						
Pre	□□	□	□	□	96	66.32 (4.26) [¶]
post	□	□	□	□	217	88.16 (3.35)

*The age adjusted prevalence of metabolic syndrome was compared across the levels of cardiovascular risk factors and between men and women using SUDAAN's χ^2 test. Metabolic syndrome was defined based on IDF definition.

†Hypercholesterolemia was defined as total cholesterol \geq 200 mg/dl or using cholesterol lowering medications.

* P for trend <0.0001 ; § $P <0.01$ (comparing the levels of cardiovascular risk factors); ¶ $P <0.01$ (comparing men and women)

Table 3.4. Sensitivity, specificity and distance in the receiving operating characteristic (ROC) curve for waist circumference cutoff values in Mexican American adults*

<u>2 or more metabolic risk factors</u>			
WC cutoff (cm)	Sensitivity	Specificity	Distance in ROC curve
Men			
65	98.2	2.50	0.97
70	97.9	3.90	0.96
75	97.4	7.42	0.92
80	95.4	15.3	0.84
85	91.1	28.9	0.71
90	80.7	45.6	0.57
95	66.7	60.4	0.51
100	49.7	73.4	0.56
105	32.2	84.9	0.69
Women			
65	98.2	2.50	0.97
70	97.9	3.90	0.96
75	97.4	7.60	0.92
80	95.3	16.9	0.83
85	91.0	29.3	0.71
90	80.9	45.8	0.57
95	66.7	60.4	0.51
100	50.5	73.3	0.56
105	32.2	84.8	0.69

* Metabolic risk factors were defined according to IDF definition (21): elevated triglyceride, \geq 150 mg/dl or specific treatment for hypertriglyceridemia; reduced HDL cholesterol, $<$ 40 mg/dl for men and $<$ 50 mg/dl for women or specific treatment for this lipid abnormality; elevated blood pressure, systolic blood pressure \geq 130 mmHg, diastolic blood pressure \geq 85 mmHg or treatment for previously diagnosed hypertension; elevated fasting plasma glucose \geq 100 mg/dl or previously diagnosed type 2 diabetes.

Table 3.5. The age adjusted prevalence of the metabolic syndrome and central obesity among Mexican American adults aged 20-80 years by gender, NHANES 1999-2006*

Characteristics	Metabolic syndrome [†]				Central obesity			
	Total (n=1042)	Men (n=559)	Women (n=483)	<i>P</i>	Total (n=3139)	Men (n=1726)	Women (n=1413)	<i>P</i>
	% (SEM)	% (SEM)	% (SEM)		% (SEM)	% (SEM)	% (SEM)	
IDF waist circumference[‡]	58.4 (2.14)	55.8 (2.88)	64.8 (3.25)	0.06	75.0 (1.25)	69.8 (1.82)	82.5 (1.43)	0.0001
Modified waist circumference[§]	48.2 (1.91)	55.8 (2.88)	37.8 (3.03)	0.0003	63.4 (1.29)	69.8 (1.82)	54.2 (2.06)	0.0001

*The age adjusted prevalence of metabolic syndrome and central obesity was compared in men and women using SUDAAN's *t* test. Statistical significance was set at *P* <0.05.

[†]Metabolic syndrome was defined according to IDF definition (21): elevated triglyceride, ≥ 150 mg/dl or specific treatment for hypertriglyceridemia; reduced HDL cholesterol, < 40 mg/dl for men and < 50 mg/dl for women or specific treatment for this lipid abnormality; elevated blood pressure, systolic blood pressure ≥ 130 mmHg, diastolic blood pressure ≥ 85 mmHg or treatment for previously diagnosed hypertension; elevated fasting plasma glucose ≥ 100 mg/dl or previously diagnosed type 2 diabetes; central obesity, waist circumference ≥ 90 cm for men and ≥ 80 cm for women.

[‡]Waist circumference ≥ 90 cm for men and ≥ 80 cm for women.

[§]Waist circumference ≥ 90 for both men and women.

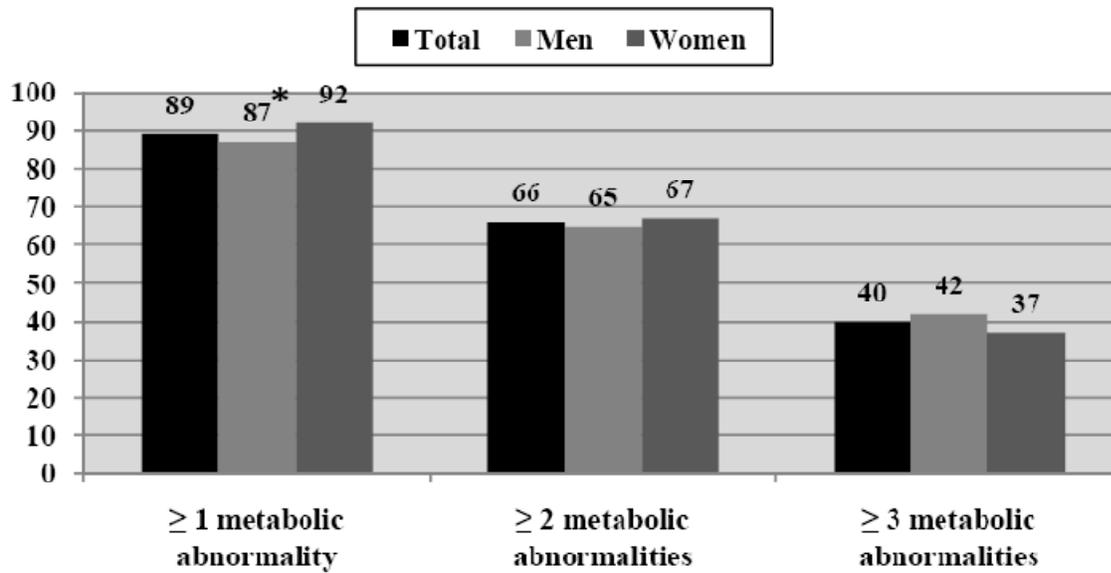


Figure 3.1. Prevalence of the metabolic abnormalities among Mexican American adults aged 20-80 years, NHANES 1999-2006. * Significant difference in prevalence among men and women ($P = 0.001$).

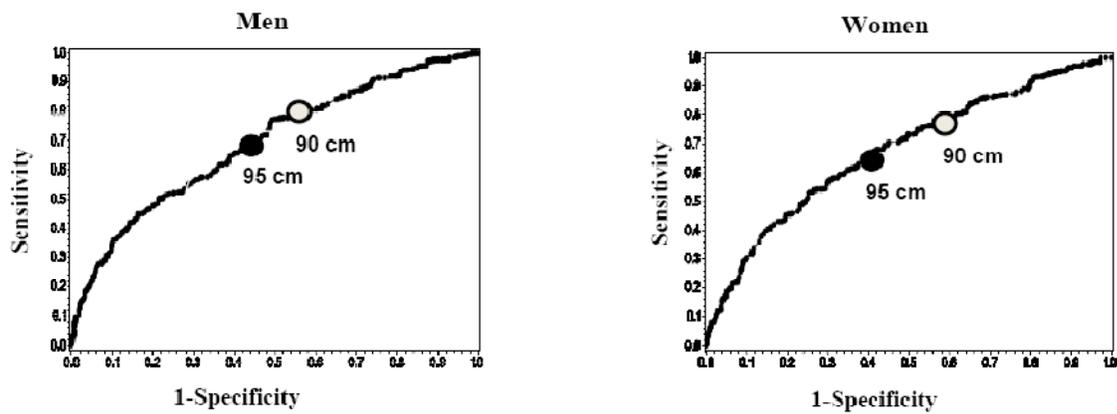


Figure 3.2. The ROC curves for waist circumference to predict the presence of two or more metabolic syndrome risk factors based on IDF definition in men and women. ●, waist circumference cutoff with maximum sensitivity and specificity. ○, waist circumference cutoff with 80% sensitivity in predicting the presence of risk factors.

Chapter 4: Abdominal Adiposity, Overall Obesity and Metabolic Syndrome in Mexican American Adults: Findings from the National Health and Nutrition Examination Surveys 1999-2006

ABSTRACT

Background: Abdominal adiposity is one of the main features in identifying individuals with metabolic syndrome (MetS). The association between abdominal adiposity and the components of MetS is not well studied in Mexican Americans.

Objective: The objective of this study was to examine the association between abdominal adiposity and overall obesity with the elements of MetS in Mexican American adults. We also compared the odds ratios of developing MetS risk factors according to quartiles of WC in this population.

Design: We analyzed data from 3265 Mexican American adults aged 20-80 years who participated in the NHANES 1999-2006. Regression analysis was used to determine the relationship between WC and BMI with fasting plasma glucose, systolic and diastolic blood pressure and lipid abnormalities in each gender after adjusting for relevant confounders. Logistic regression was used to estimate the odds ratios of developing MetS components according to quartiles of waist circumference.

Results: All correlation coefficient of WC and BMI with the components of MetS were significant among men ($P < 0.05$). In both genders, higher WC was significantly associated with higher risk of having metabolic abnormalities. Compared with individuals in the lowest WC quartile, those in the highest quartile were 9 times more likely (95% CI: 5.00, 14.96) to have 2 or more metabolic risk factors ($P < 0.0001$).

Conclusion: WC had a stronger association with almost all of the MetS risk factors than BMI in Mexican American men and women. Higher levels of WC were associated with an increased risk of metabolic abnormalities.

KEY WORDS Metabolic syndrome, waist circumference, body mass index, obesity, abdominal adiposity, NHANES, Mexican American

INTRODUCTION

Metabolic syndrome, the clustering of metabolic risk factors including central obesity, insulin resistance, atherogenic dyslipidemia, hyperglycemia and hypertension is associated with increased risk of cardiovascular disease (CVD) and type 2 diabetes mellitus (1). This syndrome is one of the major medical and public health problems in the United States and worldwide and is prevalent among all ethnic groups in USA (2-8). According to International Diabetes Federation (IDF) criteria, Mexican Americans have the highest age adjusted prevalence of metabolic syndrome (around 50%) (3).

Central obesity is one of the main features in identifying individuals with metabolic syndrome. The hypotheses relating central obesity to metabolic syndrome focus on the hormonal role of adipose tissue (particularly visceral adipose tissue) and secretion of adipokines (cytokines) and other bioactive substances such as free fatty acids. Adipose tissue actively secretes large number of hormones and adipokines including leptin, adiponectin, tumor necrosis factor α (TNF α), interleukin 6 (IL-6), monocyte chemotactic protein 1, inducible nitric oxide synthase (iNOS), plasminogen activator inhibitor 1 (PAI-1) and resistin. These adipokines have autocrine, paracrine and endocrine actions for controlling different metabolic functions (9-11). The expanding adipose tissue also discharges high levels of FFA into the portal and systemic circulation (12-14); this may result in accumulation of lipid in areas other than adipose tissue or ectopic fat storage syndrome. In muscles and liver, increased FFA is associated with insulin resistance (15, 16) and dyslipidemia (17).

The association between obesity and the components of metabolic syndrome has been investigated by anthropometric measurements such as body mass index (BMI), waist to hip ratio (WHR) and waist circumference (18-21). Body mass index in Kg/m^2 , is a measure of overall

obesity and provides estimation of total body fat with no further information on the distribution of excess fat storage. Waist to hip ratio measures abdominal fat accumulation, and has less power in predicting health risk factors when compared to waist circumference. Waist circumference reflects the amount of abdominal adipose tissue storage as well as total fat mass, providing a measure of body fat distribution. It also complements BMI in predicting obesity related diseases and health risks (19-21). Several studies have shown that waist circumference is a better predictor of metabolic abnormalities and cardiovascular disease risk factors than BMI (21-23).

Little information is available on the association of abdominal adiposity, overall obesity and the components of metabolic syndrome in Mexican Americans (24). Most of the previous studies have focused on non Hispanic Whites or non representative population samples (18-21). Therefore the aim of the present study was to examine the association between abdominal adiposity, measured by waist circumference and overall obesity, measured by body mass index with the components of metabolic syndrome including, triglyceride, blood pressure, fasting plasma glucose and HDL cholesterol in Mexican American adults using National Health and Nutrition Examination Survey (NHANES) 1999-2006 data. We also investigated the odds for developing metabolic syndrome risk factors according to quartiles of waist circumference in this population.

SUBJECTS and METHODS

Study population

This study analyzed data on 3265 Mexican American adults aged 20-80 years who participated in the National Health and Nutrition Examination Survey (NHANES) 1999-2006. The survey used complex, multi-stage, stratified, clustered sampling to access the health and

nutritional status of the civilian, non-institutionalized U.S. population. Participants were interviewed in their homes to obtain demographic, socioeconomic, dietary and health related information and were asked to attend the mobile examination center (MEC) to undergo medical examinations and laboratory tests. Detailed information on study design and sample selection may be found elsewhere (25). Subjects who were fasted less than 8 hours before venipuncture, pregnant and lactating women and participants with type 1 diabetes mellitus were excluded from the analysis. The study was approved by the Institutional Review Board at the University of Maryland.

Survey methods

Anthropometric measurements

Body weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively, by using standardized equipment and proper procedures (26). Waist circumference was measured with a steel measuring tape at the high point of the iliac crest in a horizontal plane at minimal respiration to the nearest 0.1 cm. BMI was calculated from measured weight and height and categorized as; underweight (BMI less than 18.5 Kg/m²), normal (BMI=18.5-24.9 Kg/m²), overweight (BMI=25-29.9 Kg/m²) and obese (BMI = 30 Kg/m² and higher) (27).

Metabolic risk factors

Metabolic syndrome was defined based on IDF criteria. According to this definition, subjects have metabolic syndrome if they have central obesity plus any two of the following factors: 1) Elevated triglycerides level: ≥ 150 mg/dl or specific treatment for this lipid abnormality; 2) Reduced high density lipoprotein cholesterol (HDLc) level: < 40 mg/dl in men and < 50 mg/dl in women or specific treatment for this lipid abnormality; 3) Elevated blood pressure: systolic blood pressure ≥ 130 or diastolic blood pressure ≥ 85 mmHg or treatment of previously

diagnosed hypertension; 4) Elevated fasting plasma glucose: ≥ 100 mg/dl or previously diagnosed type 2 diabetes (28).

The IDF emphasizes the use of gender-ethnic specific thresholds for waist circumference when measuring central obesity. For European, Sub-Saharan African, Eastern Mediterranean and Middle East (Arab) men, the specified cut point is WC ≥ 94 cm; for South Asian, Chinese, Japanese and ethnic South and Central American men, WC ≥ 90 cm; and in Women WC ≥ 80 cm is defined as central obesity (29). In this analysis, the cut off values of 90 and 80 cm were used to define central obesity in Mexican American men and women, respectively.

Serum triglyceride (TG) concentration was measured enzymatically after hydrolyzing to glycerol. Serum total cholesterol (TC) was also measured enzymatically after hydrolyzing cholesteryl esters to free cholesterol and fatty acids. HDL cholesterol concentration was measured on a Roche Hitachi Analyzer after the precipitation of other lipoproteins with a heparin-manganese chloride mixture. Hypercholesterolemia was defined as TC ≥ 200 mg/dl or using cholesterol lowering medications. Low Density Lipoprotein (LDL) cholesterol was calculated according to Friedewald formula: $[LDLc] = [TC] - [HDLc] - [TG/5]$. Fasting plasma glucose concentration was measured using an enzymatic reaction (enzyme hexokinase method) by the Diabetic Diagnostic Laboratory at the University of Missouri. C-reactive protein (CRP) was quantified by particle-enhanced assay (latex enhanced nephelometry). Detailed description of laboratory methods is available on NHANES website in the Laboratory Procedures Manual (30). Blood pressure was determined in mobile examination center using mercury sphygmomanometer in a sitting position after 5 minutes rest. Up to four blood pressure measurements were obtained. Participants who had three or four blood pressure readings, the average of the last two measurements were used in the analysis. Those who had two blood

pressure readings, the last measurement and participants who only had one reading, that measurement was considered as their blood pressure value (31, 32).

Confounding variables

Age, education, income, smoking and drinking habits, physical activity, marital status, language spoken at home, family history of diabetes, angina and stroke and menopausal status for women may be associated with development of metabolic syndrome. As potential confounders, these variables were included in regression models. Age was modeled as a continuous variable. Education was measured as the highest grade completed or the highest degree received by the respondent and was further categorized to less than high school, high school diploma and more than high school. Income was measured based on Poverty Income Ratio (PIR) and modeled as a continuous variable. For descriptive purposes, three PIR categories (<1.85, 1.85-3.50 and >3.50) were defined to represent low, middle and high income level, respectively (33). Cigarette smoking was categorized as never smoked (if they had smoked <100 cigarettes in their lifetime), former smoker (≥ 100 lifetime cigarettes, not currently smoking), and current smoker (≥ 100 lifetime cigarettes, currently smoking). Alcohol intake was determined from number and frequency of alcoholic beverages consumed such as liquor, beer, wine and wine coolers in the past 30 days. The total number of alcoholic drinks consumed per month was calculated and modeled as a continuous variable. The total alcohol intake was further divided into 4 categories: <1, 1 to 4, 5 to 7 and >7 drinks per month and applied in descriptive analysis (34, 35). Physical activity was defined based on frequency and duration of moderate or vigorous intensity leisure time activities and moderate tasks around the home or yard. Total minutes per week spent performing these activities were computed and modeled as continuous variable. For descriptive purposes 3 categories (0 min/week, < 150 and ≥ 150 min/week) of moderate or

vigorous physical activity were produced (34, 36 and 37). Marital status was classified into two categories as married including living as married, and unmarried including being widowed, divorced, separated, never married or living with a partner. Language spoken at home was divided into five categories as only Spanish, more Spanish than English, both equally, more English than Spanish and only English. Family history of diabetes, stroke/hypertension and angina were defined based on the presence of diabetes, stroke/hypertension and angina in biological relatives. Information on family history of hypertension/stroke was only available for 1999-2004 NHANES (38). Postmenopausal status was determined if there had been complete menses cessation ≥ 12 month (39).

Statistical analysis

Descriptive statistics were applied for all variables, including mean and standard error of the mean (SEM) for continuous variables and relative frequencies for categorical variables. SUDAAN's t-test and Chi square test were applied to compare the means of continuous variables and frequencies of categorical variables in male and female subjects, respectively. The estimates were considered unstable if the relative standard error for means or frequencies were greater than 30%. Regression analysis was used to address the associations between WC and BMI with triglycerides, fasting plasma glucose, HDL cholesterol, systolic and diastolic blood pressure (all continuous variables), in each gender after adjusting for age, income, alcohol intake, physical activity and the levels of education, smoking, marital status, language spoken at home, family history of diabetes, angina and stroke and menopausal status for women. Logistic regression was used to estimate the odds ratios (ORs) of developing metabolic syndrome components (hypertriglyceridemia, hyperglycemia, hypertension and low HDL cholesterol) according to quartiles of waist circumference after controlling for potential confounders including age,

income, alcohol intake, physical activity and the levels of education, smoking, marital status, language spoken at home, family history of diabetes, angina and stroke. The reference point was set at 25 percentile for waist circumference. Multicollinearity among independent variables and also between confounders was tested in regression model by checking variance inflation factor (VIF). Any variable with VIF greater than 4 was excluded from the model (no variable with VIF greater than 4 was detected). We also checked for outliers by plotting predicted and observed standardized residuals. The outliers at the 0.01 level (standardized residuals > 2.58) were removed from the analysis.

Data preparation (sorting, appending, merging and recoding) was performed using Statistical Analysis Software (SAS) system version 9.2 (SAS Institute Inc, Cary, NC). SAS Callable SUDAAN (Software for the Statistical Analysis of Correlated Data) version 10.0 (Research Triangle Institute, Research Triangle Park, NC) was used for data analyses. Statistical significance was set at 0.05 unless otherwise indicated. The appropriate sample weights, stratum variable (SDMVSTRA) and primary sampling unit (PSU) variable (SDMVPSU) were included in all analyses to account for the complex survey design, unequal probabilities of selection, non-response and over-sampling of selected population subgroups (40).

Results

The basic characteristics of the study population and the prevalence of metabolic risk factors are summarized in **Table 4.1**. The mean age was 37.1 ± 0.4 years for men and 39.5 ± 0.6 years for women ($P = 0.0001$). Men were significantly taller and heavier and had larger WC than women. Significant differences in triglyceride, total cholesterol, LDL and HDL cholesterol, systolic and diastolic blood pressure and CRP values were found between genders. Family history of diabetes mellitus, angina and hypertension/stroke were more prevalent in women (P

=0.0001). All metabolic risk factors were found to be significantly different between men and women. Overall 89% of the population had one or more metabolic abnormality. Mexican American women were more likely to have one or more metabolic abnormalities than men (92.3% vs. 86.9%, $P=0.001$). There were no significant differences in prevalence of two or more or three or more metabolic abnormalities among genders. Based on IDF definition metabolic syndrome was prevalent in 58.4% of the population (55.8% among men and 64.8% among women, $P=0.06$) (data not shown). **Table 4.2** presents the socio-economic and behavioral characteristics of the study population. Generally, men were more likely to be married, speak Spanish at home, be current smokers, less educated and drink more alcohol as compared to women. Except for the middle income category, there were no significant differences in the values of income and physical activity in men and women.

Correlation coefficients for WC and BMI with metabolic syndrome risk factors are shown in **Table 4.3** WC and BMI were highly correlated in both men and women ($r= 0.935$, $n=777$ in men and $r= 0.895$, $n=619$ in women; $P <0.0001$ for both). All correlation coefficients of WC and BMI with the components of metabolic syndrome were significant among men ($P <0.05$). In women, WC and BMI were significantly correlated with HDL cholesterol. In both genders the correlation coefficients were stronger between WC and metabolic risk factors than those of BMI; however the reverse pattern was noticed in correlation between WC and BMI with HDL cholesterol in women.

The odds ratios (ORs) and 95% confidence interval (CI) for one or more metabolic syndrome risk factors according to quartiles of waist circumference are presented in **Table 4.4** The ORs of metabolic syndrome risk factors increased from 1st to 4th quartile of waist circumference (P for trend <0.001 for all). Compared with individuals in the lowest WC quartile, those in the highest

quartile had an OR of 4.18 (95% CI: 1.96, 8.93) for elevated triglyceride, 3.50 (95% CI: 1.69, 7.26) for elevated blood pressure, 5.71 (95% CI: 3.24, 10.09) for reduced HDL cholesterol and 2.34 (95% CI: 1.32, 4.14) for elevated fasting plasma glucose, respectively, after adjustment for relevant confounders ($P < 0.001$ for all). These subjects were also 9 times more likely (95% CI: 5.00, 14.96) to have 2 or more metabolic risk factors when compared to the lowest WC quartile and after adjustment for the mentioned confounders ($P < 0.0001$).

Discussion

Our findings suggest that waist circumference had a stronger association with almost all of the metabolic syndrome risk factors than body mass index in Mexican American men and women. This finding is consistent with the results from previous studies in which WC showed greater association with cardiovascular disease and diabetes risk factors when compared to BMI in Hispanic and non Hispanic white populations (24, 41-43). Most recently, Wang et al. (41) compared the predictive power of WC, WHR and BMI in diagnosing type 2 diabetes mellitus in 27270 men from Health Professionals Follow-Up Study and found WC to be a better predictor than BMI or WHR. This may be because waist circumference, a simple anthropometric measure, reflects the amount of abdominal adipose tissue storage and is considered as the best marker of abdominal visceral fat (44-46). Adipose tissue, particularly visceral adipose tissue, actively secretes large number of hormones and adipokines such as leptin, adiponectin, tumor necrosis factor α (TNF α), interleukin 6 (IL-6), plasminogen activator inhibitor 1 (PAI-1), inducible nitric oxide synthase (iNOS), resistin and more. These adipokines have autocrine, paracrine and endocrine actions for controlling different metabolic functions (9-11). The expanding adipose tissue also discharges high levels of free fatty acids into the portal and systemic circulation (12-

14); this may result in promoting insulin resistance and dyslipidemia in muscles and liver (15-17).

We also observed that higher levels of waist circumference were associated with an increased risk of metabolic abnormalities including hypertension, hyperglycemia and lipid abnormalities. This association was independent of age, gender, education, income, language spoken at home, marital status, lifestyle factors and family history of diabetes, angina and stroke. Subjects in the highest quartile of waist circumference were 9 times more likely, even after controlling for confounders, to have two or more metabolic risk factors. This finding is consistent with the reports from previous studies where abdominally obese subjects had higher risk for developing metabolic syndrome, cardiovascular disease or type 2 diabetes mellitus (19, 39 and 44). Findings from analyzing national surveys are also in agreement with our results. Park et al. in the analysis of NHANES III data observed higher odds ratios for developing metabolic syndrome in overweight and obese individuals (47).

Obesity is correlated with inflammatory responses, characterized by abnormal adipokines production and overproducing of some inflammatory markers (9, 11). Recent data indicate that obese adipose tissue is infiltrated by macrophages, which are responsible for the most part of the locally produced TNF α and large amounts of IL-6 and inducible nitric oxide synthase expression (48, 49). Adipose tissue TNF α increases adipocyte lipolysis and may increase insulin resistance by promoting the fatty acid release from adipose tissue into the portal and systemic circulation (15, 16). IL-6 also increases lipolysis and fat oxidation in humans (50) and raises plasma concentration of fibrinogen, PAI-1 and CRP (51). Overproduction of IL-6 by adipose tissue could directly alter liver metabolism by inducing very low density lipoprotein (VLDL) secretion

and hypertriglyceridemia, since visceral adipose tissue (VAT) is closely connected to liver by the portal venous system (52).

Our study has some limitations. The cross –sectional nature of the study would not allow us to establish causal relationships between metabolic syndrome risk factors and waist circumference. In addition, our results are not applicable to all Hispanics as only Mexican Americans were over sampled in NHANES and the small number of ‘other Hispanics’ in data set were not sufficient to be analyzed as a separate group.

To our knowledge, this is the first study to investigate the association between abdominal adiposity and overall obesity with the components of metabolic syndrome in Mexican American adults using 8 years of continuous NHANES 1999-2006 data. The findings of the present study are derived from a representative sample of Mexican American adults in the United States and are applicable to this population.

In summary, our findings indicated that waist circumference had a stronger association with almost all of the metabolic syndrome risk factors than body mass index in Mexican American men and women. We also observed that the risk of having metabolic abnormalities increases sharply in subjects with central obesity. This study not only helps to better understand the association between waist circumference and metabolic risk factors in Mexican American adults but also emphasizes the importance of central obesity in increasing risk of having metabolic abnormalities. Multifaceted strategies for prevention, treatment and management of overweight and obesity are required. Lifestyle modifications including nutritional education, weight control programs and physical activity interventions are essential.

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Appendices 2

Table 4.1. Basic characteristics and metabolic risk indicators among Mexican American adults aged 20-80 years, NHANES 1999-2006*

Variables	Total		Men		Women	
	n	Mean or % (SEM) [†]	n	Mean or % (SEM)	n	Mean or % (SEM)
Age (y)	3265	38.07 (0.52)	1794	37.08 (0.46)	1471	39.50 (0.67) [§]
Height (cm)	3223	165.05 (0.18)	1780	169.97 (0.25)	1443	157.88 (0.23) [§]
Weight (kg)	3203	76.56 (0.41)	1764	80.69 (0.59)	1439	70.57 (0.58) [§]
Body mass index (kg/m ²)	3196	28.04 (0.15)	1761	27.85 (0.18)	1435	28.32 (0.24)
< 18.5 (%)	24	0.81 (0.21)	6	0.35 (0.15) [¶]	18	1.47 (0.48) [¶]
≥ 18.5 to < 25 (%)	856	28.99 (1.36)	458	27.91 (1.67)	398	30.55 (1.70)
≥ 25 to < 30 (%)	1327	40.48 (0.92)	824	44.86 (1.09)	503	34.15 (1.42) [§]
≥ 30 (%)	987	29.71 (1.16)	472	26.87 (1.48)	515	33.83 (1.85) [§]
Waist Circumference (cm)	3139	95.02 (0.41)	1726	96.69 (0.55)	1413	92.62 (0.58) [§]
Fasting plasma glucose (mg/dl)	1421	104.16 (1.07)	789	104.91 (1.31)	632	103.08 (1.77)
Total cholesterol (mg/dl)	1407	196.37 (1.47)	783	199.90 (1.91)	624	191.22 (2.00) [§]
HDL cholesterol (mg/dl)	1408	49.20 (0.48)	784	46.33 (0.50)	624	53.39 (0.69) [§]
LDL cholesterol (mg/dl)	1343	117.82 (1.21)	737	123.03 (1.54)	606	110.51 (1.57) [§]
Triglycerides (mg/dl)	1407	155.65 (6.12)	783	166.00 (8.70)	624	140.55 (6.86) [§]
SBP (mmHg)	2939	119.20 (0.51)	1631	120.56 (0.60)	1308	117.19 (0.66) [§]
DBP (mmHg)	2939	70.33 (0.31)	1631	70.97 (0.41)	1308	69.38 (0.37) [§]
C-reactive protein (mg/l)	1415	2.65 (0.10)	786	2.17 (0.10)	629	3.35 (0.13) [§]
Family history (%)						
Diabetes mellitus	1584	50.12 (1.37)	830	46.61 (1.66)	754	55.21 (1.62) [§]
Angina	267	8.16 (0.63)	103	5.52 (0.74)	164	12.01 (0.98) [§]
Hypertension/Stroke	562	24.45 (1.27)	268	20.91 (1.20)	294	29.46 (2.04) [§]
Metabolic risk factors (%) [‡]						
Elevated triglyceride	640	38.27 (1.94)	370	42.44 (2.48)	270	32.18 (2.09) [§]
Reduced HDL cholesterol	604	38.28 (1.71)	280	30.63 (2.20)	324	49.46 (2.01) [§]
Elevated blood pressure	1175	24.59 (1.22)	669	27.33 (1.37)	506	20.77 (1.63) [§]
Elevated fasting plasma glucose	669	39.65 (1.99)	411	44.91 (2.03)	258	32.04 (3.25) [§]
Central obesity	2509	75.00 (1.25)	1299	69.81 (1.82)	1210	82.48 (1.43) [§]
Menopausal status (%)						
Pre	□	□	□	□	559	70.42 (1.83)
post	□	□	□	□	590	29.58 (1.83)

* HDL, high density lipoprotein; LDL, low density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure. The means of all continuous variables and frequencies of all categorical variables were compared in men and women using SUDAAN's *t* test and χ^2 test, respectively. Statistical significance was set at $P < 0.05$.

[†]Values are means (SEM) for continuous variables and percentages (SEM) for categorical variables.

[‡]Metabolic risk factors were defined according to IDF definition (29): elevated triglyceride, ≥ 150 mg/dl or specific treatment for hypertriglyceridemia; reduced HDL cholesterol, < 40 mg/dl for men and < 50 mg/dl for women or specific treatment for this lipid abnormality; elevated blood pressure, systolic blood pressure ≥ 130 mmHg, diastolic blood pressure ≥ 85 mmHg or treatment for previously diagnosed hypertension; elevated fasting plasma glucose ≥ 100 mg/dl or previously diagnosed type 2 diabetes; central obesity, waist circumference ≥ 90 cm for men and ≥ 80 cm for women.

[§] Significant difference between men and women. [¶] Unstable estimates.

Table 4.2. Socio-economic and behavioral characteristics of the study population, NHANES 1999-2006*

Characteristics	Total		Men		Women	
	n	% (SEM)	n	% (SEM)	n	% (SEM)
Education (y)						
<12	2000	55.14 (1.25)	1124	56.82 (1.70)	876	52.71 (1.56)
12	563	20.69 (0.89)	306	20.76 (1.23)	257	20.59 (1.37)
>12	699	24.12 (1.25)	362	22.35 (1.59)	337	26.68 (1.47) [§]
Marital status						
Married	2015	60.41 (1.38)	1186	61.63 (1.78)	829	58.64 (1.39)
Unmarried	1159	39.59 (1.38)	565	38.37 (1.78)	594	41.36 (1.39)
Language spoken at home						
Only Spanish	1582	47.98 (2.33)	900	50.08 (2.81)	682	44.96 (2.12) [§]
Spanish > English	338	10.35 (0.81)	198	10.74 (1.01)	140	9.79 (1.07)
Spanish = English	433	12.12 (1.20)	207	10.68 (1.33)	226	14.20 (1.45) [§]
English > Spanish	356	11.54 (1.17)	192	11.33 (1.30)	164	11.84 (1.43)
Only English	548	18.01 (1.25)	293	17.17 (1.50)	255	19.23 (1.73)
Income						
Low	1739	57.83 (1.91)	936	56.37 (2.20)	801	60.02 (2.02)
Middle	734	25.48 (1.60)	443	27.37 (1.84)	291	22.64 (1.52) [§]
High	485	16.69 (1.09)	267	16.26 (1.28)	218	17.34 (1.37)
Smoking status						
Never	1815	57.40 (0.99)	758	46.39 (1.27)	1057	73.34 (1.31) [§]
Former	782	19.45 (0.83)	560	24.24 (1.03)	222	12.51 (1.09) [§]
Current	665	23.15 (0.82)	476	29.37 (1.15)	189	14.15 (0.87) [§]
Alcohol intake (drink/mon)						
<1	1565	53.11 (1.35)	626	38.65 (2.04)	939	73.67 (1.16) [§]
1-4	719	31.39 (1.23)	526	40.49 (1.92)	193	18.46 (1.10) [§]
5-7	100	4.34 (0.42)	67	5.01 (0.72)	33	3.39 (0.56) [§]
>7	219	11.16 (0.87)	180	15.85 (1.37)	39	4.48 (0.61) [§]
Physical activity (min/wk)						
0	1112	33.11 (1.58)	589	33.30 (1.88)	523	32.85 (1.76)
≤ 150	809	26.71 (1.07)	449	27.06 (1.46)	360	26.19 (1.23)
> 150	1220	40.18 (1.73)	697	39.64 (1.99)	523	40.96 (1.94)

*The frequencies of categorical variables were compared in men and women using SUDAAN's χ^2 test. Statistical significance was set at $P < 0.05$.

[§] Significant difference between men and women.

Table 4.3. Correlation coefficients of waist circumference or body mass index with metabolic syndrome risk factors*

	WC	TG	HDLc	FPG	SBP	DBP
Men						
Waist circumference	1.00	0.497	-0.558	0.492	0.516	0.496
Body mass index	0.931	0.429	-0.492	0.417	0.445	0.428
Women						
Waist circumference	1.00	0.324 [§]	-0.393	0.339	0.337 [§]	0.337 [§]
Body mass index	0.908	0.315 [§]	-0.402	0.325 [§]	0.295 [§]	0.298 [§]

* WC, waist circumference; TG, triglyceride; HDLc, high density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose. SUDAAN's regress procedure was used to determine the correlation coefficients of WC and BMI with metabolic risk factors after adjusting for age, income, alcohol intake, physical activity and levels of education, smoking, marital status, language spoken at home, family history of diabetes, angina and stroke and menopausal status in women.

Except for the correlation coefficient of WC and BMI with TG, FPG, SBP and DBP in women ([§]), all other correlation coefficients were significant ($P < 0.05$).

Table 4.4. Odds ratios and 95% confidence interval for metabolic syndrome risk factors according to quartiles of waist circumference in Mexican American adults*

Components of metabolic syndrome	Quartile of waist circumference				P for trend
	Q1 (<86.0 cm) n = 276	Q2 (86.0-94.1 cm) n = 312	Q3 (94.2-103.2 cm) n = 403	Q4 (>103.2 cm) n = 408	
Elevated triglyceride	1.00	2.80 (1.30-6.04) [†]	3.75 (1.88-7.51)	4.18 (1.96-8.93)	0.0005
Elevated blood pressure	1.00	2.21 (1.23-3.96)	3.06 (1.65-5.69)	3.50 (1.69-7.26)	0.001
Elevated fasting plasma glucose	1.00	1.38 (0.73-2.60)	1.93 (0.93-4.01)	2.34 (1.32-4.14)	0.001
Reduced HDL cholesterol	1.00	2.09 (1.16-3.76)	4.44 (2.55-7.73)	5.71 (3.24-10.09)	<0.0001
2 or more metabolic risk factors [‡]	1.00	3.87 (2.08-7.20)	6.88 (3.80-11.47)	8.93 (5.00-14.96)	<0.0001

*Odds ratios of having metabolic risk factors were compared across the quartile of waist circumference (the lowest quartile as reference group). The logistic regression model was adjusted for age, income, alcohol intake, physical activity (all continuous variables) and the levels of gender, education, smoking, marital status and language spoken at home and family history of diabetes, angina and stroke.

[†]All such values are adjusted OR (95% CI).

[‡]Metabolic risk factors (excluding central obesity) were defined according to IDF definition (29): elevated triglyceride, ≥ 150 mg/dl or specific treatment for hypertriglyceridemia; elevated blood pressure, systolic blood pressure ≥ 130 mmHg, diastolic blood pressure ≥ 85 mmHg or treatment for previously diagnosed hypertension; elevated fasting plasma glucose ≥ 100 mg/dl or previously diagnosed type 2 diabetes; reduced HDL cholesterol, < 40 mg/dl for men and < 50 mg/dl for women or specific treatment for this lipid abnormality.

Chapter 5: Metabolic Syndrome and C - reactive protein Levels among Mexican American Adults: Findings from the National Health and Nutrition Examination Surveys, 1999-2006

ABSTRACT

Background: Several studies have found associations between low grade inflammation and metabolic syndrome (MetS) risk factors, cardiovascular disease (CVD) and diabetes mellitus.

Little information is available on C-reactive protein (CRP) distribution and its relation with MetS in Mexican Americans (MAs).

Objective: The objective of this study was to investigate the association between CRP and MetS in MA adults. We also compared the odds ratios (ORs) of developing MetS or its components (central obesity, hypertriglyceridemia, hyperglycemia, hypertension and low HDL cholesterol) according to quartiles of CRP in this population.

Design: Data from 3265 MA adults aged 20-80 years who participated in the National Health and Nutrition Examination Survey 1999-2006, were used. Regression analysis was used to address the associations between log transformed CRP with the components of MetS after adjusting for the relevant confounders. Logistic regression was used to estimate the odds ratios of developing MetS according to quartile of CRP after controlling for potential confounders.

Results: CRP concentrations were higher in subjects with MetS. Significant associations were observed between CRP and MetS components. Higher CRP concentrations were significantly associated with higher risk of having MetS. In multiple logistic regression analysis with age, gender, drinking, smoking, marital status, medication use, arthritis and all the components of MetS, only central obesity and gender were significant predictors of elevated CRP concentration.

Conclusion: MAs with MetS and low grade inflammation may be at higher risk for developing CVD and diabetes. Appropriate approaches for prevention, treatment and management of MetS and/or chronic inflammation are needed.

KEY WORDS Metabolic syndrome, Low grade inflammation, C-reactive protein, Central obesity, NHANES, Mexican American

INTRODUCTION

Metabolic syndrome, the clustering of metabolic risk factors including central obesity, insulin resistance, atherogenic dyslipidemia, hyperglycemia and hypertension is associated with increased risk of cardiovascular disease (CVD) and type 2 diabetes mellitus (1). This syndrome is one of the major medical and public health problems in the United States and worldwide and is prevalent among all ethnic groups in USA (2-8). According to International Diabetes Federation (IDF) criteria, nearly 50% of Mexican Americans have metabolic syndrome (3).

A proinflammatory state is frequently present in patients with metabolic syndrome and is recognized by elevated inflammatory markers such as interleukin-1, interleukin-6, tumor necrosis factor- α , intercellular adhesion molecule-1, C- reactive protein (CRP) and elevated leukocyte count (9-11). CRP, an acute phase reactant produced by liver is the most studied biomarker of low grade inflammation and increases in response to infection, injury and chronic inflammation. Physical activity, smoking, alcohol consumption, estrogen use, lipid lowering statin and anti-inflammatory medications have been documented to alter the CRP concentrations (11, 12). CRP distributions vary by gender and ethnicity (13-16). Previous studies have shown higher levels of CRP among women than men. Mexican American and Black individuals also have higher CRP concentrations when compared to Caucasians (17, 18). Several studies have found associations between higher levels of CRP and metabolic syndrome risk factors (19-21), cardiovascular disease (22-24) and diabetes mellitus (25-27). Little information is available on CRP distribution and its relation with metabolic syndrome in Mexican Americans. Most of the previous studies have focused on individual components of metabolic syndrome, non Hispanic Whites or non representative population samples (16, 19, 26 and 28). Therefore the aim of the present study was to investigate the distribution of CRP and its association with metabolic

syndrome in Mexican American adults using National Health and Nutrition Examination Survey (NHANES) 1999-2006 data. We also estimated the odds ratios for developing metabolic syndrome or its components (central obesity, hypertriglyceridemia, hyperglycemia, hypertension and low HDL cholesterol) according to quartiles of CRP in this population.

SUBJECTS and METHODS

Study population

This study analyzed data on 3265 Mexican American adults aged 20-80 years who participated in the National Health and Nutrition Examination Survey (NHANES) 1999-2006. The survey used complex, multi-stage, stratified, clustered sampling to access the health and nutritional status of the civilian, non-institutionalized U.S. population. Participants were interviewed in their homes to obtain demographic, socioeconomic, dietary and health related information and were asked to attend the mobile examination center (MEC) to undergo medical examinations and laboratory tests. Detailed information on study design and sample selection may be found elsewhere (29). Subjects who were fasted less than 8 hours before venipuncture, pregnant and lactating women and participants with type 1 diabetes mellitus or serum CRP level greater than 10 mg/L (indication of acute illness or injury) were excluded from the analysis. The study was approved by the Institutional Review Board at the University of Maryland.

Survey methods

Metabolic syndrome was defined based on IDF criteria. According to this definition, subjects have metabolic syndrome if they have central obesity plus any two of the following factors: 1) Elevated triglycerides level: ≥ 150 mg/dl or specific treatment for this lipid abnormality; 2) Reduced high density lipoprotein cholesterol (HDLc) level: < 40 mg/dl in men and < 50 mg/dl in women or specific treatment for this lipid abnormality; 3) Elevated blood pressure: systolic

blood pressure ≥ 130 or diastolic blood pressure ≥ 85 mmHg or treatment of previously diagnosed hypertension; 4) Elevated fasting plasma glucose: ≥ 100 mg/dl or previously diagnosed type 2 diabetes (30). The IDF emphasizes the use of gender-ethnic specific thresholds for waist circumference when measuring central obesity. For Europid, Sub-Saharan African, Eastern Mediterranean and Middle East (Arab) men, the specified cut point is WC ≥ 94 cm; for South Asian, Chinese, Japanese and ethnic South and Central American men, WC ≥ 90 cm; and in Women WC ≥ 80 cm is defined as central obesity (31). In this analysis, the cut off values of 90 and 80 cm were used to define central obesity in Mexican American men and women, respectively.

Body weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively, by using standardized equipment and proper procedures (32). Waist circumference was measured with a steel measuring tape at the high point of the iliac crest in a horizontal plane at minimal respiration to the nearest 0.1 cm. Body mass index (BMI) was calculated from measured weight and height and categorized as; underweight (BMI less than 18.5 Kg/m^2), normal (BMI= $18.5\text{-}24.9 \text{ Kg/m}^2$), overweight (BMI= $25\text{-}29.9 \text{ Kg/m}^2$) and obese (BMI = 30 Kg/m^2 and higher) according to World Health Organization classification (33).

Serum triglyceride (TG) concentration was measured enzymatically after hydrolyzing to glycerol. Serum total cholesterol (TC) was also measured enzymatically after hydrolyzing cholesteryl esters to free cholesterol and fatty acids. HDL cholesterol concentration was measured on a Roche Hitachi Analyzer after the precipitation of other lipoproteins with a heparin-manganese chloride mixture. Hypercholesterolemia was defined as TC ≥ 200 mg/dl or using cholesterol lowering medications. Low Density Lipoprotein (LDL) cholesterol was calculated according to Friedewald formula: $[\text{LDLc}] = [\text{TC}] - [\text{HDLc}] - [\text{TG}/5]$. Fasting plasma

glucose concentration was measured using an enzymatic reaction (enzyme hexokinase method) by the Diabetic Diagnostic Laboratory at the University of Missouri. CRP was quantified by particle-enhanced assay (latex enhanced nephelometry) on a BN II nephelometer at the University of Washington Medical Center (Seattle, WA). Detailed description on laboratory methods is available on NHANES website in the Laboratory Procedures Manual (34). Blood pressure was determined in mobile examination center using mercury sphygmomanometer in a sitting position after 5 minutes rest. Up to four blood pressure readings were obtained. Participants who had three or four blood pressure readings, the average of the last two measurements were used in the analysis. Those who had two blood pressure readings, the last measurement and participants who only had one reading, that measurement was considered as their blood pressure value (35, 36).

Confounding variables

Age, education, income, smoking and drinking habits, physical activity, marital status, language spoken at home, chronic inflammation, family history of diabetes, angina and stroke, lipid lowering statin and anti-inflammatory medications, estrogen containing medications and menopausal status in women may be associated with development of metabolic syndrome or alter the CRP concentrations (11, 28, 37 and 38). As potential confounders, these variables were included in regression models. Age was modeled as a continuous variable. Education was measured as the highest grade completed or the highest degree received by the respondent and was further categorized to less than high school, high school diploma and more than high school. Income was measured based on Poverty Income Ratio (PIR) and modeled as a continuous variable. For descriptive purposes, three PIR categories (<1.85, 1.85-3.50 and >3.50) were defined to represent low, middle and high income level, respectively (39). Cigarette smoking was

categorized as never smoked (if they had smoked <100 cigarettes in their lifetime), former smoker (≥ 100 lifetime cigarettes, not currently smoking), and current smoker (≥ 100 lifetime cigarettes, currently smoking). Alcohol intake was determined from number and frequency of alcoholic beverages consumed such as liquor, beer, wine and wine coolers in the past 30 days. The total number of alcoholic drinks consumed per month was calculated and modeled as a continuous variable. The total alcohol intake was further divided into 4 categories: <1, 1 to 4, 5 to 7 and >7 drinks per month and applied in descriptive analysis (40, 41). Physical activity was defined based on frequency and duration of moderate or vigorous intensity leisure time activities and moderate tasks around the home or yard. Total minutes per week spent performing these activities were computed and modeled as continuous variable. For descriptive purposes 3 categories (0 min/week, < 150 and ≥ 150 min/week) of moderate or vigorous physical activity were produced (40, 42 and 43). Marital status was classified into two categories as married including living as married, and unmarried including being widowed, divorced, separated, never married or living with a partner. Language spoken at home was divided into five categories as only Spanish, more Spanish than English, both equally, more English than Spanish and only English. Family history of diabetes, stroke/hypertension and angina were defined based on the presence of diabetes, stroke/hypertension and angina in biological relatives. Information on family history of hypertension/stroke was only available for 1999-2004 NHANES (44). Postmenopausal status was determined if there had been complete menses cessation ≥ 12 month (38). Information on over the counter and prescription medications that may alter CRP levels including lipid lowering statin medications, nonsteroidal anti-inflammatory medications and estrogen containing medications was obtained from the dietary supplements and prescription

medication questionnaire (45-47). Chronic inflammation was determined if participant has been diagnosed with arthritis (44).

Statistical analysis

Descriptive statistics was applied for all variables, including mean and standard error of the mean (SEM) for continuous variables and relative frequencies for categorical variables.

SUDAAN's t-test and Chi square test were applied to compare the means of continuous variables and frequencies of categorical variables in male and female subjects, respectively. The estimates were considered unstable if the relative standard error for means or frequencies were greater than 30%. Since CRP values were not normally distributed, the log transformed CRP were used in all analyses. The results were back transformed and reported as geometric mean of CRP. Regression analysis was used to address the associations between log transformed CRP with triglycerides, fasting plasma glucose, HDL cholesterol, systolic and diastolic blood pressure (all continuous variables), in each gender after adjusting for age, income, alcohol intake, physical activity and the levels of education, smoking, marital status, language spoken at home, chronic inflammation, family history of diabetes, angina and stroke, medication use, menopausal status and estrogen use in women. Logistic regression was used to estimate the odds ratios (ORs) of developing metabolic syndrome and its components (central obesity, hypertriglyceridemia, hyperglycemia, hypertension and low HDL cholesterol) according to quartiles of CRP after controlling for potential confounders mentioned above. The reference point was set at 25 percentile for CRP. Multicollinearity among independent variables and also between confounders was tested in regression model by checking variance inflation factor (VIF). Any variable with VIF greater than 4 was excluded from the model (no variable with VIF greater than 4 was detected). We also

checked for outliers by plotting predicted and observed standardized residuals. The outliers at the 0.01 level (standardized residuals > 2.58) were removed from the analysis.

Data preparation (sorting, appending, merging and recoding) was performed using Statistical Analysis Software (SAS) system version 9.2 (SAS Institute Inc, Cary, NC). SAS Callable SUDAAN (Software for the Statistical Analysis of Correlated Data) version 10.0 (Research Triangle Institute, Research Triangle Park, NC) was used for data analyses. Statistical significance was set at 0.05. The appropriate sample weights, stratum variable (SDMVSTRA) and primary sampling unit (PSU) variable (SDMVPSU) were included in all analyses to account for the complex survey design, unequal probabilities of selection, non-response and over-sampling of selected population subgroups (48).

Results

The basic characteristics of the study population and the prevalence of metabolic risk factors are summarized in **Table 5.1**. The mean age was 37.1 ± 0.4 years for men and 39.5 ± 0.6 years for women ($P = 0.0001$). Men were significantly taller and heavier and had larger WC than women. The geometric mean concentration of CRP was 2.65 mg/l for the whole population. Women had higher CRP concentrations compared to men (3.35 mg/l vs. 2.17 mg/l, $P < 0.01$). In addition, the percentage of women with CRP concentrations greater than 3 mg/l was significantly higher than men (46.6% vs. 24.7%, $P < 0.0001$). Significant differences in triglyceride, total cholesterol, LDL and HDL cholesterol, systolic and diastolic blood pressure values were found between genders. Family history of diabetes mellitus, angina and hypertension/stroke were more prevalent in women ($P = 0.0001$). All metabolic risk factors were found to be significantly different between men and women. Overall 89% of the population had one or more metabolic abnormality. Mexican American women were more likely to have one or more metabolic

abnormalities than men (92.3% vs. 86.9%, $P = 0.001$). Based on IDF definition metabolic syndrome was prevalent in 58.4% of the population (55.8% among men and 64.8% among women, $P = 0.06$) (data not shown). Compared to men the prevalence of arthritis and medication use was double in women ($P = 0.001$). **Table 5.2** presents the socio-economic and behavioral characteristics of the study population. Generally, men were more likely to be married, speak Spanish at home, be current smokers, less educated and drink more alcohol as compared to women. Except for the middle income category, there were no significant differences in the values of income and physical activity in men and women.

The geometric mean concentrations of CRP were significantly higher among subjects with metabolic syndrome than those who did not have metabolic syndrome (2.31 mg/l vs. 0.81 mg/l, $P < 0.01$). Participants with central obesity, hypertriglyceridemia, hypertension and reduced HDL cholesterol also had higher levels of CRP concentrations than subjects without those conditions ($P < 0.01$ for all). The age adjusted prevalence of elevated CRP was higher in subjects with metabolic syndrome than those without the syndrome (42.7% vs. 17.2%, $P < 0.01$) (**Table 5.3**). The CRP levels increased gradually with increasing the numbers of metabolic syndrome components from 0.7 to 3.1 mg/l (**Figure 5.1**).

The age adjusted prevalence of metabolic syndrome increased from 26.9% to 81.6% as the CRP concentrations increased, $P < 0.0001$ (**Table 5.4**). The increment pattern was observed in both genders across the CRP quartiles. Women in the highest CRP quartile had significantly higher prevalence of metabolic syndrome than men (87.8% vs. 75.2%, $P < 0.01$). C-reactive protein was significantly associated with almost all the elements of metabolic syndrome (except for diastolic blood pressure). All correlation coefficients were stronger among women than men (**Table 5.5**).

The odds ratios (ORs) and 95% confidence interval (CI) for metabolic syndrome and its components according to quartiles of CRP are presented in **Table 5.6**. The ORs of metabolic syndrome or its components increased across the CRP quartiles. Compared with individuals in the lowest CRP quartile, those in the highest quartile had an OR of 2.11 (95% CI: 1.23, 3.61) for elevated triglyceride, 0.93 (95% CI: 0.51, 1.69) for elevated fasting plasma glucose, 6.91 (95% CI: 3.56, 11.40) for central obesity, 1.65 (95% CI: 0.72, 3.76) for hypertension and 2.88 (95% CI: 1.68, 4.94) for reduced HDL cholesterol, respectively, after adjustment for age, gender, alcohol intake, smoking (model 1), marital status, language spoken at home, medication use and arthritis (model 2). In order to decrease the number of variables in the logistic regression models, education, income and physical activity were dropped from the original model as their β coefficient was equal to zero and their effect was not significant. Individuals with highest CRP concentrations were 9.9 times more likely (95% CI: 4.53, 16.63) to have metabolic syndrome when compared to the lowest CRP quartile and after adjustment for the mentioned confounders ($P < 0.0001$). In multiple logistic regression analysis with age, gender, drinking, smoking, marital status, medication use, arthritis and all the components of metabolic syndrome, only central obesity and gender were significant predictors of elevated CRP concentration (**Table 5.7**).

Discussion

In the present study, we found higher C-reactive protein concentrations among Mexican Americans with metabolic syndrome compared to individuals without the syndrome. We also observed higher prevalence of metabolic syndrome in Mexican Americans with elevated CRP concentrations. These results are consistent with the reports from previous studies which investigated the associations between metabolic syndrome and low grade inflammation markers

(12, 49 and 50). Using data from 8570 participants of NHANES III, Ford (50) found higher age adjusted prevalence of elevated CRP concentrations among subjects with metabolic syndrome compared to subjects without the syndrome (29% vs. 12%). Metabolic syndrome was defined according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III). In 2005, Ye and colleagues investigated the distribution of CRP and its association with metabolic syndrome among 3289 Chinese men and women who participated in Nutrition and Health of Aging Population in China. They defined metabolic syndrome based on NCEP ATP III for Asian Americans and reported higher prevalence of metabolic syndrome among subjects with elevated CRP concentrations (12).

The present study also revealed significant associations between CRP and waist circumference, body mass index, triglyceride, HDL cholesterol, fasting plasma glucose concentrations and systolic blood pressure. The correlation coefficients were stronger among women compared to men. These associations were independent of age, education, income, language spoken at home, marital status, lifestyle factors, family history of diabetes, angina and stroke, medication use, arthritis and menopausal status in women. Consistent with these findings, Ford and colleagues examined the distribution and correlates of CRP concentrations among 2205 adult American women from NHANES 1999-2000. Using multiple linear regression they observed significant associations between CRP and waist circumference, triglyceride and total cholesterol concentrations and systolic blood pressure (18). In the analysis of Nutrition and Health of Aging Population data in China, Ye and colleagues observed significant associations between CRP, waist circumference and the elements of metabolic syndrome among 3289 Chinese men and women. The correlation coefficients were calculated by Spearman partial correlation after adjustment for age, gender and place of residence (Beijing or Shanghai) and

were lower than correlation coefficients we calculated using multiple linear regression after adjustment for relevant continuous and categorical confounding variables.

We also observed that higher levels of CRP concentrations were associated with an increased risk of having central obesity, hypertriglyceridemia, reduced HDL cholesterol and metabolic syndrome. This association was independent of age, gender, alcohol intake, smoking, language spoken at home, marital status, arthritis and medication use. Subjects in the highest quartile of CRP were 9.9 times more likely, even after controlling for confounders, to have metabolic syndrome. In logistic regression analysis with age, gender, drinking, smoking, marital status, medication use, arthritis and all the five components of metabolic syndrome, central obesity had the largest odds ratio for having elevated CRP concentrations, suggesting that central obesity is mostly responsible for increased CRP levels among individuals with metabolic syndrome. Findings from analyzing national surveys are also in agreement with our results. Ford (50) in the analysis of data from 8570 participants of NHANES III observed the highest odds ratio for having elevated CRP levels among individuals with abdominal obesity. Obesity is correlated with inflammatory responses, characterized by abnormal adipokines production and overproducing of some inflammatory markers (20, 51). Recent data indicate that obese adipose tissue is infiltrated by macrophages, which are responsible for the most part of the locally produced tumor necrosis factor α (TNF α) and large amounts of interleukin 6 (IL-6) and inducible nitric oxide synthase expression (52, 53). IL-6 can increase plasma concentration of fibrinogen, plasminogen activator inhibitor 1 (PAI-1) and CRP (54).

Our study has some limitations. The cross-sectional nature of the study would not allow us to establish causal relationships between metabolic syndrome risk factors and C-reactive protein. In addition, our results are not applicable to all Hispanics as only Mexican Americans were over

sampled in NHANES and the small number of ‘other Hispanics’ in data set were not sufficient to be analyzed as a separate group.

To our knowledge, this is the first study to investigate the association between C-reactive protein and metabolic syndrome in Mexican American adults using 8 years of continuous NHANES 1999-2006 data. The findings of the present study are derived from a representative sample of Mexican American adults in the United States and are applicable to this population.

In summary, we found higher C-reactive protein concentrations among Mexican Americans with metabolic syndrome. We also observed that higher levels of CRP concentrations were associated with an increased risk of having metabolic syndrome and its components. Considering the high prevalence of metabolic syndrome and low grade inflammation in Mexican Americans, they are at higher risk for developing cardiovascular disease and diabetes mellitus. To prevent or delay the development of these conditions, proper approaches for prevention, treatment and management of metabolic syndrome and/or chronic inflammation are necessary. Lifestyle modifications, nutritional education, weight control programs, physical activity and pharmacological interventions are suggested.

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Appendices 3

Table 5.1. Basic characteristics and metabolic risk factors among Mexican American adults aged 20-80 years, NHANES 1999-2006*

Variables	Total		Men		Women	
	n	Mean or % (SEM) [†]	n	Mean or % (SEM)	n	Mean or % (SEM)
Age (y)	3265	38.07 (0.52)	1794	37.08 (0.46)	1471	39.50 (0.67) [§]
Height (cm)	3223	165.05 (0.18)	1780	169.97 (0.25)	1443	157.88 (0.23) [§]
Weight (kg)	3203	76.56 (0.41)	1764	80.69 (0.59)	1439	70.57 (0.58) [§]
Body mass index (kg/m ²)	3196	28.04 (0.15)	1761	27.85 (0.18)	1435	28.32 (0.24)
< 18.5 (%)	24	0.81 (0.21)	6	0.35 (0.15) [¶]	18	1.47 (0.48) [¶]
≥ 18.5 to < 25 (%)	856	28.99 (1.36)	458	27.91 (1.67)	398	30.55 (1.70)
≥ 25 to < 30 (%)	1327	40.48 (0.92)	824	44.86 (1.09)	503	34.15 (1.42) [§]
≥ 30 (%)	987	29.71 (1.16)	472	26.87 (1.48)	515	33.83 (1.85) [§]
Waist Circumference (cm)	3139	95.02 (0.41)	1726	96.69 (0.55)	1413	92.62 (0.58) [§]
Fasting plasma glucose (mg/dl)	1421	104.16 (1.07)	789	104.91 (1.31)	632	103.08 (1.77)
Total cholesterol (mg/dl)	1407	196.37 (1.47)	783	199.90 (1.91)	624	191.22 (2.00) [§]
HDL cholesterol (mg/dl)	1408	49.20 (0.48)	784	46.33 (0.50)	624	53.39 (0.69) [§]
LDL cholesterol (mg/dl)	1343	117.82 (1.21)	737	123.03 (1.54)	606	110.51 (1.57) [§]
Triglycerides (mg/dl)	1407	155.65 (6.12)	783	166.00 (8.70)	624	140.55 (6.86) [§]
SBP (mmHg)	2939	119.20 (0.51)	1631	120.56 (0.60)	1308	117.19 (0.66) [§]
DBP (mmHg)	2939	70.33 (0.31)	1631	70.97 (0.41)	1308	69.38 (0.37) [§]
C-reactive protein (mg/l)	1415	2.65 (0.10)	786	2.17 (0.10)	629	3.35 (0.13) [§]
<1 mg/l (%)	356	30.08 (1.42)	249	36.80 (1.76)	107	20.33 (2.41) [§]
1-3 mg/l (%)	523	36.24 (1.55)	310	38.45 (2.21)	213	33.04 (2.38)
3-10 mg/l (%)	533	33.68 (1.75)	221	24.75 (2.23)	312	46.64 (2.74) [§]
Family history (%)						
Diabetes mellitus	1584	50.12 (1.37)	830	46.61 (1.66)	754	55.21 (1.62) [§]
Angina	267	8.16 (0.63)	103	5.52 (0.74)	164	12.01 (0.98) [§]
Hypertension/Stroke	562	24.45 (1.27)	268	20.91 (1.20)	294	29.46 (2.04) [§]
Metabolic risk factors (%) [‡]						
Elevated triglyceride	640	38.27 (1.94)	370	42.44 (2.48)	270	32.18 (2.09) [§]
Reduced HDL cholesterol	604	38.28 (1.71)	280	30.63 (2.20)	324	49.46 (2.01) [§]
Elevated blood pressure	1175	24.59 (1.22)	669	27.33 (1.37)	506	20.77 (1.63) [§]
Elevated fasting plasma glucose	669	39.65 (1.99)	411	44.91 (2.03)	258	32.04 (3.25) [§]
Central obesity	2509	75.00 (1.25)	1299	69.81 (1.82)	1210	82.48 (1.43) [§]
≥ 1 metabolic risk factor	1355	89.18 (1.21)	747	86.98 (1.63)	608	92.33 (1.29) [§]
≥ 2 metabolic risk factor	1355	66.24 (1.47)	747	65.39 (2.05)	608	67.46 (1.99)
≥ 3 metabolic risk factor	1355	39.89 (1.72)	747	41.77 (2.32)	608	37.20 (2.59)
Prevalence (%)						
Arthritis	572	9.62 (0.82)	227	6.23 (0.79)	345	14.43 (1.21) [§]
Medication use	427	10.42 (0.86)	197	7.19 (0.66)	230	15.67 (1.48) [§]
Estrogen use	□	□	□	□	11	0.82 (0.42) [¶]
Menopausal status (%)						
Pre	□	□	□	□	559	70.42 (1.83)
post	□	□	□	□	590	29.58 (1.83)

*HDL, high density lipoprotein; LDL, low density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure. The means of all continuous variables and frequencies of all categorical variables were compared in men and women using SUDAAN's *t* test and χ^2 test, respectively. Statistical significance was set at $P < 0.05$.

[†] Values are means (SEM) for continuous variables and percentages (SEM) for categorical variables.

[‡] Metabolic risk factors were defined according to IDF definition (31). ^{||}Statin lipid lowering medications or anti-inflammatory medications. [§] Significant difference between men and women. [¶] Unstable estimates.

Table 5.2. Socio-economic and behavioral characteristics of the study population, NHANES 1999-2006*

Characteristics	Total		Men		Women	
	n	% (SEM)	n	% (SEM)	n	% (SEM)
Education (y)						
<12	2000	55.14 (1.25)	1124	56.82 (1.70)	876	52.71 (1.56)
12	563	20.69 (0.89)	306	20.76 (1.23)	257	20.59 (1.37)
>12	699	24.12 (1.25)	362	22.35 (1.59)	337	26.68 (1.47) [§]
Marital status						
Married	2015	60.41 (1.38)	1186	61.63 (1.78)	829	58.64 (1.39)
Unmarried	1159	39.59 (1.38)	565	38.37 (1.78)	594	41.36 (1.39)
Language spoken at home						
Only Spanish	1582	47.98 (2.33)	900	50.08 (2.81)	682	44.96 (2.12) [§]
Spanish > English	338	10.35 (0.81)	198	10.74 (1.01)	140	9.79 (1.07)
Spanish = English	433	12.12 (1.20)	207	10.68 (1.33)	226	14.20 (1.45) [§]
English > Spanish	356	11.54 (1.17)	192	11.33 (1.30)	164	11.84 (1.43)
Only English	548	18.01 (1.25)	293	17.17 (1.50)	255	19.23 (1.73)
Income						
Low	1739	57.83 (1.91)	936	56.37 (2.20)	801	60.02 (2.02)
Middle	734	25.48 (1.60)	443	27.37 (1.84)	291	22.64 (1.52) [§]
High	485	16.69 (1.09)	267	16.26 (1.28)	218	17.34 (1.37)
Smoking status						
Never	1815	57.40 (0.99)	758	46.39 (1.27)	1057	73.34 (1.31) [§]
Former	782	19.45 (0.83)	560	24.24 (1.03)	222	12.51 (1.09) [§]
Current	665	23.15 (0.82)	476	29.37 (1.15)	189	14.15 (0.87) [§]
Alcohol intake (drink/mon)						
<1	1565	53.11 (1.35)	626	38.65 (2.04)	939	73.67 (1.16) [§]
1-4	719	31.39 (1.23)	526	40.49 (1.92)	193	18.46 (1.10) [§]
5-7	100	4.34 (0.42)	67	5.01 (0.72)	33	3.39 (0.56) [§]
>7	219	11.16 (0.87)	180	15.85 (1.37)	39	4.48 (0.61) [§]
Physical activity (min/wk)						
0	1112	33.11 (1.58)	589	33.30 (1.88)	523	32.85 (1.76)
≤ 150	809	26.71 (1.07)	449	27.06 (1.46)	360	26.19 (1.23)
> 150	1220	40.18 (1.73)	697	39.64 (1.99)	523	40.96 (1.94)

*The frequencies of categorical variables were compared in men and women using SUDAAN's χ^2 test. Statistical significance was set at $P < 0.05$.

[§]Significant difference between men and women.

Table 5.3. Geometric mean concentrations and the age adjusted prevalence of elevated CRP (mg/l) concentrations by presence and absence of metabolic syndrome or its components among Mexican American adults, NHANES 1999-2006

Metabolic syndrome or components	Total		Men		Women		Total		Men		Women	
	n	Geometric mean (SEM) [†]	n	Geometric mean (SEM)	n	Geometric mean (SEM)	n	% (SEM) [‡]	n	% (SEM)	n	% (SEM)
Metabolic syndrome												
Yes	665	2.31 (1.05) [§]	370	1.87 (1.05)	295	3.25 (1.06) [¶]	661	42.76 (3.28) [§]	367	31.60 (3.96)	294	62.56 (5.64) [¶]
No	278	0.81 (1.08)	192	0.74 (1.08)	86	0.99 (1.20)	276	17.24 (2.74)	190	12.27 (2.65)	86	25.33 (5.47) [¶]
Central obesity												
Yes	1153	2.05 (1.04) [§]	598	1.69 (1.05)	555	2.55 (1.05) [¶]	1145	40.47 (1.89) [§]	593	31.33 (2.81)	552	51.51 (2.71) [¶]
No	252	0.74 (1.09)	181	0.73 (1.09)	71	0.77 (1.19)	251	14.49 (2.64)	180	12.22 (2.78)	71	15.98 (4.00)
Hypertriglyceridemia												
Yes	622	2.03 (1.04) [§]	365	1.56 (1.05)	257	3.38 (1.05) [¶]	618	38.83 (3.01) [§]	361	28.98 (3.47)	257	62.65 (5.26) [¶]
No	800	1.44 (1.05)	422	1.18 (1.07)	378	1.84 (1.08) [¶]	794	32.46 (2.17)	419	24.70 (2.97)	375	41.95 (3.03) [¶]
Hyperglycemia												
Yes	670	1.71 (1.07)	410	1.40 (1.07)	260	2.61 (1.10) [¶]	666	33.16 (3.23)	407	24.34 (3.12)	259	59.07 (6.18) [¶]
No	761	1.58 (1.06)	380	1.25 (1.07)	381	2.07 (1.07) [¶]	755	33.74 (2.38)	376	26.45 (3.13)	379	42.27 (3.10) [¶]
Hypertension												
Yes	542	1.99 (1.07) [§]	302	1.75 (1.08)	240	2.58 (1.12) [¶]	533	34.35 (4.41)	296	28.53 (4.49)	237	63.19 (5.90) [¶]
No	860	1.58 (1.04)	463	1.24 (1.06)	397	2.13 (1.07) [¶]	859	34.52 (2.04)	462	25.54 (2.52)	397	45.80 (3.03) [¶]
Reduced HDL cholesterol												
Yes	572	2.09 (1.05) [§]	267	1.59 (1.11)	305	2.66 (1.07) [¶]	568	42.08 (2.87) [§]	263	30.25 (3.63)	305	52.81 (4.32) [¶]
No	851	1.42 (1.06)	521	1.23 (1.06)	330	1.89 (1.09) [¶]	845	29.93 (2.15)	518	23.97 (2.49)	327	40.96 (2.89) [¶]

[†]Geometric mean concentrations of CRP were compared across the levels of metabolic syndrome or its components and between men and women using SUDAAN's *t* test. Metabolic syndrome was defined according to IDF definition (31). Estimates are unstable and should be interpreted cautiously (relative standard error of mean greater than 30%).

[‡]Age adjusted prevalence of elevated CRP concentrations were compared across the levels of metabolic syndrome or its components and between men and women using SUDAAN's *t* test.

[§]*P* <0.01(comparing the presence or absence of metabolic syndrome or its components); [¶]*P* <0.01(comparing men and women).

Table 5.4. The age adjusted prevalence of metabolic syndrome according to quartiles of CRP among Mexican American adults, NHANES 1999-2006*

	Quartile of CRP				P for trend
	Q1 (<0.75 mg/l)	Q2 (0.75-1.75 mg/l)	Q3 (1.76-3.74 mg/l)	Q4 (>3.74 mg/l)	
Total (n=937)	26.98 (3.56) [†]	60.53 (4.04)	70.71 (3.54)	81.56 (4.00)	< 0.0001
Men (n=557)	28.24 (3.91)	61.17 (5.18)	70.77 (5.05)	75.15 (5.32) [§]	< 0.0001
Women (n=380)	20.26 (5.55)	56.82 (7.63)	70.94 (6.25)	87.82 (3.70)	< 0.0001

*Metabolic syndrome was defined according to IDF definition (31):elevated triglyceride, ≥ 150 mg/dl or specific treatment for hypertriglyceridemia; reduced HDL cholesterol, < 40 mg/dl for men and < 50 mg/dl for women or specific treatment for this lipid abnormality; elevated blood pressure, systolic blood pressure ≥ 130 mmHg, diastolic blood pressure ≥ 85 mmHg or treatment for previously diagnosed hypertension; elevated fasting plasma glucose ≥ 100 mg/dl or previously diagnosed type 2 diabetes; central obesity, waist circumference ≥ 90 cm for men and ≥ 80 cm for women.

[†]Values are percent (SEM); [§]P <0.01(comparing men and women);

Table 5.5. Correlation coefficients of log transformed CRP and the components of metabolic syndrome among Mexican American adults, NHANES 1999-2006*

	BMI	WC	TG	HDLc	FPG	SBP	DBP
All	0.59	0.60	0.44	-0.46	0.43	0.42	0.41 [§]
Men	0.55	0.54	0.43	-0.42	0.41	0.41	0.39 [§]
Women	0.64	0.69	0.50 [§]	-0.53	0.48 [§]	0.51 [§]	0.51 [§]

*BMI, body mass index; WC, waist circumference; TG, triglyceride; HDLc, high density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose. SUDAAN's regress procedure was used to determine the correlation coefficients of log CRP with the components of metabolic syndrome after adjusting for age, income, alcohol intake, physical activity and levels of education, smoking, marital status, language spoken at home, arthritis, medication use, family history of diabetes, angina and stroke and menopausal status in women.

Except for the correlation coefficient of log CRP with TG, FPG, SBP and DBP in women and DBP in men ([§]), all other correlation coefficients were significant ($P < 0.01$).

Table 5.6. Odds ratios and 95% confidence interval for metabolic syndrome and its components according to quartiles of CRP among Mexican American adults, NHANES 1999-2006*

Metabolic syndrome or its components	Quartile of CRP				P for trend
	Q1 (<0.75 mg/l) n = 279	Q2 (0.75-1.75 mg/l) n = 341	Q3 (1.76-3.74 mg/l) n = 400	Q4 (>3.74 mg/l) n = 411	
Metabolic syndrome[†]					
Model 1	1.00	4.90 (2.63-9.12)	9.87 (4.94-14.72)	12.66 (6.02-19.64)	0.0001
Model 2	1.00	5.97 (2.94-10.13)	12.90 (5.87-20.32)	9.90 (4.53-16.63)	0.0001
Hypertriglyceridemia					
Model 1	1.00	1.87 (1.23-2.85)	2.41 (1.55-3.74)	2.53 (1.61-3.98)	0.0001
Model 2	1.00	1.70 (1.04-2.79)	2.61 (1.62-4.18)	2.11 (1.23-3.61)	0.007
Hyperglycemia					
Model 1	1.00	0.97 (0.60-1.58)	1.38 (0.87-2.20)	1.11 (0.64-1.94)	0.697
Model 2	1.00	0.98 (0.60-1.58)	1.45 (0.86-2.46)	0.93 (0.51-1.69)	0.804
Central obesity					
Model 1	1.00	3.54 (2.20-5.71)	5.61 (3.07-9.24)	8.82 (4.91-14.85)	0.0001
Model 2	1.00	3.34 (2.04-5.45)	5.54 (2.85-9.80)	6.91 (3.56-11.40)	0.0001
Hypertension					
Model 1	1.00	1.56 (0.89-2.71)	2.36 (1.20-4.64)	1.80 (0.94-3.46)	0.075
Model 2	1.00	1.53 (0.85-2.75)	2.33 (1.12-4.85)	1.65 (0.72-3.76)	0.227
Reduced HDL cholesterol					
Model 1	1.00	1.80 (1.19-2.74)	1.88 (1.02-3.46)	2.35 (1.43-3.85)	0.001
Model 2	1.00	2.02 (1.26-3.26)	2.33 (1.24-4.40)	2.88 (1.68-4.94)	0.001

*Odds ratios of having metabolic syndrome or its components were compared across the quartiles of CRP (the lowest quartile as reference group). The logistic regression model was adjusted for age, gender, alcohol intake and smoking in model 1 and further adjusted for marital status, language spoken at home, medication use and arthritis in model 2. Values are adjusted OR (95% CI).

[†]Metabolic syndrome was defined according to IDF definition (31):elevated triglyceride, ≥ 150 mg/dl or specific treatment for hypertriglyceridemia; reduced HDL cholesterol, < 40 mg/dl for men and < 50 mg/dl for women or specific treatment for this lipid abnormality; elevated blood pressure, systolic blood pressure ≥ 130 mmHg, diastolic blood pressure ≥ 85 mmHg or treatment for previously diagnosed hypertension; elevated fasting plasma glucose ≥ 100 mg/dl or previously diagnosed type 2 diabetes; central obesity, waist circumference ≥ 90 cm for men and ≥ 80 cm for women.

Table 5.7. Association between elevated CRP and elements of metabolic syndrome among Mexican American adults*

Characteristics	Total (n=1440)		Men (n=793)		Women (n=647)	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Central obesity		0.0008		0.002		0.005
Yes	2.96 (1.61-5.41)		2.61 (1.42-4.81)		4.88 (1.62-10.64)	
No	1.00		1.00		1.00	
Hypertriglyceridemia		0.768		0.743		0.371
Yes	1.06 (0.70-1.62)		0.92 (0.56-1.51)		1.39 (0.67-2.91)	
No	1.00		1.00		1.00	
Hyperglycemia		0.684		0.582		0.181
Yes	1.10 (0.69-1.76)		0.85 (0.46-1.55)		1.64 (0.79-3.42)	
No	1.00		1.00		1.00	
Hypertension		0.607		0.699		0.478
Yes	1.16 (0.65-2.06)		1.15 (0.55-2.44)		1.30 (0.62-2.76)	
No	1.00		1.00		1.00	
Low HDL cholesterol		0.438		0.689		0.084
Yes	1.20 (0.75-1.94)		0.89 (0.50-1.60)		1.66 (0.93-2.97)	
No	1.00		1.00		1.00	
Age (y)	1.00 (0.98-1.03)	0.671	1.01 (0.98-1.04)	0.399	0.99 (0.96-1.02)	0.438
Gender		0.003		-		-
Men	1.00		-		-	
Women	1.97 (1.26-3.08)		-		-	
Drinking	0.99 (0.95-1.03)	0.672	0.99 (0.95-1.03)	0.579	1.02 (0.89-1.18)	0.737
Smoking				0.286		0.516
Never	1.00	0.055	1.00		1.00	
Former	0.63 (0.40-1.00)		0.70 (0.38-1.29)		0.62 (0.23-1.69)	
Current	1.23 (0.82-1.87)		1.20 (0.67-2.15)		1.19 (0.54-2.62)	
Marital status		0.176		0.063		0.462
Married	1.00		1.00		1.00	
Unmarried	0.78 (0.54-1.12)		0.57 (0.31-1.03)		1.25 (0.68-2.28)	
Medication use		0.589		0.301		0.852
Yes	0.86 (0.49-1.51)		0.54 (0.16-1.78)		1.07 (0.50-2.30)	
No	1.00		1.00		1.00	
Arthritis		0.609		0.789		0.616
Yes	0.88 (0.53-1.45)		0.88 (0.33-2.35)		0.81 (0.34-1.92)	
No	1.00		1.00		1.00	

*Metabolic syndrome components were defined according to IDF definition (31): hypertriglyceridemia, ≥ 150 mg/dl or specific treatment for hypertriglyceridemia; reduced HDL cholesterol, < 40 mg/dl for men and < 50 mg/dl for women or specific treatment for this lipid abnormality; hypertension, systolic blood pressure ≥ 130 mmHg, diastolic blood pressure ≥ 85 mmHg or treatment for previously diagnosed hypertension; hyperglycemia, glucose ≥ 100 mg/dl or previously diagnosed type 2 diabetes; central obesity, waist circumference ≥ 90 cm for men and ≥ 80 cm for women.

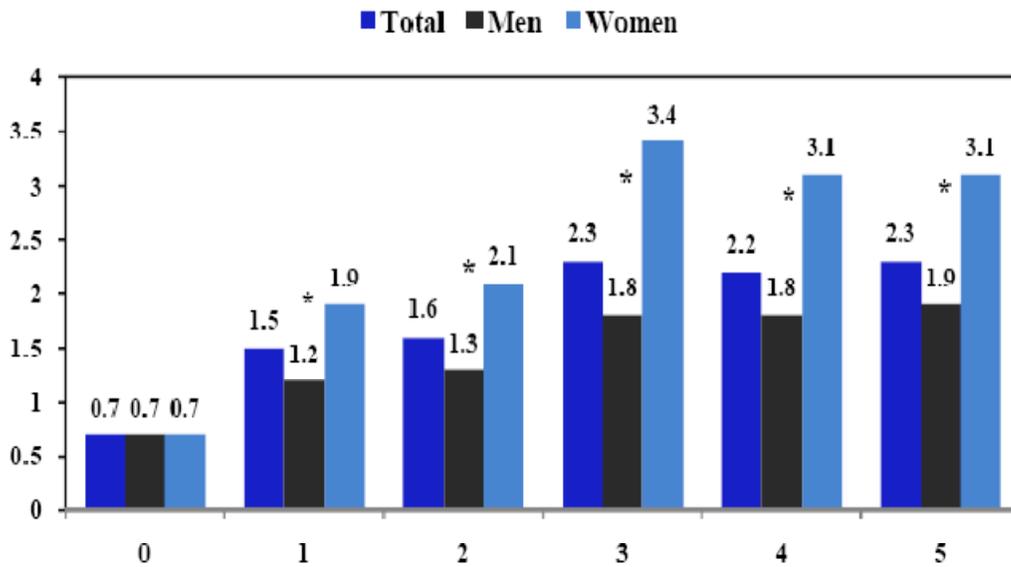


Figure 5.1. Geometric mean CRP concentrations by the number of components of metabolic syndrome in Mexican American men and women, NHANES 1999-2006.
 * Significant difference in CRP concentrations among men and women ($P < 0.01$).

Chapter 6: Conclusion

In the present study, I used data from the National Health and Nutrition Examination Survey (NHANES) 1999-2006, to determine the appropriate waist circumference cutoff values for diagnosis of central obesity in Mexican American adults and compared the prevalence of metabolic syndrome based on IDF definition with and without the modified waist circumference in Mexican Americans. I also examined the association between abdominal adiposity, measured by waist circumference and overall obesity, measured by body mass index with the components of metabolic syndrome including, triglyceride, blood pressure, fasting plasma glucose and HDL cholesterol in Mexican American adults and investigated the odds for developing metabolic syndrome risk factors according to quartiles of waist circumference in this population. To study the final objectives of the dissertation, I investigated the distribution of CRP and its association with metabolic syndrome in Mexican Americans and estimated the odds ratios for developing metabolic syndrome or its components (central obesity, hypertriglyceridemia, hyperglycemia, hypertension and low HDL cholesterol) according to quartiles of CRP in this population.

According to ROC curve analysis, the optimal waist circumference cutoff values with maximum sensitivity and specificity for predicting the presence of two or more metabolic risk factors and the shortest distance on the ROC curve was 95 cm for both men and women. The sensitivity and specificity of this cutoff were 66.7% and 60.4% in both genders, respectively. Since IDF criteria requires the presence of central obesity for the diagnosis of metabolic syndrome, we justified to choose a cutoff point that obtains at least 80% sensitivity even if it causes a significant decrease in specificity. Therefore, the appropriate waist circumference to predict two or more metabolic risk factors in Mexican Americans with 80% sensitivity was 90 cm in men and women, with a corresponding specificity of 45.6% in men and 45.8% in women.

After applying the modified waist circumference of 90 cm, we noticed 34% reduction in the prevalence of central obesity in women (82.5% to 54.2%). The age adjusted prevalence of metabolic syndrome in women also decreased from 64.8% to 37.8%.

Waist circumference and BMI were highly correlated in both men and women ($r= 0.935$, $n=777$ in men and $r= 0.895$, $n=619$ in women; $P < 0.0001$ for both). All correlation coefficients of WC and BMI with the components of metabolic syndrome were significant among men ($P < 0.05$). In women, WC and BMI were significantly correlated with HDL cholesterol. In both genders the correlation coefficients were stronger between WC and metabolic risk factors than those of BMI; however the reverse pattern was noticed in correlation between WC and BMI with HDL cholesterol in women. The Odds ratios of metabolic syndrome risk factors increased from 1st to 4th quartile of waist circumference (P for trend < 0.001 for all). Compared with individuals in the lowest WC quartile, those in the highest quartile had an OR of 4.18 (95% CI: 1.96, 8.93) for elevated triglyceride, 3.50 (95% CI: 1.69, 7.26) for elevated blood pressure, 5.71 (95% CI: 3.24, 10.09) for reduced HDL cholesterol and 2.34 (95% CI: 1.32, 4.14) for elevated fasting plasma glucose, respectively, after adjustment for relevant confounders ($P < 0.001$ for all). These subjects were also 9 times more likely (95% CI: 5.00, 14.96) to have 2 or more metabolic risk factors when compared to the lowest WC quartile and after adjustment for the mentioned confounders ($P < 0.0001$).

The geometric mean concentrations of CRP were significantly higher among subjects with metabolic syndrome than those who did not have metabolic syndrome (2.31 mg/l vs. 0.81 mg/l, $P < 0.01$). Participants with central obesity, hypertriglyceridemia, hypertension and reduced HDL cholesterol also had higher levels of CRP concentrations than subjects without those conditions ($P < 0.01$ for all). The age adjusted prevalence of elevated CRP was also higher in subjects with

metabolic syndrome than those without the syndrome (42.7% vs. 17.2%, $P < 0.01$). The age adjusted prevalence of metabolic syndrome increased from 26.9% to 81.6% as the CRP concentrations increased, $P < 0.0001$. The increment pattern was observed in both genders across the CRP quartiles. C-reactive protein was significantly associated with almost all the elements of metabolic syndrome (except for diastolic blood pressure). All correlation coefficients were stronger among women than men.

The Odds ratios of having metabolic syndrome or its components increased across the CRP quartiles. Individuals with highest CRP concentrations were 9.9 times more likely (95% CI: 4.53, 16.63) to have metabolic syndrome when compared to the lowest CRP quartile and after adjustment for age, gender, alcohol intake, smoking (model 1), marital status, language spoken at home, medication use and arthritis (model 2) ($P < 0.0001$). In multiple logistic regression analysis with age, gender, drinking, smoking, marital status, medication use, arthritis and all the components of metabolic syndrome, only central obesity and gender were significant predictors of elevated CRP concentration, suggesting that central obesity is mostly responsible for increased CRP levels among individuals with metabolic syndrome.

The present study has some limitations. The cross-sectional nature of the study would not allow establishing causal relationships between metabolic syndrome risk factors and waist circumference or metabolic syndrome and C-reactive protein. In addition, the results are not applicable to all Hispanics as only Mexican Americans were over sampled in NHANES and the small number of 'other Hispanics' in data set were not sufficient to be analyzed as a separate group.

To our knowledge, this is the first study to investigate the appropriate waist circumference cutoff values for diagnosis of central obesity and metabolic syndrome in Mexican American

adults. In addition, it is the first study to examine the association between abdominal adiposity and overall obesity with the components of metabolic syndrome and the associations between CRP and metabolic syndrome in Mexican Americans using 8 years of continuous NHANES 1999-2006 data. The findings of the present study are derived from a representative sample of Mexican American adults in the United States and are applicable to this population.

The results from this study will contribute in:

- Understanding the importance of appropriate assessment of central obesity in screening metabolic syndrome
- Providing practical guidance in identifying individuals with metabolic syndrome
- Understanding the association between waist circumference and metabolic risk factors in Mexican American adults
- Emphasizing the importance of central obesity in increasing risk of having metabolic abnormalities
- Understanding the association between C-reactive protein and metabolic syndrome in Mexican American adults

As current CRP cutoff values are derived from European and European American population studies, future research is needed to evaluate the appropriateness of these thresholds in predicting metabolic or CVD risk in other ethnic groups such as Hispanic Americans, African Americans and Native Americans. Nationwide studies to investigate the ethnic differences in CRP distribution and its association with metabolic syndrome are needed. Further research should also investigate the appropriate body mass index and waist circumference cutoff values in predicting metabolic syndrome or CVD risk among different ethnic groups such as African Americans, Middle Eastern and All Hispanic populations.

Considering the high prevalence of metabolic syndrome, central obesity and low grade inflammation in Mexican Americans, they are at higher risk for developing cardiovascular

disease and diabetes mellitus. To prevent or delay the development of these conditions, multifaceted strategies for prevention, treatment and management of obesity, metabolic syndrome and/or chronic inflammation are necessary. Lifestyle modifications, nutritional education, weight control programs, physical activity and pharmacological interventions are suggested.

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