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Defining Abdominal Obesity as a Risk Factor for Coronary Heart Disease in the US Hispanic Community Health Study/Study Of Latinos (HCHS/SOL)

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DEFINING ABDOMINAL OBESITY AS A RISK FACTOR FOR CORONARY HEART DISEASE IN THE US HISPANIC COMMUNITY HEALH STUDY/STUDY OF LATINOS (HCHS/SOL)

By

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Defining Abdominal Obesity as a Risk Factor for Coronary Heart Disease in the US Hispanic Community Health Study/ Study of Latinos (HCHS/SOL) (August 2016)

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It is now well established that pronounced differences exist in prevalence of abdominal obesity across gender and ethnicity. Hispanic/Latinos, in particular, have been shown to have markedly distinct prevalence when compared to other ethnic populations around the world. Various organizations have highlighted the need to examine whether overall abdominal obesity cut points are appropriate for the use in this ethnic minority, particular highlighting the need of research among Hispanic/Latino residing in Western countries. This study used data from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL), the largest study of Hispanic/Latinos in the US, to: (1) establish optimal definitions for abdominal obesity among Hispanic/Latino adults, (2) determine the level of agreement between the presence of the metabolic syndrome diagnosed by the current Joint Interim Statement (IJS) definition and an updated definition with optimal abdominal obesity cut points, and (3) examine the association between the presence of the metabolic syndrome, diagnosed by both the IJS and our updated definition, and coronary heart disease (CHD). The sample was comprised of 16,289 individuals (59.94% female). Our results indicate than among US Hispanic/Latino adults, waist circumference cut points of >102 cm in men and >97 cm in women provide optimal discrimination for cardiovascular risk as judged by the presence of CHD. When using these cut points to create an updated metabolic syndrome definition among women, we found disagreement

between our updated definition and the current IJS criteria for metabolic syndrome. The prevalence of the metabolic syndrome was overestimated by about 5% points among women based on IJS criteria when compared to our updated definition. Further, we determined that the performance of our updated metabolic syndrome definition as predictor of CHD was comparable to that of the IJS definition. In this paper, we provide for the first time an empirically-derived definition of abdominal obesity for use among Hispanic/Latino adults in the US. Future reports should examine our recommended waist circumference definition cut points and the performance of our updated metabolic syndrome definition as a predictor of cardiovascular risk among US Hispanic/Latinos in prospective designs.

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The opinions, ideas, and interpretations included in this dissertation are mine alone, and not those of the HCHS/SOL investigators.

I thank the staff and participants of HCHS/SOL for their important contributions. Investigators website - http://www.cscc.unc.edu/hchs/

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Chapter 1

INTRODUCTION

Over the past thirty years, there has been an alarming increase in the overall prevalence of obesity, defined as at body mass index (BMI) of 30 km/m^2 or higher, in the adult population of the United States (US) (Flegal, Carroll, Kit, & Ogden, 2012). Although this epidemic appears to be leveling off and no significant increase in the prevalence was observed between the years 2003 and 2010, obesity continues to affect over 78 million adults in the country. In fact, in 2010 the US age-adjusted prevalence of obesity was 35.5% (95% CI, 31.9%-39.2%) among adult men and 35.8% (95% CI, 34.0%-37.7%) among adult women, with the highest prevalence rates reported among some racial and ethnic minority groups and those of lower income and education.

Increased weight is a major contributor to chronic diseases and thus accounts for nearly 150 billion dollars in yearly medical care costs (Finkelstein, Trogdon, Cohen, & Dietz, 2009). It is now well established that obesity is associated with an increased risk of all-cause and cardiovascular disease (CVD) mortality, and therefore has been classified as the second cause of preventable death in the US following cigarette smoking (Mokdad, Marks, Stroup, & Gerberding, 2004; Mozaffarian et al., 2015). In addition, obesity has been shown to significantly predict morbidity from coronary heart disease, stroke, metabolic conditions such as type 2 diabetes mellitus (T2DM), cancer, osteoarthritis, sleep apnea and other respiratory disorders (Jensen et al., 2014). Therefore, as the obesity epidemic worsens, the prevalence of most if not all of these conditions will continue to be impacted.

Of special interest are obesity-related metabolic conditions that significantly increase the risk for heart disease, the leading cause of death among adults in the US (CDC, 2014). One of the most prevalent obesity related metabolic conditions is the metabolic syndrome, a group of anthropometric, hemodynamic and metabolic disturbances that appear to cluster together, and have been shown to significantly contribute to CVD morbidity and mortality (Jensen et al., 2014; Mozaffarian et al., 2015).

Metabolic Syndrome: Prevalence and Contribution to CVD Risk

The metabolic syndrome is a group of co-existing and interrelated cardiometabolic disturbances that include abdominal obesity, dyslipidemia (low levels of high-density lipoprotein cholesterol [HDL-C] and high levels of triglycerides), hypertension and hyperglycemia (Alberti et al., 2009). The prevalence of the metabolic syndrome has risen over the last two decades (in line with the obesity epidemic) and in 2010, the age-adjusted prevalence of the metabolic syndrome among US adults was 34.3% (36.1% in men and 32.4% in women) (Ford, Li, & Zhao, 2010).

Prevalence of the metabolic syndrome increases with age, peaking among those aged 60-69 years old, an age at which almost 60% of men and 55% of women have the syndrome (Ford et al., 2010). In addition, gender and ethnicity appear to interact to increase the risk for metabolic syndrome among certain groups. For example, in the US third National Health and Nutrition Examination Survey (NHANES III), African American, Mexican-American, and Non-Hispanic White men and women were shown to have varying metabolic syndrome prevalence rates (Ford, Giles, & Dietz, 2002; Ford et al., 2010). Mexican-Americans (particularly women) were shown to be disproportionally affected by the syndrome when compared to African-American and Non-Hispanic Whites. In fact, the prevalence of the metabolic syndrome among Mexican-American women was the highest at 41.9%. The high prevalence of this condition among US Hispanic/Latinos was further explored in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL), a study of over 16,000 US Hispanic/Latinos of various ancestries (Heiss et al., 2014). Consistent with the NHANES III findings, the prevalence of the metabolic syndrome in HCHS/SOL was high: 33.7% among men and 36.0% among women.

The burden of metabolic syndrome in US adults, particularly among Hispanic/Latinos, is of concern given that these cluster of abnormalities appear to be intricately related to the development and progression of CVD (Alberti et al., 2009). In fact, a meta-analysis pooled the results of 87 studies that included 951,083 patients of various ethnicities in order to evaluate the contribution of the syndrome to CVD morbidity and mortality (Mottillo et al., 2010). They showed that patients with the metabolic syndrome have a CVD relative risk (RR) increase of 2.35 (95% Confidence Intervals [CI]: 2.02 to 2.73) when compared to those without the syndrome. Moreover, the metabolic syndrome was associated with an increased risk of CVD mortality (RR: 2.40; 95% CI: 1.87 to 3.08), all-cause mortality (RR: 1.58; 95% CI: 1.39 to 1.78), myocardial infarction (RR: 1.99; 95% CI: 1.61 to 2.46), and stroke (RR: 2.27; 95% CI: 1.80 to 2.85).

Defining the Metabolic Syndrome

Although there is considerable evidence of the contribution of the metabolic syndrome to CVD morbidity and mortality, the syndrome was subject to substantial criticism during the early 2000's due to the presence of competing diagnostic criteria (Kahn et al., 2005). For years there was little agreement among medical professionals and organizations on specifically which factors constituted the metabolic syndrome. Various organizations, including the World Health Organization (WHO), the International Diabetes Federation (IDF), the American Heart Association (AHA) and the National Heart, Lung, and Blood Institute (NHLBI) endorsed different definitions of the metabolic syndrome. The choice of metabolic syndrome components and their cut-points was largely based on experts' opinions rather than empirical evidence, particularly in the case of older definitions.

A group of experts in diabetes commissioned by the WHO proposed for the first time in 1998 a formal definition of the metabolic syndrome (Alberti & Zimmet, 1998). This definition required the presence of (1) impaired glucose regulation or diabetes, and (2) insulin resistance, together with two or more of the following components: (3) raised arterial pressure ≥160/90 mmHg; (4) raised plasma triglycerides (≥1.7 mmol/l; 150 mg/dl) and/or low HDL-C (<0.9 mmol/l or 35 mg/dl for men, <1.0 mmol/l or 39 mg/dl for women); (5) central obesity (waist to hip ratio ≥ 0.90 cm for men; 0.85 for women and/or BMI ≥30 kg/m^2; (6) microalbuminuria (urinary albumin excretion rate ≥20 µg/min or albumin to creatinine ratio ≥20 mg/g). This report provided no description of the process by which specific components and their cut-points were selected.

In 2001, the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII) proposed the second major criteria for the metabolic syndrome (Expert Panel on Detection & Treatment of High Blood Cholesterol in, 2001). In contrast to the WHO definition, the NCEP-ATPIII criteria for the metabolic syndrome did not require the presence of a single factor, such as insulin resistance or diabetes, for diagnosis. Instead 3 out of 5 of the following risk factors were needed for establishing a diagnosis: (1) central obesity: waist circumference ≥ 102 cm or 40 inches for men, ≥ 88 cm or 36 inches for women; (2) dyslipidemia: triglycerides ≥ 1.7 mmol/L (150 mg/dl); (3) dyslipidemia: HDL-C < 1.0 mmol/l (40 mg/dl, male), < 1.3 mmol/L (50 mg/dl, female); (4) elevated blood pressure ≥ 130/85 mmHg; (5) impaired fasting glucose ≥ 6.1 mmol/L (110 mg/dl). These components and their cut-points were chosen by the expert panel based on clinical experience and after reviewing relevant literature.

In spite of efforts to reconcile the competing definitions, in 2005 both the AHA/NHLBI (Grundy et al., 2005) and the IDF (Alberti, Zimmet, Shaw, & Group, 2005) issued separate recommendations for the diagnosis of the syndrome. The AHA/NHLBI retained all components and requirements of the NCEP-ATPIII definition, but reduced the impaired fasting glucose threshold from 110 mg/dl to 100 mg/dl (Grundy et al., 2005). This decision was made following the publication of an expert report by the American Diabetes Association (Genuth et al., 2003) which lowered the threshold after reviewing data that showed that a cut-point of 100 mg/dl was more effective at predicting risk for T2DM in various multi-ethnic samples when compared to the 110 mg/dl cut-point (unpublished data).

On the other hand, and while also resembling the NCEP-ATPIII diagnostic criteria for metabolic syndrome, the IDF made important remarks on the importance of the central obesity component (Alberti et al., 2005). Within this definition, the presence of central obesity was required for diagnosis due to the strength of its relationship with CVD and its interrelationship with all other metabolic syndrome components. In addition, the IDF was the first professional organization to recognize the importance of ethnic-specific central obesity criteria. It incorporated ethnic-specific waist circumference cut-points based on available data showing different predictive value of abdominal obesity across populations. Ethnic-specific recommendations were given for Europids, South Asians, Chinese, Japanese, Ethnic South and Central Americans, Sub-Sahara Africans, and Eastern Mediterranean (Arab) populations. These recommendations highlighted that ethnicity and not country of residence should be the basis for classification of individuals. The remaining four components of the metabolic syndrome were identical to those proposed by the NCEP-ATPIII (Expert Panel on Detection & Treatment of High Blood Cholesterol in, 2001).

Due to the considerable amount of research the metabolic syndrome generated and in order to increase comparability among studies, harmonizing the definition of the syndrome became imperative. Finally, in 2009 various organizations around the world, including the IDF, the AHA, the NHLBI, the World Heart Federation, the International Atherosclerosis Society and the International Association for the Study of Obesity, came together to issue a Joint Interim Statement containing an updated and unified criteria for the metabolic syndrome (Alberti et al., 2009). This new definition requires the presence of 3 out of 5 of the following components for diagnosis of the metabolic syndrome: (1)

Elevated waist circumference: population and country-specific definitions; (2) Elevated triglycerides: ≥150 mg/dl or 1.7 mmol/l (drug treatment for elevated triglycerides is an alternate indicator); (3) Reduced HDL-C: <40 mg/dl or 1.0 mmol/l in men, <50 mg/dl or 1.3 mmol/l in women (drug treatment for reduced HDL-C is an alternate indicator); (4) Elevated blood pressure: Systolic ≥130 mmHg and/or diastolic ≥85 mmHg (antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator); and (5) Elevated fasting glucose: ≥100 mg/dl (drug treatment of elevated glucose is an alternate indicator).

In addition to unifying the metabolic syndrome diagnosis, an important portion of the Joint Interim Statement was devoted to the discussion of ethnic-specific cut-points for abdominal obesity (Alberti et al., 2009). In line with previous recommendations by the IDF, the statement acknowledged the inadequacy of the current abdominal obesity definitions in characterizing Non-Caucasian populations, and proposed varying waist circumference cut-points across ethnicities. Further information on the importance of ethnic-specific abdominal obesity definitions is provided in the following section.

Importance of Ethnic-specific Abdominal Obesity Definitions

After two decades of research on the topic, it is a now well established that the metabolic syndrome is a useful screening tool to identify individuals at high risk for CVD (Alberti et al., 2009; Mottillo et al., 2010). Given this predictive ability, it is reasonable to believe that differences in prevalence of the metabolic syndrome across ethnicities reflect differences in CVD risk and these may thus account for the varying rates of CVD morbidity and mortality around the world.

Accumulating evidence indicates, however, that the metabolic syndrome (diagnosed by the NCEP-ATP III criteria which includes standard abdominal obesity cut-points across ethnicities) has surprisingly low prevalence in some populations that exhibit high burden of CVD. For example, Asian populations such as Japanese, Mongolians and Koreans have been shown to exhibit elevated rates of CVD while having low incidence of the metabolic syndrome (Shiwaku et al., 2005). The opposite is also true: in a UK multiethnic study, African-Caribbeans were found to have high rates of the metabolic syndrome, while exhibiting the lowest incidence of CVD mortality when compared to South Asians and White Europeans (Tillin et al., 2005). The inconsistent association between metabolic syndrome and CVD across ethnic groups may be attributed to the fact that: (1) distinct populations may have markedly different risk factors for CVD; or (2) the metabolic syndrome definition may be flawed when applied to different ethnicities.

Although both explanations are plausible, research conducted to date indicates that the inaccuracy in the predictive ability of the metabolic syndrome across ethnicities is a result of erroneous definitions of abdominal obesity among Non-Caucasian populations (Banerjee & Misra, 2007). Given the parameters for identification of individuals with abdominal obesity were derived from Caucasian samples, it is likely these waist circumference cut-points do not adequately capture CVD risk among other ethnicities. Various studies, primarily conducted in Asian populations provide support for this notion. For example, Chinese, Indian and South Asian individuals exhibit metabolic abnormalities, including hypoglycemia, hypertension and dyslipidemia, at much lower levels of waist circumference than Caucasian populations (Gray et al., 2011; Razak et al., 2005; Shiwaku et al., 2005; Vikram et al., 2003).

Cumulatively, these data suggest that abdominal obesity definitions should be specific to each ethnicity, and the Joint Interim Statement for the metabolic syndrome (Alberti et al., 2009) now requires ethnic-specific criteria for abdominal obesity. Although some of these recommendations are based on empirical evidence, as is the case for Asian countries, the lack of research in other populations has prevented the adequate determination of empirically based cut-points for various ethnic groups.

The best approach to establish new ethnic-specific abdominal obesity cut-points is still undetermined. Arbitrarily altering the abdominal obesity definition to increase prevalence of the metabolic syndrome in a specific population is misleading and insufficient (Banerjee & Misra, 2007). Instead, it is important that new definitions reflect closely the risk patterns of a given population and improve accuracy in the prediction of CVD outcomes.

Empirical Approaches to Establish Optimal Cut-points

There is considerable reservation in the methodological literature on the practice of dichotomizing quantitative variables. Some of the negative consequences of dichotomization practices include loss of information about individual differences, loss of effect size and power, potential to overlook non-linear relationships, among others (MacCallum, Zhang, Preacher, & Rucker, 2002). While the use of continuous variables is ideal in the context of medical research, particularly when examining relationship among variables, in clinical practice the use categories facilitates diagnostic and treatment decisions. Therefore, determination of cut-points is important for diagnostic purposes.

A common issue with the determination of categories is that cut-points proposed and used are often arbitrary and subjective (Royston, Altman, & Sauerbrei, 2006). For example, when dichotomizing some variables, such as age, it is common practice to take a "round number" such as 5 or 10 and divide individuals in age groups (30 to 40, 40 to 50, etc). Another common approach is to take the sample median and split the sample in two groups, below and above the median. In extreme cases, more than one value is tried out for dichotomization and the chosen value is the one that, in some sense, gives the most satisfactory result (such as one that may reduce the *p*-value in a regression). These approaches lead to arbitrary and inaccurate cut-points, which not only may result in erroneous research conclusions but may also negatively impact clinical decision-making. Adequate methodological tools are thus needed to prevent these negative consequences. Fortunately, the tools for the evaluation and selection of cut-points are now readily available, based on Signal Detection Methods (Kraemer, 1992). Signal Detection techniques are well established and have been widely used in medical research for determining the sensitivity and specificity of a diagnostic test for identifying a specific disorder (Kraemer, Noda, & O'Hara, 2004).

The concepts of sensitivity and specificity are central to signal detection theory and to understanding classification accuracy (Griner, Mayewski, Mushlin, & Greenland, 1981; Kraemer, 1992). *Sensitivity* (also called true positive rate [TPR] or true positive fraction [TPF]) refers to a test's ability to identify a condition correctly. For example, in a medical context, sensitivity refers to the probability that a medical test will be positive when the disease is present. Mathematically it would be expressed as: number of true positives/(number of true positives + number of true negatives). On the other hand, *specificity* (also called true negative rate [TNF] or true negative fraction [TNF]) refers to a test's ability to exclude a condition correctly. In medicine this would translate to the proportion of healthy patients (known to not have a disease) that test negative for it; and it would be mathematically expressed as: number of true negatives/(number of true negatives + number of false positives).

Receiver-operating characteristic (ROC) curve analysis is a signal detection method used for assessing the accuracy of a classifier or predictor (Greiner, Pfeiffer, & Smith, 2000; Griner et al., 1981). It has many advantageous features, one of the most important being its ability to incorporate both sensitivity and specificity into a single performance metric. Essentially, in a ROC curve the TPR (sensitivity) is plotted in function of the false positive rate (100 - specificity) for a wide range of cut-points of a parameter (Alemayehu & Zou, 2012; Greiner et al., 2000). An optimal cut-point that maximizes both sensitivity and specificity can thus, be selected.

ROC analysis has been extensively used in medical research for the evaluation of screening and diagnostic tests (Alemayehu & Zou, 2012), and most importantly, it has been consistently used for the determination of optimal waist circumference cut-points for various ethnicities (Bao et al., 2008; Kawada et al., 2011; Nishimura, Nakagami, Tominaga, Yoshiike, & Tajima, 2007; W. Wang et al., 2010; Wang, Ma, & Si, 2010). However, ROC analyses are still subject to some limitations (Eng, 2005). First, only binary states can be considered as outcomes or reference standards for the ROC curve, for example the presence or absence of a disease. Therefore, in situations where more than two possible outcomes are possible, ROC analyses cannot be applied. Second, the outcome against which the ROC curve is constructed must reflect a true state or diagnosis. An outcome that is dichotomized arbitrarily so it can be used as a reference standard would potentially introduce inaccuracy in the ROC analysis. This highlights the critical importance of choosing the correct diagnostic outcome, or reference standard, within this methodological approach.

The choice of optimal cut-point of a continuous variable depends completely on the purpose to which the categorical classification is to be put (Kraemer et al., 2004). If the purpose were to differentiate individuals at high risk for CVD, manifest CVD or CVD mortality would be ideal outcome for the ROC curve. If the purpose were to classify individuals at high risk for diabetes, a diabetes diagnosis should be used as an outcome variable, and so on. When establishing optimal abdominal definitions, the most common ROC outcomes used have been: (1) obesity markers: BMI and excess visceral adipose tissue (Aschner et al., 2011; Gray et al., 2011); (2) T2DM (Barbosa, Lessa, Almeida Filho, Magalhães, & Araújo, 2006; Sanchez-Castillo et al., 2003); (3) CVD risk factors: hypertension and abnormal lipid profile (Perez et al., 2003; Sanchez-Castillo et al., 2003; Vikram et al., 2003); and (4) CVD markers: abdominal carotid intima-media thickness, manifest CVD, CVD mortality (Gray et al., 2011; Medina-Lezama et al., 2010).

There is no consensus on a single outcome as being ideal to establish abdominal obesity cut-points. However, when conceptualizing abdominal obesity as a component of the metabolic syndrome and given the fact that the syndrome serves the purpose of screening individuals at high risk for CVD (Alberti et al., 2009), CVD markers are likely to be the most appropriate outcomes. The use of distinct outcomes for establishing optimal abdominal obesity definitions has made comparability across studies difficult. Surprisingly, there is relatively high concordance across studies in the selection of optimal ethnic-specific waist circumference cut-points (Aschner et al., 2011; Barbosa et al., 2006; Medina-Lezama et al., 2010). This agreement is likely due to fact that, even when CVD markers were not used to establish cut-points, all other outcomes typically chosen for this purpose can be classified as cardiometabolic risk factors and they have direct and established associations with CVD (Yusuf et al., 2004).

As outline earlier, most of the research on establishing waist circumference cut-points has been conducted in Asian samples. The methodological approaches used in these studies can be replicated in order to determine empirically based definitions specific to other populations. Hispanic/Latinos, in particular, are known to have a cardiometabolic profile that is vastly different to that of other ethnicities (Chirinos, Morey-Vargas, Goldberg, Chirinos, & Medina-Lezama, 2013; Daviglus et al., 2012; Heiss et al., 2014; Sorlie et al., 2014) and therefore, are likely to benefit from ethnic specific criteria for abdominal obesity.

Ethnic-specific Definitions for Hispanic/Latinos

Hispanic/Latinos in the US have been shown to have the highest rates of metabolic syndrome when compared to their African/American and Caucasian counterparts (Ford et al., 2002; Ford et al., 2010). Given the alarming rates of metabolic abnormalities, recent studies have further explored its presentation among members of this ethnic minority group (Chirinos et al., 2013; Heiss et al., 2014).

In the HCHS/SOL, study of 9,789 women and 6,530 men of various Hispanic/Latino subgroups including Caribbean, Central American and South American adults, the cardiometabolic profile of Hispanic/Latinos in the US was extensively characterized (Heiss et al., 2014). Approximately 21% of men and 14% of women had no cardiometabolic abnormalities, 34% of men and 36% of women had three or more, and 3.8% of men and 4.6% of women had five abnormalities. One of the most remarkable features in these data was the high proportion of women who meet the metabolic syndrome diagnostic criteria by virtue of exceeding the threshold values of waist circumference. In fact 96% of women with the metabolic syndrome had the abdominal obesity component. The median values of waist circumference observed and progressively larger increments in girth values across increasing numbers of risk factors present were also noteworthy, and highlight the salient contribution of waist circumference among Hispanic/Latinos. Surprisingly, in spite of the high rates of abdominal obesity in this sample, the prevalence of CHD was low (4.2% and 2.4% in men and women, respectively) (Daviglus et al., 2012).

The seemingly mismatch in the rates of abdominal obesity and CHD among Hispanic/Latino adults raises the question of what is actually the correct definition of abdominal obesity for this population. The Joint Interim Statement has acknowledged the lack of data for Hispanic/Latinos (Ethnic South and Central American) and indicated that waist circumference cut-points developed for South Asians (≥80 cm for women, and ≥90 cm for men) should be used until more specific data are available. Given the prevalence rates of both abdominal obesity and CVD among Hispanic/Latinos are vastly different from the prevalence in South Asian countries (Daviglus et al., 2012; Heiss et al., 2014), these cut-points might be just as inaccurately at classifying individuals with abdominal obesity, as those developed for Caucasians.

Establishing waist-circumference cut-points that accurately differentiate individuals at high risk for CVD is therefore important for all Hispanic/Latinos around the world, but perhaps it is most crucial for those residing in the US. Research findings have consistently shown that acculturation to the mainstream American culture, confers additional cardiovascular risk for US Hispanic/Latinos (Daviglus et al., 2012; Heiss et al., 2014; Sorlie et al., 2014). In fact, the 2013 AHA/American College of Cardiology (ACC)/ The Obesity Society (TOS) Obesity Guidelines has identified the need to examine whether overall abdominal obesity cut-points are appropriate for use in ethnic minorities within Western countries, particularly highlighting the need of research among Hispanic Americans (Jensen et al., 2013). No such research is currently available in US samples of Hispanic/Latinos.

Proposed Abdominal Obesity Cut-points for Hispanic/Latinos

Given the need for empirically based abdominal obesity definitions among Hispanic/Latinos, various groups have attempted to provide optimal waist circumference cut-points for Central and South American Hispanics outside the US. The generalizability of these recommendations, however, is limited due to the fact that these definitions have been derived from studies with limited samples sizes or that have included only one Hispanic/Latino subgroup.

The first recommendations for Central American Hispanic/Latinos were given in 2003 based on data from the Mexican National Health Survey, a study of 11,730 men and 26,647 women (Sanchez-Castillo et al., 2003). Authors aimed to determine optimal anthropometric cut-points for predicting the likelihood ratios of both T2DM and hypertension with the use of ROC analyses. Waist circumference cut-points for predicting T2DM were 93 to 98 cm in men and 94 to 99 cm in women, and cut-points for hypertension were 92 to 96 cm and 93 to 96 cm for men and women, respectively.

South American groups have also developed regional waist circumference cut-points with the use of smaller samples. A study of 145 healthy men aimed to determine the optimal level of waist circumference associated with and abnormal lipid profile (triglycerides >2.25 mmol/l and total-cholesterol/HDL-C ratio > 5) in Colombian men (Perez et al., 2003). ROC analyses determined a waist circumference cut-point of 88 cm was optimal to identify men with pre-established lipid profile. Brazilian cut-points were determined based on a population-based study of 1439 adults (57.7% women) (Barbosa et al., 2006). Optimal waist circumference cut-points to identify T2DM and obesity based of ROC analyses were 84 cm for women and 88 cm for men. Finally, the Peruvian group PREVENCION, recommended waist circumference cut-points for Andean Hispanic/Latinos based on a population based study of 1448 adults in Arequipa, Peru (Medina-Lezama et al., 2010). Waist circumference cut-points of 87 cm in women and 97 cm in men were optimal to identify abnormal carotid intima-media thickness and manifest CVD.

Although the aforementioned studies had sound methodological designs and were based on population-based samples, the inclusion of a single Hispanic/Latino subgroup (Mexicans, Brazilians, Colombian or Peruvian) limits the generalizability of these results to all Hispanic/Latinos. In effort to increase representation of multiple countries and subgroups, a recent study recruited adults from various Central and South American countries, including Mexico, El Salvador, Venezuela, Colombia and Paraguay, to develop waist circumference cut-points recommendations in the Latin American Region (Aschner et al., 2011). Based on ROC analyses, waist circumference thresholds of 90-92 cm for women and 94 cm for men were identified as best predictors for visceral adiposity. Unfortunately, these recommendations were developed based on a total sample size of 179 men and 278 women.

Clearly the research available on waist circumference cut-points for Hispanic/Latinos is still insufficient. Unfortunately, the use of waist circumference cut-offs applicable to populations that are likely to be genetically, clinically and culturally different may result in the misclassification of risk among Hispanic/Latinos in the US and around the world. Future research efforts should be directed at establishing empirically based definitions of abdominal obesity in this highly vulnerable population with the use of large and representative samples of Hispanic/Latinos within and outside the US.

The Present Study

The need for population- and ethnic-specific thresholds for abdominal obesity was emphasized in Joint Interim Statement (Alberti et al., 2009) given that it is now well established that pronounced differences exist in abdominal obesity across gender and ethnic group. Hispanic/Latinos, in particular, have been shown to have markedly distinct prevalence of abdominal obesity when compared to other ethnic populations around the world (Chirinos et al., 2013; Daviglus et al., 2012; Heiss et al., 2014; Sorlie et al., 2014).

In fact, the prevalence of abdominal obesity appears to be significantly greater in Hispanic/Latinos residing in the US as compared to those residing in their home countries. However, the prevalence of CVD among Hispanic/Latinos is not in concordance to these high abdominal obesity rates. The 2013 AHA/American College of Cardiology (ACC)/ The Obesity Society (TOS) Obesity Guidelines have highlighted the need to examine whether overall abdominal obesity cut-points were appropriate for use in ethnic minorities within Western countries, particularly emphasizing the need of research among Hispanic Americans (Jensen et al., 2013).

Previous groups have attempted to provide optimal cut-points for waist circumference among Hispanic/Latinos outside the US. However, the generalizability of these results is limited due to the inclusion of only one Hispanic subgroup (Barbosa et al., 2006; Medina-Lezama et al., 2010; Perez et al., 2003; Sanchez-Castillo et al., 2003) and/or the use relatively small sample sizes (Aschner et al., 2011; Perez et al., 2003).

Therefore, at the moment and until more specific data are available, the Joint Interim Statement has recommended the use of the cut-off values proposed for South Asian populations, which defined abdominal obesity as waist circumference of ≥90 cm in men and ≥80 cm in women for ethnic South and Central Americans regardless of their country of residence (Federation). The use of waist circumference cut-offs applicable to populations that are likely to be genetically, clinically and culturally different may result in the misclassification of risk among Hispanic/Latinos in the US and around the world.

HCHS/SOL is the largest study of Hispanic/Latinos in the US. Due to the inclusion of more than 16 000 US Hispanic/Latino adults it provides an ideal opportunity to identify optimal cut-off points for waist circumference applicable to Hispanic/Latinos in the U.S. and perhaps even those residing in other countries until more region-specific data are available. The inclusion of various Hispanic/Latino subgroups, such as Dominicans, Central/South Americans, Cubans, Mexicans and Puerto Ricans, ensures the representation of various ancestries and enhances the generalizability of results.

Study Aims and Hypothesis

Specific Aim 1: To establish optimal definitions for abdominal obesity among US Hispanic/Latino men and women to predict the presence of coronary heart disease (CHD).

Hypothesis 1: The optimal cut points for abdominal obesity to predict the presence of CHD among US Hispanic/Latino men and women will differ from the current definitions for other ethnic groups.

Specific Aim 2: To determine the level of agreement between the presence of the metabolic syndrome diagnosed by the current Joint Interim Statement definition (which recommends generic cut-points for “Non-Europids”) and an updated definition with optimal abdominal obesity cut-points (derived from previous aim), in US Hispanic/Latino men and women.

Hypothesis 2: In the HCHS/SOL sample, there will be disagreement between the metabolic syndrome diagnosed by an updated definition and the Joint Interim Statement diagnostic definition.

<u>Specific Aim 3:</u> To examine the relationship between the presence of the metabolic syndrome, diagnosed by both the Joint Interim Statement definition and an updated metabolic syndrome definition (with appropriate abdominal obesity cut-points), and the presence of coronary heart disease (CHD) among US Hispanic/Latinos after adjustment for relevant demographic characteristics.

Hypothesis 3: An updated metabolic syndrome definition will hold a stronger association with the presence of CHD among US Hispanic/Latinos than the Joint Interim Statement definition after adjustment for relevant demographic characteristics.

Chapter 2

METHODS

Participants

Participants included in the study are those of the HCHS/SOL study. The National Institutes of Health (NIH)-supported HCHS/SOL is a population-based cohort study that aimed to characterize the health of US Hispanics/Latinos in regards to chronic conditions and their putative antecedent factors (Sorlie et al., 2010). During its baseline visit, a total of 16,415 self-identified Hispanic/Latino adults between the ages of 18 and 74 were recruited from randomly selected households in 4 cities: Miami, Florida; San Diego, California; Chicago, Illinois; and, the Bronx, New York. The HCHS/SOL study was designed to include Hispanic/Latinos of various backgrounds in pre-established proportions enrolling participants from Cuban, Dominican, Mexican, Puerto Rican, Central American and South American decent (Lavange et al., 2010).

Sampling

The HCHS/SOL study had a multi-stage, stratified, probabilistic sample design. Census blocks groups were randomly selected in specified geographic areas of each study site, and households were randomly selected in each sample block group. Households were screened for eligibility and self-identified Hispanic/Latino persons aged 18 to 74 years were selected in each household. Further details on the design and sampling strategy of the HCHS/SOL study have been previously reported (Lavange et al., 2010; Sorlie et al., 2010).

Inclusion/exclusion criteria. Self-identified Hispanic/Latino adults between the ages of 18-74 residing in the four sampled areas were eligible to participate. Persons were excluded from the study if: (1) they were on active military duty, (2) they were not currently living at home, (3) they were planning to move from the are within 6 months, and/or (4) they were physically unable to attend the clinical examination. Pregnant women were scheduled to participate in the clinical visit approximately three months postpartum. There was no other exclusion criteria based on health status.

Procedures

All examination and interviewer-administered questionnaires were conducted by trained and certified study personal following a standardized protocol. Study protocol manuals are available at http://www.cscc.unc.edu/hchs/. Study participants were asked to fast and to abstain from smoking 12 hours prior to the examination, and to avoid vigorous physical activity the morning of the examination.

Measures

Abdominal obesity and other metabolic syndrome components. Waist circumference was measured to the nearest 0.1 cm at the uppermost lateral border of the right ilium using a measuring tape. After 5 minutes in the seated position, systolic (SBP) and diastolic blood pressure (DBP) were measured 3 times at 1-minute intervals using an automatic sphygmomanometer (Omron model HEM-907 XL, Omron Healthcare Inc., Bannockburn, IL), and the average of the 3 readings was used. Measurements of HDL-C, triglycerides, and glucose were obtained from collected fasting blood samples. Blood samples were obtained following a non-traumatic venipuncture protocol. Fresh as well as frozen specimens were shipped to the HCHS/SOL Central Laboratory for assays and long-term storage. HDL-C was measured by a magnesium/dextran sulfate method and plasma glucose was measured using a hexokinase enzymatic method (Roche Diagnostics). Triglycerides were measured in serum on a Roche Modular P chemistry analyzer, using a glycerol blanking enzymatic method (Roche Diagnostics, Indianapolis, IN). The assay methodologies and their performance are described in HCHS/SOL Manual 7 (Addendum) at http://www.cscc.unc.edu/hchs/public/docfilter.php?study=hchs&filter_type=public.

Metabolic syndrome Joint Interim Statement criteria. As specified in the Joint Scientific Statement (Alberti et al., 2009), participants will be classified as having the metabolic syndrome if they met three or more of the following criteria: 1) waist circumference ≥102 cm in men and ≥88 cm in women; 2) triglycerides ≥150 mg/dl; 3) HDL-C <40 mg/dl in men and <50 mg/dl in women; 4) blood pressure ≥130 mm Hg systolic and/or ≥85 mm Hg diastolic and/or on medication; 5) fasting glucose ≥100 mg/dl and/or on medication.

CHD. The presence of CHD will be used as a marker of CVD. Each participant received a standard digital 12-lead electrocardiogram (ECG; GEMSIT MAC 1200 portable electrocardiograph) and readings were electronically transmitted to a Central ECG Reading Center (The Epidemiological Cardiology Research Center (EPICARE) of Wake Forest University's School of Medicine). The Minnesota Code system of classification was used to ascertain possible old myocardial infarction (MI). Self-reported information on angina, heart attack, and coronary procedures (angioplasty, stent, or bypass surgery to the arteries of the heart) was collected via standard questionnaire and interview. Prevalent CHD will be specified as a dichotomous variable that combined information from ECG reports of possible old MI as well as self-report of heart attack, coronary procedures, and angina.

Covariates. Standard questionnaires and interviews were used to collect information on age, sex, Hispanic/Latino subgroup, smoking history, education and total household income. Age will be examined as a continuous variable. Gender will be treated as a dichotomous variable (male vs. female). Hispanic/Latino subgroups will be represented by six dummy coded variables: Mexicans, Puerto Ricans, Cubans, Dominicans and Central Americans. South Americans will serve as the references group. Smoking history will be treated as a dichotomous variable (current vs. former). Education will be treated as a dichotomous variable (no high school diploma vs. high school diploma or higher). Household income will be examined as a 5-level categorical variable (<$10,000, $10,000 to $20,000, >$20,000 to $40,000, >$40,000 to $75,000, or >$75,000). In addition, HCHS/SOL study site will be used as a control variable. Study sites will be represented by three dummy coded variables: Chicago, Bronx and San Diego. The Miami site will serve as the reference group.

Chapter 3

DATA ANALYSIS PLAN

Preliminary Analysis

Preliminary statistical analyses included descriptive statistics and assessment of distributions. All analyses accounted for the complex sampling design with the use of sampling weights, probability and cluster units. SPSS version 22.0 was used for data preparation and descriptive analysis. SAS version 9.3 was used for ROC analyses. Mplus version 7.0 was used for inferential analyses.

Descriptive statistics were calculated (e.g. mean and standard deviation) for all demographic and biological variables included in the analyses. The t- test was used to examine significant differences by sex in demographic and biological continues variables. The chi-square test of independence was used to test differences among categorical variables.

Primary Analysis

Statistical analyses are outlined in correspondence to each specific aim.

Analysis of aim 1: Receiver operator characteristic (ROC) analyses were constructed to identify optimal waist circumference cut points (Alemayehu & Zou, 2012; Eng, 2005). Separate analyses were conducted for men and women. Sensitivity and specificity values were examined to determine optimal waist circumference cut-points for each sex. The waist circumference value (cm) resulting in the largest sum of sensitivity and specificity for the presence of coronary heart disease (CHD) was selected as optimal cut-points. Presence of CHD was specified as a dichotomous variable that combines information from ECG reports of possible old MI as well as self-report of heart attack, coronary procedures, and angina. Sensitivity and specificity are presented in Table 1.

Analysis of aim 2: The agreement between the presence of metabolic syndrome diagnosed by the Joint Interim Statement definition and an updated definition was calculated using the Cohen's kappa coefficient. Overall and Hispanic/Latino subgroup prevalence rates were estimated for men and women, separately, and are presented in Table 2 along with kappa coefficient values. The difference in prevalence rates estimated by each metabolic syndrome criteria was also calculated.

Analysis of aim 3: The association between presence of the metabolic syndrome and presence of CHD was examined using logistic regression. Two separate logistic regression models were fitted, one with each metabolic syndrome criteria as the independent variable. CHD was entered as a dichotomous dependent variable. Both logistic regression models adjusted for the following variables: age, sex, Hispanic/Latino subgroup, current or previous smoking history, education, total household income and HCHS/SOL study site. Odds ratios and *p*-values, and confidence intervals for each model are presented in Table 3. All statistical tests were two-sided at the 0.05 significance level.

Missing Data

Only participants with available data on metabolic syndrome components, CHD and the covariates listed (age, sex, Hispanic/Latino subgroup, current or previous smoking history, education, total household income and study site) were used in this study. A total of 9,763 women and 6,526 men (total n=16,289) were available for these analyses.

Chapter 4

RESULTS

Descriptive Characteristics of the Study Sample

The study sample was comprised by 9,763 women and 6,526 men (total n=16,289). Approximately 10.0% of individuals identified as Dominican, 7.4% as Central American, 20.0% as Cuban, 37.4% as Mexican, 16.1% as Puerto Rican and 5.0% as South American. The mean age for men and women are 40.2 and 41.8 years, respectively. Mean waist circumference value was 98.2 cm for men and 96.6 cm for women. The percentage of individuals with prevalent CHD was 6.8% men and 5.4% women. Further descriptive characteristics of the study sample are presented in Table 1.

Optimal Waist Circumference Cut-points

ROC analyses were used to identify optimal waist circumference cut-points for Hispanic/Latino men and women, separately. We examined sensitivity and specificity values of waist circumference to identify the presence of CHD. Table 2 presents sensitivity and specificity values across different waist circumference values for both men and women. The value with the largest sum of sensitivity and specificity was selected as the optimal cut point waist circumference cut-point. According to these selection criteria, the optimal waist circumference value for men with a sensitivity of 50.6% and a specificity of 64.0% was 102 cm. This value is in line with the current recommendations for waist circumference cut-points in men outlined in the JIS metabolic syndrome definition.

For women, however, the optimal waist circumference value was 97 cm, which yielded a sensitivity of 65.4% and a specificity of 51.3%. This value is higher than the current IJS recommendations for waist circumference in women, which is 88 cm. Our analyses indicated that when identifying the presence of CHD among Hispanic/Latino women, a cut-point of 88 cm has a great level of sensitivity at 88.7% while significantly compromising specificity which was found to be at only 24.2%.

Additional ROC analyses were conducted to identify optimal waist circumference cut-points to predict other CVD outcomes. These outcomes included CHD without the presence of angina as well as CVD, which was defined as the presence of CHD in addition to a history of stroke. Similar to the previous analyses presented, these analyses were conducted for Hispanic/Latino men and women, separately. Sensitivity and specificity values for each outcome are presented in Table 3. Results were in line to our initial analyses and supported a cut-point of 102 cm for Hispanic/Latino men and 97 cm for Hispanic/Latino women.

Prevalence of Metabolic Syndrome by Definition

Based on the previous results, and using a waist circumference cut-point of 97 cm for women, we updated the metabolic syndrome criteria and estimated new age-adjusted prevalence estimates for metabolic syndrome among our sample. This updated definition generated lower prevalence estimates than the original JIS metabolic syndrome definition. The original JIS definition and our updated definition differed in classifying 5.1% of women in our overall sample. Furthermore, the Cohen's kappa coefficient, which measures the level of agreement between definitions, was 0.89 indicating some disagreement between the original JIS definition and our updated definition of the metabolic.

In addition to the overall results, we estimated prevalence estimates and level of agreement among women across the different Hispanic/Latino subgroups. These results are presented in Table 3. The lowest level of agreement between definitions was among Dominicans and Mexicans (κ=0.86), and the highest level of agreement was found among South Americans (κ=0.90). Further, it is important to note that across the different subgroups, between-sex differences were less pronounced when using the updated metabolic syndrome definition (for women) than the original IJS definition.

Updated Metabolic Syndrome Definition and CHD

In order to examine the association between the presence of metabolic syndrome and CHD, two separate logistic regression models were fitted, one with each metabolic syndrome criteria as the independent variable. When using the traditional IJS definition for the metabolic syndrome, we found that adjusting for age, Hispanic/Latino subgroup, smoking, education and household income, the presence of the metabolic syndrome was associated with a 2.60 increase in the odds of having CHD (95% CI: 1.94-3.49).

In the case of our updated definition, the presence of metabolic syndrome was associated with an increase of 2.46 in the odds of presenting with CHD (1.82-3.1) after controlling for the same covariates. This suggests that although the cut-point for waist circumference was higher at 97 cm, the predictive value of our updated definition of the metabolic syndrome is comparable to that recommended in the IJS.

IJS Metabolic Syndrome Definition vs. Updated Definition

In an effort to illustrate the difference between individuals meeting IJS criteria for the metabolic syndrome and our updated criteria, we estimated mean cardiovascular risk factor values among individuals in these two groups as well as among individuals not meeting metabolic syndrome criteria under either definition. These results are presented in Table 4. Of note is the fact that mean values for most metabolic syndrome components, with the exception of systolic blood pressure and triglycerides, were comparable between the group without metabolic syndrome and those meeting IJS criteria.

Similarly, we estimated the percentage of individuals with prevalent CHD, diabetes mellitus and stroke on each group. Figure 1A shows prevalent CHD among participants meeting metabolic syndrome criteria according to our updated definition (*right panel)*, participants meeting criteria according to the traditional IJS definition *(center panel)*, and individuals not meeting metabolic syndrome criteria under either definition *(left panel)*. Similar comparisons were made for prevalent stroke and diabetes mellitus on Figures 1B and 1C. As can be noted in these figures, either definition identified participants with increased risk for CHD, stroke and diabetes mellitus, but the presence of any condition was highest among subjects who met our updated criteria for the metabolic syndrome.

Chapter 5

DISCUSSION

In this paper, we aimed to establish optimal definitions for abdominal obesity among US Hispanic/Latino men and women to predict the presence of CHD. For the first time, we provide empirically-derived recommendations for waist circumference cut-points in a large epidemiological sample of Hispanic/Latinos living in the US. Our results indicate than among US Hispanic/Latino adults, waist circumference cut-points of >102 cm in men and >97 cm in women provide optimal discrimination for cardiovascular risk as judged by the presence of CHD. When using these cut-points to create an updated metabolic syndrome definition among women, we found disagreement between our updated definition and the current IJS criteria for metabolic syndrome. The prevalence of the metabolic syndrome was overestimated (about 5% points) among women based on IJS criteria when compared to our updated definition. Furthermore, we examined the association between our updated criteria and the presence of CHD, controlling for relevant covariates including age, Hispanic/Latino subgroup, smoking, education and household income. We determined that the performance of our updated metabolic syndrome definition as a CHD covariate was comparable to that of the IJS definition.

The optimal waist circumference value to detect the presence of CHD among Hispanic/Latino men in our sample was 102 cm. This value is in line with current recommendations for waist circumference definitions for Non-Hispanic White males made in the IJS metabolic syndrome criteria. Our results suggest, however, that the optimal waist circumference cut-point to predict the presence of CHD among US

Hispanic/Latino women is 97 cm. This value is in disagreement with current recommendation outlined in the IJS metabolic syndrome definition. In fact, current recommendations for waist circumference cut-point for Non-Hispanic White women, 88 cm, yielded high levels of sensitivity at 88.7%, but compromised specificity at only 24.2%.

While our study is the first to estimate empirically validated cut-points of abdominal obesity for Hispanic/Latino men and women in the US, other groups have attempted to provide ethnic-specific cut-points to predict the presence of cardiometabolic risk among Central and South American Hispanics outside the US. Several outcome variables have been used across these studies, including cardiovascular endpoints such as abnormal carotid intima-media thickness and cardiovascular disease, as well as cardiometabolic risk factors such as hypertension, abnormal lipid profile and obesity. Groups using cardiovascular end-points, such as the PREVENCION study, a population based study of 1,439 Peruvian adults recommended that cut-points of 97 cm in men and 87 cm in women were optimal in determining the presence of abnormal *carotid intima-media thickness* and *manifest cardiovascular disease* (Medina-Lezama et al., 2010). In regards to cardiometabolic risk factors, the Mexican National Survey, which recruited 11,730 men and 26,647 women (Sanchez-Castillo et al., 2003) established that waist circumference cut-points for predicting the presence of *T2DM* and *hypertension* were 98 for men and 96 for women. Other estimates have been provided by groups in South America based on smaller samples. For example, studies in Colombia (Perez et al., 2003) and Brazil (Barbosa et al., 2006) have determine that 84 cm is an optimal cut-point to detect the presence of *obesity* (defined by elevated BMI), and 88 cm to detect *abnormal lipid profiles*.

It is important to note that comparability across all of these studies is challenging given differences in methodological designs (population based vs. convenient samples) and most importantly, the choice of a diagnostic outcome, or reference standard (hypertension, obesity, abnormal lipid profiles, abnormal carotid intima media thickness, T2DM, manifest cardiovascular disease). A consideration of ROC analysis, the method used across all of these different studies, is that the choice of an optimal cut-point depends entirely on the outcome against which the ROC curve is to be constructed (Kraemer et al., 2004). Therefore, the choice of reference standard should be based upon the purpose to which the categorical classification is to be put. Similarly, the outcome should reflect a true state or diagnosis given that arbitrary dichotomization of outcomes may potentially introduce inaccuracy to the ROC analysis.

Our results indicate that the performance of our updated metabolic syndrome definition as a CHD covariate was comparable to that of the IJS definition. In fact, in the multivariate logistic regression model predicting the presence of CHD, which included covariates such as age, Hispanic/Latino subgroup, smoking, education and household income, the odds ratio for our updated metabolic syndrome definition was 2.46 (95% CI=1.82-3.31), compared to 2.60 (1.94-3.49) for the current JIS definition. Other reports have also shown that although significant changes in prevalent changes result from different definitions, their association with cardiometabolic correlates are often not notably affected.

Our results indicate there is considerable disagreement in the prevalence of metabolic syndrome defined according to the IJS criteria and by our updated definition. In general, it has been the case that the misclassification of obesity in certain ethnic groups has resulted in missing obesity and cardiovascular risk in large numbers of people. This has been especially relevant for populations of East Asian and South Asian origin(Rao et al., 2015). Our data suggest, however, that the misclassification of abdominal obesity among Hispanic/Latino adults results in an overdiagnosis of this component and therefore, in the overall prevalence of the metabolic syndrome. There was a 5.2% difference in the prevalence of the metabolic syndrome among women diagnosed with our updated definition (30.1%) when compared to the IJS criteria (35.3%). Although still significantly higher than the prevalence among other ethnic groups, these estimates are closer to the rates of metabolic syndrome observed among Non-Hispanic Whites and Blacks (Beltran-Sanchez, Harhay, Harhay, & McElligott, 2013). The latest prevalence estimated among US adults based on data from the 2010 NHANES indicated that the metabolic syndrome is prevalent among 20.3% and 24.5% of Non-Hispanic White and Black women, respectively.

The substantial difference in the prevalence estimates of metabolic syndrome under each definition is not surprising given that a remarkable feature of our data, noted in the primary metabolic syndrome prevalence study by Heiss et al (2014) among HCHS/SOL participants, is the high proportion of women who met the metabolic syndrome IJS criterion of three or more factor by virtue of exceeding the threshold value for abdominal girth (88 cm). In fact, approximately 96% of women in the overall sample had abdominal obesity, compared to only 73% of men. The prevalence of this component was remarkable high regardless of Hispanic/Latino background or age group. As expected given the high proportion of women meeting abdominal obesity criteria, the mean waist circumference values were also remarkably high across age groups (Heiss et al., 2014). The prevalence of the abdominal obesity component among US Hispanic/Latino women is striking, particularly when compared to the prevalence of this component among other ethnic groups. Data from NHANES 2010 indicated that abdominal obesity is prevalent only among 62.4% of Non-Hispanic women and among 79.3% of Black women (Beltran-Sanchez et al., 2013). This evidence supports the need for ethnic-specific waist circumference cut-points for US Hispanic/Latino women.

Overdiagnosis of obesity has also occurred among other ethnic minority groups. For example, using NHANES III data, a study compared BMI with total body fat and percentage body fat (%BF) measured through bioelectrical impedance among Black and Non-Hispanic White adults (Burkhauser & Cawley, 2008). They showed that, in spite of having a significantly higher BMI, Blacks had between 1.3 kg (men) and 3.2 kg (women) greater fat-free mass than Non-Hispanic Whites. When %BF, instead of BMI, was used to define obesity, the race/ethnic gap in obesity prevalence decreased significantly (particularly among women). Overdiagnosis of obesity is not limited to Blacks. It has also been demonstrated that for the same level of body fat, Polynesians have a 4.5 kg/m^2 higher BMI than non-Hispanic whites (Deurenberg, Yap, & van Staveren, 1998). Although waist circumference measures are less susceptive to the contribution of lean body mass than BMI, it is possible that the difference in waist circumference cut-points among Hispanic/Latino and other groups is a result of differences in %BF. This highlights the need for research on non-anthropometric imaging techniques to measure adiposity and predict cardiovascular risk among ethnic minority populations. These include imaging techniques such as computer tomography, magnetic resonance imaging and ultrasonography, as well as other modalities such as DEXA, bioelectrical impedance analysis and air displacement plethysmography. Their performance among many ethnic groups including Hispanic/Latinos has not yet been studied (Rao et al., 2015).

Important strengths of our study include our large sample size and our population-based approach. The HCHS/SOL cohort was selected through a stratified multi-stage area probability sample (Lavange et al., 2010), which allows us to estimate prevalence of diseases and baseline risk factors among non-institutionalized Hispanic/Latino adults aged 18-74 residing in four defines community areas (Miami, FL; Chicago, IL; San Diego, CA; and the Bronx, NY). Although the target population is limited to the four communities rather than the entire nation, HCHS/SOL's hybrid design, which uses probability sampling within pre-selected diverse regions, is superior to the convenience samples, which are typically exploited in epidemiological cohort studies. Furthermore, our study aimed to include Hispanic/Latino adults of various subgroups such as Dominicans, Central and South Americans, Mexicans, Puerto Ricans and Cubans. This ensured the representation of US Hispanic/Latino adults of various ancestries enhancing the generalizability of our results.

Our study is not without limitations. This particular study aimed to recruit and represent Hispanic/Latino adults of various subgroups living in the US. As such, it is an ideal cohort for the estimation of ethnic-specific definitions of abdominal obesity among US Hispanic/Latinos. However, due to the fact that it did not include individuals of other ethnic groups, such as African-Americans or Caucasians, it did not allow for comparisons across ethnicities. Our study is also limited by its cross-sectional design. Given the fact that abdominal girth and presence of CHD were assessed at the same time, we are unable to infer temporal precedence. A prospective study examining the incidence and extent of cardiovascular problems between individuals with and without the metabolic syndrome according to our proposed cut-points is needed to further ascertain the accuracy of our abdominal obesity definition in classifying cardiovascular risk. Nevertheless, pending prospect data, our study provides important insight on the need to use ethnic-specific abdominal obesity definitions among US Hispanic/Latino adults.

Chapter 6

CONCLUSION

Taken together, our results indicate that among Hispanics/Latino adults living in the US, waist circumference cut points of 102 cm in men and 97 in women provide optimal discrimination for the presence of CHD. Using these cut-points in the context of an updated metabolic syndrome definition, we determined there was considerable disagreement between our definition and the current IJS metabolic syndrome definition. Current IJS criteria overestimated the prevalence of metabolic syndrome in approximately 5% of women in our sample, when compared to our updated definition. Finally, we examined the association between our updated metabolic syndrome criteria and CHD after adjusting for age, Hispanic/Latino subgroup, smoking, education and household income and determined that the performance of our definition in association with CHD was comparable to that of the IJS definition, further supporting the use of our definition of metabolic syndrome among Hispanic/Latino adults living in the US. Future reports should examine our recommended waist circumference definition cut-points and the performance of our updated metabolic syndrome definition as a predictor of cardiovascular risk among US Hispanic/Latinos in prospective designs.

Author Disclosure Statement

The authors of this manuscript have no conflict of interest to disclose.

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Table 1. Descriptive characteristics of study sample

	All (n=16289) Mean (SE)	Men (n=6526) Mean (SE)	Women (n=9763) Mean (SE)
Age, years	41.038 (0.247)	40.224 (0.307)	41.786 (0.284)
Hispanic subgroup			
Dominican, (%)	10.000	8.200	11.600
Central American, (%)	7.400	7.300	7.500
South American, (%)	5.000	4.800	5.200
Cuban, (%)	20.000	21.800	18.300
Mexican, (%)	37.400	36.600	38.100
Puerto Rican, (%)	16.100	17.000	15.300
Other, (%)	4.100	4.300	4.000
GAD or higher, (%)	67.600	68.200	67.100
Income			
< $ 10K, (%)	14.600	11.500	17.600
$10K - $20K, (%)	31.600	29.500	33.700
$20K - $40K, (%)	33.300	34.400	32.200
$40K - $75K, (%)	14.500	16.800	12.400
> $75K, (%)	5.900	7.900	4.000
Current smoking, (%)	21.400	26.800	16.400
Body mass index, km/m2	29.361 (0.093)	28.888 (0.100)	29.796 (0.134)
Waist circumference, cm	97.353 (0.222)	98.229 (0.258)	96.548 (0.311)
Systolic blood pressure, mmHg	119.883 (0.247)	123.396 (0.281)	116.654 (0.319)
Diastolic blood pressure, mmHg	72.169 (0.169)	73.534 (0.224)	70.914 (0.203)
Total Cholesterol, mg/dL	194.293 (0.555)	194.422 (0.803)	194.174 (0.690)
HDL-Cholesterol, mg/dL	48.516 (0.167)	44.85 (0.210)	51.868 (0.225)
LDL-Cholesterol, mg/dL	119.737 (0.475)	121.132 (0.677)	118.485 (0.613)
Triglycerides, mg/dL	133.11 (1.294)	148.061 (2.265)	119.435 (1.131)
Glucose, gr/dL	101.815 (0.382)	104.273 (0.512)	99.562 (0.510)
Stroke, (%)	2.300	2.400	2.2
Diabetes mellitus, (%)	15.500	14.700	16.2
Coronary Heart Disease, (%)	6.000	6.800	5.400

* $p<0.05$; HDL= High density lipoprotein; LDL=Low density lipoprotein.

Table 2. Sensitivity and specificity of waist circumference measurements to predict manifest coronary heart disease

Gender	WC (cm)	Sensitivity (%)	Specificity (%)	Youden Index
Men	95	72.8	39.4	112.2
	96	69.7	42.6	112.3
	97	67.2	46.1	113.3
	98	64.8	49.6	114.4
	99	61.2	53.1	114.3
	100	56.4	57.0	113.4
	101	53.4	61.0	114.4
	102*	**50.6**	**64.0**	**114.6**
	103	47.0	66.6	113.6
	104	42.5	69.3	111.8
	105	38.8	72.0	110.8
	106	37.5	74.3	111.8
	107	36.3	76.5	112.8
Women	87	90.0	21.5	111.5
	88	87.7	24.2	111.9
	89	85.5	27.0	112.5
	90	84.4	29.7	114.1
	91	81.9	33.0	114.9
	92	78.7	36.0	114.7
	93	76.4	39.0	115.4
	94	73.1	42.1	115.2
	95	70.4	45.2	115.6
	96	68.1	48.3	116.4
	97*	**65.4**	**51.3**	116.7
	98	62.3	54.1	116.4
	99	58.5	57.1	115.6
	100	56.0	60.1	116.1

WC=waist circumference

Table 3. Sensitivity and specificity to predict other CVD outcomes

		CHD (no angina)			CVD		
Gender	**WC (cm)**	**Sensitivity (%)**	**Specificity (%)**	**Youden Index**	**Sensitivity (%)**	**Specificity (%)**	**Youden Index**
Men	95	74.5	39.4	113.9	74.0	39.6	113.6
	96	71.4	42.6	114.0	70.9	42.8	113.7
	97	69.4	46.1	115.5	68.6	46.3	114.9
	98	**67.0**	**49.5**	**116.5**	66.0	49.8	115.7
	99	63.2	53.1	116.3	62.3	53.3	115.6
	100	58.3	57.0	115.3	57.7	57.2	114.9
	101	55.0	61.0	116.0	54.7	61.3	116.0
	102	**52.3**	**63.9**	**116.3**	**52.3**	**64.3**	**116.5**
	103	49.0	66.6	115.6	48.4	66.9	115.3
	104	43.9	69.3	113.2	44.2	69.6	113.8
Women	90	85.9	29.4	115.3	84.0	29.6	113.6
	91	84.4	32.8	117.2	82.1	33.0	115.1
	92	81.4	35.8	117.2	79.0	36.0	115.0
	93	78.7	38.8	117.5	76.0	39.0	115.0
	94	75.2	41.9	117.1	72.9	42.1	115.0
	95	71.7	45.0	116.7	69.7	45.2	114.8
	96	70.0	48.0	118.0	68.0	48.3	116.2
	97	**67.3**	**51.0**	**118.3**	**65.1**	**51.3**	**116.3**
	98	**64.5**	**53.8**	**118.3**	**62.9**	**54.1**	**116.9**
	99	60.6	56.9	117.4	58.6	57.1	115.7
	100	58.3	59.8	118.2	56.2	60.1	116.3

CHD=Coronary Heart Disease; CVD=Cardiovascular Disease; WC=Waist Circumference.

Table 4. Age-standardized prevalence of the metabolic syndrome according to both definitions in men and women across Hispanic/Latino subgroups

	Women			Men
	JIS Definition	**Updated Definition**	**k Statistic**	**JIS Definition/ Updated Definition**
Overall	0.353 (0.338 - 0.367)	0.301 (0.288 - 0.315)	0.8859	0.330 (0.315 - 0.345)
Dominican	0.317 (0.283 - 0.350)	0.255 (0.224 - 0.287)	0.8551	0.289 (0.242 - 0.335)
Central American	0.379 (0.348 - 0.409)	0.317 (0.287 - 0.348)	0.8696	0.321 (0.279 - 0.362)
Cuban	0.337 (0.308 - 0.366)	0.280 (0.254 - 0.306)	0.8626	0.343 (0.316 - 0.369)
Mexican	0.355 (0.328 - 0.381)	0.303 (0.278 - 0.328)	0.8925	0.332 (0.307 - 0.356)
Puerto Rican	0.405 (0.370 - 0.441)	0.356 (0.322 - 0.390)	0.8961	0.315 (0.277 - 0.352)
South American	0.260 (0.221 - 0.298)	0.227 (0.190 - 0.265)	0.9088	0.265 (0.214 - 0.315)
Mix/Other	0.384 (0.289 - 0.479)	0.361 (0.259 - 0.462)	0.9497	0.370 (0.285 - 0.456)

JIS= Joint Interim Statement.

Table 5. Metabolic syndrome as a predictor of Coronary Heart Disease among women

	JIS Definition		**Updated Definition**	
	OR (95% CI)	***p*-value**	**OR (95% CI)**	***p*-value**
Multivariate Model				
Age (10 years)	1.488 (1.331-1.665)	**<0.001***	1.514 (1.359-1.687)	**<0.001**
Central American	0.539 (0.318-0.913)	0.054	0.53 (0.315-0.894)	**0.046***
Cuban	0.573 (0.394-0.834)	**0.015***	0.558 (0.384-0.812)	**0.011***
Mexican	0.443 (0.309-0.633)	**<0.001***	0.434 (0.304-0.621)	**<0.001**
Puerto Rican	1.091 (0.781-1.524)	0.668	1.064 (0.758-1.495)	0.762
South American	0.756 (0.491-1.164)	0.286	0.719 (0.468-1.107)	0.208
More than one/Other Subgroup	1.506 (0.527-4.307)	0.521	1.434 (0.506-4.061)	0.569
Smoking	1.06 (0.773-1.453)	0.761	1.077 (0.781-1.485)	0.704
Education	1.064 (0.836-1.355)	0.671	1.068 (0.84-1.358)	0.653
Household Income	0.749 (0.661-0.85)	**<0.001***	0.753 (0.662-0.856)	**<0.001***
Metabolic Syndrome Definition	2.603 (1.942-3.491)	**<0.001***	2.457 (1.823-3.311)	**<0.001***

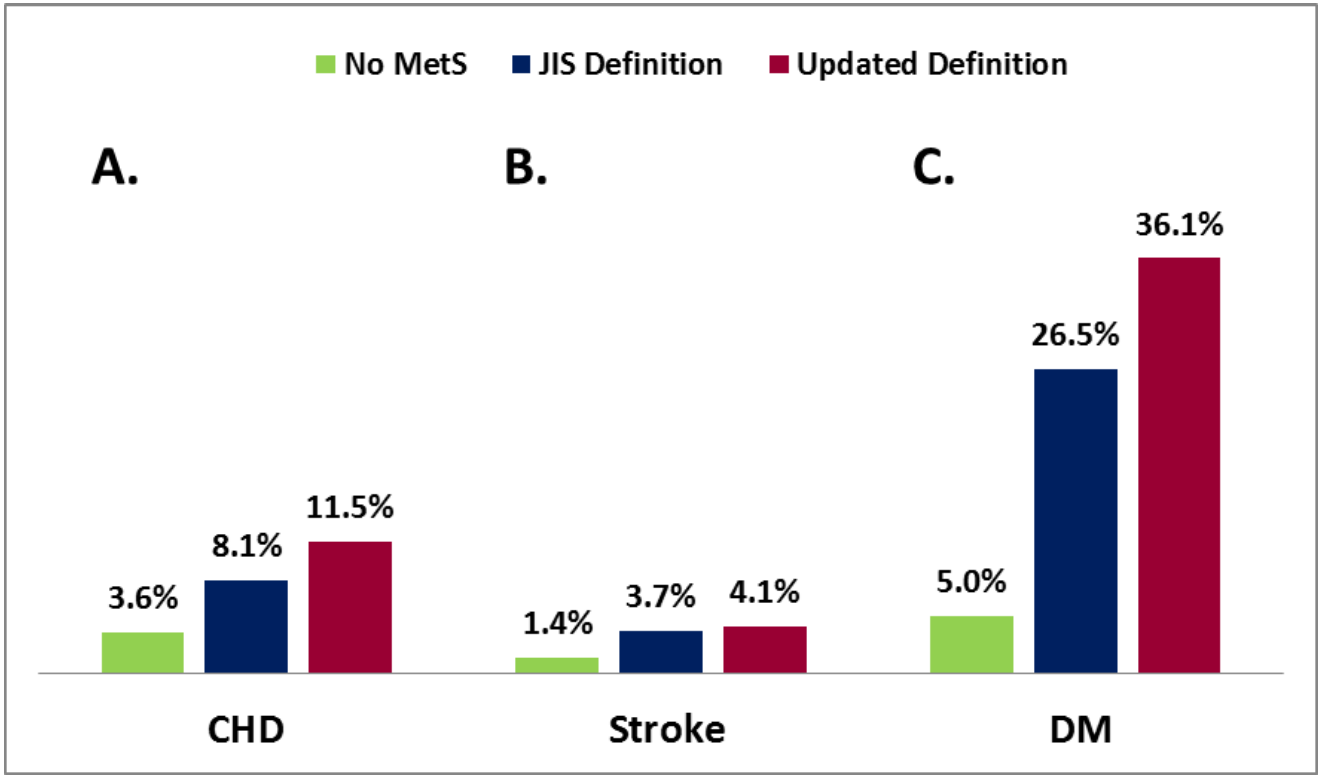
*$p<0.05$; JIS=Joint Interim Statement; OR=Odds Ratio; CI=Confidence Interval.

Table 6. Mean values of metabolic syndrome components among women by each metabolic syndrome definition

	No MetS	JIS Definition	Updated Definition
	Mean	**Mean**	**Mean**
MetS Components			
Waist Circumference	93.082	92.287	107.572
Systolic Blood Pressure	115.769	124.106	129.007
Diastolic Blood Pressure	69.621	73.001	77.96
HDL Cholesterol	51.581	48.434	41.538
Triglycerides	101.922	155.457	202.236
Fasting Glucose	94.177	106.152	118.843

MetS=Metabolic Syndrome; JIS= Joint Interim Statement; HDL=High-density Lipoprotein.

Figure 1. Prevalence of coronary heart disease, stroke and diabetes mellitus by metabolic syndrome definition



MetS=Metabolic syndrome; JIS=Joint Interim Statement; CHD=Coronary Heart Disease; DM= Diabetes Mellitus