METABOLIC SYNDROME AND SUBCLINICAL ATHEROSCLEROSIS: ASSOCIATION, REMODELING AND ITS ASSOCIATED RISK FACTORS

by

Julius Obiri Yeboah Asubonteng

MPH, Biostatistics, Yale University, 2008

Submitted to the Graduate Faculty of

the Department of Epidemiology and

the Graduate School of Public Health in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

University of Pittsburgh

2014

UNIVERSITY OF PITTSBURGH

GRADUATE SCHOOL OF PUBLIC HEALTH

This dissertation was presented

By

Julius Obiri Yeboah Asubonteng

It was defended on

April 11, 2014

and approved by

Committee Member: Faith Selzer, PhD, Research Assistant Professor, Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh

Committee Member: Stephen Wisniewski, PhD, Professor and Associate Dean for Research, Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh

Committee Member: Rebecca Thurston, PhD, Associate Professor of Psychiatry, Psychology, and Epidemiology, Department of Psychiatry, University of Pittsburgh

Committee Member: Suresh Mulukutla, MD, Assistant Professor of Medicine and Epidemiology, University of Pittsburgh Medical Center

Dissertation Advisor: Emma Barinas-Mitchell, PhD, Assistant Professor of Epidemiology, Graduate School of Public Health, University of Pittsburgh

Emma Barinas-Mitchell, PhD

METABOLIC SYNDROME AND SUBCLINICAL ATHEROSCLEROSIS: ASSOCIATION, REMODELING AND ITS ASSOCIATED RISK FACTORS

Julius Obiri Yeboah Asubonteng, PhD

University of Pittsburgh, 2014

ABSTRACT

This dissertation sought to examine the metabolic syndrome (MetS) and its association with subclinical atherosclerosis, carotid artery remodeling and its related risk factors, as well as the longitudinal effect of MetS status changes on carotid artery remodeling, in midlife women in three manuscripts.

In the first manuscript, the MetS, via all definitions, was significantly associated with measures of subclinical atherosclerosis. The MetS components most strongly and consistently associated with carotid IMT and plaque were higher blood pressure and greater fasting glucose across all definitions considered in the current study.

In the second manuscript, the MetS was significantly associated with maladaptive remodeling of the common carotid artery. Our findings also showed that the association between MetS and carotid artery remodeling was independent of select measure of inflammatory, hemodynamic, and metabolic risk factors. Finally, we observed differential maladaptive remodeling patterns of the common carotid artery with MetS status by race/ethnicity.

In the third manuscript, midlife women with persistent MetS status were observed to have maladaptive remodeling of the carotid artery compared to those who never developed MetS over time after adjusting for potential confounders. Higher systolic blood pressure and larger waist circumference were significant and consistent determinants of adverse carotid artery remodeling in our current study.

Each manuscript contributes uniquely to public health. Metabolic syndrome is associated with subclinical atherosclerosis in midlife women. Pharmacological intervention and lifestyle changes to target and prevent the metabolic syndrome construct or its components among midlife women may subsequently slow or reduce progression of atherosclerosis.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ACKNOWLEDGEMENTS

At long last the graduate school saga is over! The experiences of the last couple years have taught me a number of lessons both good and bad, and I'm equally humbled by them. For all those who have been part of this saga, I'm grateful for your challenge, help and encouragement!

First, I owe a debt of gratitude to my academic advisor and committee member Dr. Faith Selzer, and my dissertation advisor Dr. Emma Barinas-Mitchell for their guidance and direction. To my committee members Dr. Suresh Mulukutla, Dr. Rebecca Thurston and Dr. Stephen Wisniewski, I could not have come this far without insightful comments and directions you offered me. I'll forever be grateful to you all for teaching me the ropes of research.

To my friends, Twaha Bukenya, you have been a wonderful friend, brother and mentor to me for the last 13 years. I'm what I'm today because of your kindness, ideas and direction. Thank you, Twaha! I hope to do the same to a fellow African as I go into the industry. Bob Tibo thanks a lot for your kindness since my Yale days. I'm now ready to go to East Africa with you!

To the friends I have made in Pittsburgh, Jessica White, Carrie Hanley, Ashima Singh, Nancy Niemczyk and Andrew Althouse, thank you all for having answers to my questions. Jessica, you're the best! Lori Smith, I couldn't have come to Pitt without your help and efforts. You're such a caring person, Thank you!

To my family, thanks for supporting me over the years. I have finally honored my promise. Charlie, the credit belongs to you! Thank you for believing in me. Eugene, without a doubt, your financial support made differences.

To the loving memory of my father, thanks a lot for teaching us the value of education. It has been a while since you left us, but I believe you are with us in spirit. I know you were worried about me back in my secondary school days, but I wish I could come home and report my progress thus far. Your concerns have shaped me to be a better person.

To my wife, Linda, you're the best! I'm sorry I had to be away all these years. Finally, I'm ready to shoulder the rest of the challenge with you.

To my children, I'm sorry for the pain I have put you guys through. Hopefully, you will grow up to appreciate and understand me better. Kofi, grown-ups go to school, too! Adjoa, daddie will come home soon. Kwaku, it's your turn now!

1.0 GENERAL INTRODUCTION

1.1 EPIDEMIOLOGY OF CARDIOVASCULAR DISEASE IN MIDLIFE WOMEN

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in women across all race and ethnic groups [1]. While the mortality rate due to CVD in the United States (US) over the last several decades has been declining, this rate of decline is slower for women than men [2] In 2009, the overall rate of death attributable to CVD was 237.1 per 100,000 persons. Among women, the death rate for whites was 190.4 per 100,000, and 267.9 per 100,000 for blacks [2].

While women experience almost as many CVD events as men, events in women tend to occur at an older age [3]. The risk of death from CVD in women lags 10 years behind that of men, although the gap in incidence rates narrows after menopause [4]. Data from the Center for Disease Control and Prevention (CDC) indicate that the prevalence of modifiable risk factors among women have increased over the last decade. There are also racial and ethnic differences in both CVD events and their risk factors. Rates of diabetes and obesity are on the rise and vary significantly by race and ethnicity. Data show that 31.3% of white women, 53.2% of black women, and 41.8% of Mexican-American women are obese, which tracks with the incidence of diabetes of 8.2% in white women, 15.3% in black women, and 16.9% in Mexican-American women. Black women have a 69% higher death rate from CVD compared to non-Hispanic white

women [5]. The disparity in CVD mortality rates by race and ethnicity appears to be in the prevalence of CVD risk factors [6]. There is also evidence of an age effect in the racial difference in CVD events, where greater disparities are found in younger age group [7].

While CVD is not curable, per se, the modification of risk factors associated with the disease, such as lifestyle changes including quitting smoking, engaging in physical activity and use of pharmacological intervention to target the risk factors of the CVD, has lowered CVD mortality rates in women by 23% since 2000 [8]. Traditional CVD risk factors in women include tobacco use, diabetes mellitus, hypertension, dyslipidemia, obesity, and an atherogenic diet. Not surprisingly, these same factors are also associated or correlated with the metabolic syndrome (MetS).

1.2 METABOLIC SYNDROME (MetS) CONSTRUCT

1.2.1 History of the concept of metabolic syndrome

The MetS was first described by Kylin, a Swedish physician, as a clustering of hypertension, hyperglycemia and gout [9]. Reaven reintroduced the concept via Syndrome X in 1988 and proposed that insulin resistance is the main underlying component behind MetS [10]. MetS is associated with a variety of other metabolic risk factors [11] and correlated with many conventional cardiovascular risk factors [12]. It is important to point out that Reaven was putting forward a pathophysiological construct rather than a clinical or diagnostic tool, and much of the confusion about MetS has come about largely due to the lack of appreciation for this

distinction. Interestingly, obesity was not one of the core components put forth in Reaven's seminal Syndrome X paper of 1988 [10].

Several publications have appeared since Reaven's seminal paper; however, the exact pathophysiological mechanism underlying the MetS is still unknown. The pathogenesis of MetS is suspected to be through the convergence of central obesity, physical inactivity, unhealthy diet and unknown genetic factors. The etiology of MetS has been argued over for the last two decades, and as per Reaven's proposition, some investigators suggest that the underlying pathophysiology of the MetS is insulin resistance, whereas others speculate that other metabolic risk factors may be involved as well [13]. Insulin resistance is clearly related to many of the components that define MetS, and several metabolic pathways are known to link insulin resistance to other risk factors such as central obesity [14, 15]. Visceral adiposity is thought to be a predominant etiological factor, and the theory suggests that metabolically active visceral adipose tissue releases fatty acids and a variety of adipokines, which are implicated in the development of the insulin resistance state [16]. Low grade inflammation has also been postulated to play a role in development of MetS [17] and is also linked to overall and visceral adiposity and insulin resistance.

The terminology used to describe MetS has changed over the years. It used to be referred to as Syndrome X and the insulin resistance syndrome, among others. Along with these name changes, many organizations have put forward their own definition of the MetS and the associated composition of factors characterizing the MetS. The goals of these organizations have guided their selection of criteria and cut-points that define the MetS.

1.3 DEFINITIONS OF METABOLIC SYNDROME

Table 1-1 describes four commonly used definitions of MetS. In 1998, the World Health Organization (WHO) was the first organization to define specific criteria in identifying people with MetS [18]. The WHO criteria included insulin resistance as the primary requirement in their definition. According to the definition, individuals are required to be either (1) insulin resistant, (2) diagnosed with type 2 diabetes or (3) have impaired glucose tolerance. This requirement of insulin resistance has hampered the widespread use of the WHO criteria to categorize individuals with or without MetS. Coupled with insulin resistance, the definition requires that individuals meet at least two of the following criteria: obesity, dyslipidemia, hypertension and micro-albuminuria.

To address the difficulty in using the WHO criteria, the European Group for the Study of Insulin Resistance (EGIR) developed its own criteria in 1999 [19]. The goal of EGIR was to modify the WHO criteria and make it practical to use. With respect to insulin resistance, EGIR proposed using fasting insulin as a measure or surrogate for insulin resistance. In using this method to determine insulin resistance, individuals with type 2 diabetes are excluded from EGIR criteria because fasting insulin is not an appropriate method to measure insulin resistance in those with diabetes. The technique to assess obesity was changed from hip-to-waist ratio to waist circumference. Furthermore, micro-albuminuria was excluded from their definition.

The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) proposed an alternative clinical definition for MetS in 2001. The aim of NCEP was to identify individuals at long-term risk for CVD, and who are likely to benefit from clinical intervention to mitigate the risk of CVD [17]. NCEP criteria placed equal importance on all

components of MetS as compared to other definitions, which placed a higher emphasis on glucose-related components. With respect to abdominal obesity, the National Institutes of Health (NIH) obesity clinical guidelines were used to define the cut-off points for abdominal obesity in US adults. A joint effort by American Heart Association (AHA) and the National Heart Lung and Blood Institute (NHLBI) in 2005 led to an updated version of the NCEP criteria [17]. While the components of the definition were maintained, lower cut-off points were incorporated for the determination of elevated fasting glucose levels from greater 110 mg/dL to 100 mg/dL [17]. The NCEP definition is used frequently because it is practical and easy to ascertain the components.

Following the publication of the NCEP-ATP III criteria, studies about the prevalence of MetS in different parts of the world have been published using varying definitions but the most commonly used definitions were NCEP-ATP III and WHO. In all, the prevalence of MetS is similar but the concordance across definitions is relatively poor [18, 20]. In a response to this concern, the International Diabetes Federation (IDF) introduced a new definition for MetS in 2005, which is similar to NCEP- ATP III definition, but with more emphasis on central obesity [21]. Furthermore, the cut-points for abdominal obesity are different based on ethnicity and nationality.

Given the definitions of MetS from various organizations, questions regarding the ability of the different MetS criteria to predict morbidity and mortality outcomes remain (Table 1-2). The predictive ability of the varying MetS definitions is a major concern to many investigators. To address this concern, IDF and NCEP teamed up with other organizations to develop guidelines for a definition based on what has been learned to date [22] . The findings from this collaborative effort are (1) that no single component should be obligatory in the composition of the definition, and (2) that a single set of cut-off points should be used for all components with

the exception of waist circumference where population specific values are applied. This collaboration reiterated that three abnormal metabolic components out of 5 are required for the positive classification of MetS [22].

The predictive capability of MetS in the classification of people at higher risk of incident CVD and diabetes remains an issue. Thus far, various definitions have shown different predictive values in assessing CVD risk. This raises the issue of developing a definition of MetS that is more robust in differentiating individuals at greater risk of CVD and diabetes. This difficulty might have led some to conclude, prematurely, that MetS is more of an educational concept than a diagnostic tool [23].

1.4 PATHOPHYSIOLOGY OF METABOLIC SYNDROME

The pathophysiology of MetS is unknown [16]. Many postulations regarding the evolution and mechanism of how MetS affects CVD risk and outcome have been suggested, but none has been accepted to be the primary culprit because many of the suspected mechanisms overlap (Figure 1), and it is difficult to tease them apart. The school of thought of Reaven and Ferrannini suggests that insulin resistance is the central underlying mechanism of MetS. This observation is based on the fact that insulin resistance is strongly associated with metabolic risk factors and correlated with CVD risk [10, 24]. Another highly suspected mechanism is central obesity, which is strongly associated with MetS [24]. Several other underlying mechanism include the release of free fatty acids from adipocytes [25], the chronic activation of the immune system [26], an altered glucocorticoid hormone activation [27] and, the contribution of

cytokines, hormones and other molecules released by adipocytes [28]. Aging and lifestyle factors, such as diets rich in saturated fats and carbohydrates and physical inactivity are also associated with the development of MetS [29].

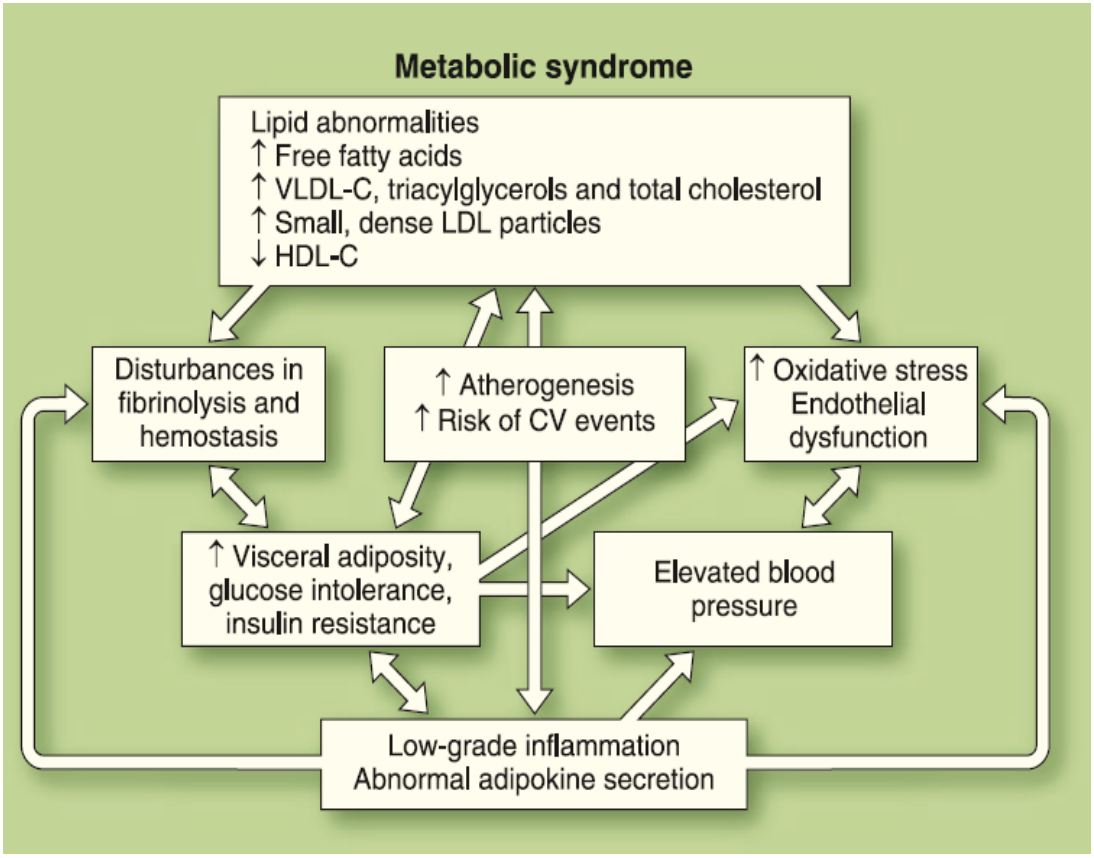


Figure 1-1 Pathogenesis of Metabolic Syndrome
Adapted from Grundy et al [30]

1.5 METABOLIC SYNDROME RISK FACTORS

Cardiovascular risk factors tend to cluster in the same way as do many of the most common factors that determine the MetS. These risk factors chiefly include central obesity, insulin resistance, hyperglycemia, hypertension and dyslipidemia. These abnormalities are often interrelated, and tend to share similar underlying mediators, mechanisms, and pathways [17].

1.5.1 Insulin resistance and glucose intolerance

Insulin resistance (IR) is a physiological condition in which cells fail to respond to the normal actions of the hormone insulin [15]. IR is widely considered the main factor initiating the biochemical processes underlying the metabolic syndrome [10]. Given this notion about MetS, the prevention and management of MetS have focused on controlling glucose and lipid levels to prevent damage to the vasculature. Although the pathophysiology processes underlying MetS are unclear, experimental and epidemiological evidence support the insulin resistance theory [31]. A defect in insulin action hampers the ability of insulin to suppress glucose production by the liver, which in turn affects glucose uptake disposal and metabolism in skeletal muscle and adipose tissue [15]. Insulin sensitivity is assessed by both the number and the affinity of insulin receptors, as well as the functional state of the intracellular signaling pathways that convert insulin binding to the various effectors [11]. A decrease in the number of insulin receptors is associated with insulin resistance [32]. Insulin is a potent growth factor that stimulates growth-promoting effects mediated through the mitogen-activated protein (MAP) kinase pathway [33]. The stimulation of MAP kinase pathways tends to be inactive in

individuals with insulin resistance leading to smooth muscle cell proliferation, higher collagen formation and elevated production of growth factors, and inflammatory cytokines that may contribute to the development of atherosclerosis [34].

1.5.2 Central obesity

Although obesity was not among the original Syndrome X risk factors postulated by Reaven, the MetS and its components are strongly associated and correlated with measures of obesity, such as waist circumferences [35]. The explanation attributed to this association is that excess adiposity lowers insulin-mediated glucose disposal and raises the likelihood of insulin resistance [36]. However, the relationship between adiposity and insulin resistance is not simple or straightforward. While weight per se is not a criterion for MetS, the distribution of fat and its location (visceral or subcutaneous) appears critical. Individuals with MetS tend to have an abnormal fat distribution with a high concentration of fat located centrally [17]. Both the accumulation of fat in a visceral location and in the upper body are highly correlated with insulin resistance [37].

In this context, body fat distribution, such as visceral adipose tissue accumulation, has been found to correlate significantly with metabolic abnormalities [38]. Waist circumference has been shown to explain more obesity related health risks compared to BMI [39]. However, others have reported that waist circumference provides additional information over BMI with respect to the risk of CVD and type 2 diabetes [40, 41]. Waist circumference and BMI, both indices of adiposity, are highly correlated and their predictive capabilities appear to be similar [42].

Abdominal obesity is one of the key components of MetS, and the overall tissue fat accumulation leading to lipotoxicity is a major cause of insulin resistance and beta-cell dysfunction and may contribute to accelerated atherosclerosis [43]. Insulin resistance leads to the increased delivery of free fatty acids (FFA) from adipose tissue and decreased FFA uptake by the muscles, resulting in elevated FFA influx to the liver [44]. In humans, there is a correlation between visceral fat accumulation and transportation of nonesterified fatty acids (NEFA) to the liver, and this raises the possibility that other factors are at play that could explain the altered metabolic profile of viscerally obese individuals [45]. Given that the metabolic syndrome is often found among people with visceral obesity, Despres et al argued that altered NEFA metabolism and endocrine function show that visceral adipose tissue is causally involved in the pathophysiology of MetS[46].

1.5.3 Hypertension

Elevated blood pressure, a risk factor for CVD, is included as a component of metabolic syndrome in all guidelines that define the construct. Although, some investigators have been reluctant to associate BP with MetS because analyses of the individual components of MetS have shown a weak association between hypertension and other components of MetS [47]. The association between elevated blood pressure and MetS is strongly correlated via obesity, and nearly half of individuals with hypertension or who are obese also have MetS [48]. Moreover, the link between insulin resistance and hypertension is well established, and it is connected via several different mechanisms [49]. Compensatory hyperinsulinemia in insulin resistance may cause elevated blood pressure by increasing sympathetic nervous system activation [50], and stimulation of vascular smooth muscle cell growth [51].

1.5.4 Dyslipidemia

Dyslipidemia is an integral component of metabolic syndrome, and a key contributor to higher cardiovascular risk in individuals with MetS. Low levels of high density lipoprotein HDL-cholesterol (HDL-c), elevated triglycerides and high levels of small, dense low density lipoprotein-cholesterol (LDL-c) molecules are the main lipid abnormalities used in definitions of MetS [52].

The processes that are thought to initiate dyslipidemia in individuals with MetS are known to start from insulin resistance at the level of adipose tissue [16]. This leads to increase in the release and a decrease in the clearance of FFAs. Adipocytes release FFA into the portal venous system and are taken up by the liver in proportion to their circulating concentration [53]. Among individuals with insulin resistance, the inhibition of FFA released from adipocytes is impaired, leading to higher levels of apolipoprotein B (Apo B), regulated at the posttranslational stage by the availability of lipids for synthesis of very low-density lipoprotein (VLDL) particles [54]. An increase in VLDL concentration could also result from a decrease in degradation or suppression of microsomal triglyceride transfer protein activity, which is the key component of the VLDL-assembly process [55]. The cholesterol ester transfer protein (CETP) and hepatic lipase are associated with the generation of low HDL levels and small, dense LDL[56].

1.6 OTHER RISK FACTORS OF METABOLIC SYNDROME

1.6.1 Risk factors associated with lifestyle

The epidemic of sedentary lifestyle and obesity has public health and economic consequences. Physical inactivity is associated with incident stroke, obesity, type 2 diabetes, insulin resistance, hypertension and other adverse conditions [57]. Furthermore, a sedentary lifestyle is also an independent risk factor for the development of MetS [58]. Yang et al observed that being physically active delayed or prevented the incidence of MetS [59].

The relationship between diet and development of MetS, however, has not been fully established. A recent systematic review by Crichton et al found that dairy consumption has a beneficial effect on the development of MetS. Seven of thirteen studies found that dairy intake was inversely associated with incident or prevalent MetS [60]. Consumption of whole-grains is inversely associated with MetS, whereas the consumption of refined-grains is positively associated with MetS [61]. A population - based cohort study conducted in Finland among middle-aged participants found that a reduction in sodium intake had a significant positive effect on the treatment of people with MetS via reduction in blood pressure [62].

The relationship between alcohol consumption and MetS is controversial. A cross-sectional analysis of data from 8,125 participants from National Health and Nutrition Examination Survey (NHANES) showed that mild to moderate alcohol consumption was associated with a lower prevalence of MetS. A beneficial effect of alcohol consumption was also found for lipids, waist circumference and fasting insulin [63]. Again, in using the 1999-2002

NHANES data to study the pattern of alcohol consumption and MetS, Fan et al observed that drinking in excess of dietary guidelines was associated with a greater prevalence of impaired fasting glucose or diabetes mellitus, hypertriglyceridemia, abdominal obesity and high blood pressure [64]. A prospective study conducted in Korea showed that heavy drinking was associated with a higher risk of developing MetS through its influence on the individual MetS components. Although, the risk of association varied with respect to the type of alcohol consumed [65]. In a large study conducted in Korea that assessed the association between alcohol consumption and the MetS, alcohol consumption was found to have a significant inverse association with low HDL-c. Also, there was dose-response relationship between alcohol consumption and the incidence of MetS, and the authors postulated that this finding might have been the result of the effect of alcohol on other components of MetS [66].

1.6.2 Genetics of metabolic syndrome

Genetics are suspected to play a role in the development of MetS and its individual components. Family and twin studies have shown that MetS and its components tend to cluster among families, especially among twins [67]. In a study of 2,508 male twin pairs, concordance for the clustering of three MetS components – diabetes, obesity and hypertension - was found in 31.6% for monozygotic pairs versus 6.7% for dizygotic pairs. [68]. A number of studies have sought to identify an underlying genetic link but to date no particular gene has emerged as a potential candidate [69]. In light of these efforts, some investigators have argued that there is no genetic basis for incident MetS [69]. In a genome-wide association study, no significant finding between MetS and candidate genes was observed, which lends some supports the notion that there is no genetic basis in the development of MetS [70].

1.7 CLINICAL OUTCOMES OF METABOLIC SYNDROME

Several prospective studies have reported an association between MetS and both incident CVD (Table 2) [71, 72], and type 2 diabetes mellitus [73]. Furthermore, people with MetS are prone to other co-morbid conditions, such as obstructive sleep apnea [74], gallstones [75], asthma, fatty liver disease, insulin resistance and polycystic ovarian syndrome in women [76].

MetS is a strong predictor of incident CVD events. In a systematic review of cardiovascular risk associated with the MetS as defined by the 2001 NCEP and the 2004 revised NCEP definition, MetS was observed to be associated with a 2-fold higher risk in CVD mortality and a 1.5 fold higher risk for all-cause mortality [71]. Findings from several studies have confirmed that CVD morbidity, mortality, and all-cause mortality are higher among individuals with MetS [71, 72]. In an NHANES III study, MetS was associated with prevalent myocardial infarctions and strokes [77]. In the Botnia study, Isomaa et al showed that middle-aged adults with MetS have a nearly a 3-fold higher risk of incident coronary heart disease, and more than a 2-fold higher risk for stroke [78]. There is also sex differential effect with CVD-risk related to MetS being one-third higher in women compared to men [12].

MetS is also a strong predictor of incident type 2 diabetes mellitus [12]. Several epidemiological studies put the risk of incident type 2 diabetes among people with MetS around 2 to 5-fold higher compared to those without MetS[79]. Several of the components of MetS appear to be more strongly associated with the development of type 2 diabetes. As expected, the evidence suggests that impaired fasting glucose is the component most strongly associated with incident type 2 diabetes [80]. Other studies have shown that both abdominal obesity and

hyperglycemia are strongly associated with incident type 2 diabetes [81]. Other studies have reported that MetS in and of itself is not predictive of type 2 diabetes when its individual components are also considered [82]. However, in the San Antonio Heart study, MetS was associated with incident type 2 diabetes independent of other CVD risk factors such as sex, age, race, family history of type 2 diabetes, fasting insulin and impaired glucose tolerance [83].

MetS in women is associated with higher risk of CVD as compared to men. Gami et al showed that CVD risk associated with MetS was one-third higher in women than in men [12]. However, the reasons for this disparity are not clearly understood. It has been postulated that central obesity, which is more prevalent among women than men independent of age, maybe the reason for higher CVD risk among women [84]. It has also been suggested that changes that occur in women during the menopausal transition, such as a decrease in HDL-c, or an increase in both LDL, and the smaller and more dense VLDL particles, put women at a higher risk of CVD compared to men (Blake, Otvos et al. 2002). The fact that MetS in women predicts the incidence of both type 2 diabetes and CVD is not surprising given the fact that the individual components of MetS are also known risk factors for CVD and type 2 diabetes. Moreover, MetS and its components are associated with the early markers of atherosclerosis [85].

1.8 TREATMENT OF METABOLIC SYNDROME

Given that MetS syndrome is associated with a higher risk for the development of type 2 diabetes and CVD [71], it is important to treat individuals with this phenotype to lower their risk or delay the onset of clinical outcomes. The clinical significance, however, of MetS is controversial. Nonetheless, it is critical to identify individuals with MetS so that effective and

early treatment can be initiated to mitigate the effects of MetS, and reduce the incidence of disease associated with it. Lifestyle modifications including, a healthy diet, physical activity, cessation of smoking and weight control/loss, and pharmacological intervention targeting specific MetS components are the main treatment options in the management of metabolic syndrome [86].

1.8.1 Lifestyle modifications

Engaging in behaviors that help to encourage weight loss are first-line treatments for MetS [86]. Weight loss has been found to be effective in treating obesity, hypertension, insulin resistance and the other components of MetS. Even a small amount of weight loss can have a significant impact in lowering triglycerides and subsequently increasing HDL-cholesterol [17]. In the Finnish Diabetes Prevention study, the lifestyle intervention alone, consisting of individualized counseling, physical activity and increasing intake of fiber, was associated with a reduction in abdominal obesity and the overall prevalence of MetS in the long term [86].

Dietary intake has been shown to have a significant impact on the resolution of MetS and its components. Besides weight loss and a restriction in caloric intake, a diet high in unsaturated fats and complex carbohydrates and low in sodium, is recommended to be followed by individuals with MetS to reduce and/or maintain weight.[17]. Consumption of foods low in carbohydrates tends to have a favorable effect on the MetS and serum lipid profiles. However, the value of low carbohydrate diets in the long term have been questioned because they are difficult to maintain [87].

Regular exercise has also been shown to influence MetS and its components, but it is not known if exercise can prevent or treat MetS [88]. Middle-aged Finnish men who engaged in moderate or high-intensity leisure-time physical activity at least 3 hours / week were half as likely as sedentary men to develop MetS during the 4 year follow-up period [88]. Also, participation in resistance type exercises improved MetS status among adults with impaired glucose tolerance [89]. Furthermore, long-term physical activity, without weight loss, may potentially prevent MetS [90].

1.8.2 Pharmacological intervention

Individuals with MetS stand to benefit from pharmacologic approaches to modify CVD risk factors. It must be pointed out that there is no specific pharmacological intervention for individuals with MetS. The current treatment guidelines specify that the focus of treatment must target the individual risk factors separately with one or multiple drugs, if necessary [52].

1.9 CRITICISM AND LIMITATIONS OF METABOLIC SYNDROME CONSTRUCT

The concept of MetS has been criticized on the basis of its pathophysiological underpinning as well as the clinical utility of the construct [31]. A number of organizations have proposed different definitions for the MetS concept with various emphases on risk factors for CVD and type 2 diabetes. The emphases on various risk factors, however, may have created confusion about the usefulness of MetS in clinical practice. This has led some investigators to

question the essence of MetS because the etiology is unknown [31]. The pathogenesis of MetS is suspected to be multifactorial. Hanley et al have demonstrated that metabolic abnormalities cluster together to a greater extent than would be expected by chance alone [91]. There are questions with respect to the risk associated with having the MetS construct and the individual components of the MetS. However, MetS has been associated with higher CVD events and the development of diabetes [12]. On the contrary, other studies have also shown that MetS does not predict CVD risk beyond the additive effects of the individual MetS components [92]. In the same vein, several studies have reported that fasting glucose alone is a good, if not better predictor, of type 2 diabetes than MetS [82]. With respect to predicting CVD risk, MetS did not perform any better than the Framingham Risk Score (FRS) [93]. However, Sipila et al have shown that MetS is a significant predictor of CVD after adjusting for the FRS [94].

The definition of MetS and its individual components have been recalibrated periodically given the debates that have stymied its usefulness in a clinical setting. The nature of the binary construct of MetS risk factors is also a source of debate among investigators. Some have argued that using a binary variable to classify a set of risk factors could lead to information loss, and therefore the questions about the predictive power of the MetS construct in discriminating those at risk [95]. Given the extent of these concerns, a WHO expert consultation group issued a report on the utility of MetS concept in relation to pathophysiology, epidemiology, clinical work and public health, while recognizing the limited usefulness of the MetS construct as a diagnostic or management tool [96].

The risk of CVD and type 2 diabetes increases with an increasing number of MetS components [97] such that, an individual positive for all 5 MetS components would be expected to be at much greater risk of CVD and possibly type 2 diabetes than someone positive for 4 or

fewer individual components. The effect of each of individual risk factors of MetS is likely not the same, and so to treat them the same is problematic [95]. Moreover, it is important to recognize that the MetS construct does not account for or incorporate important CVD risk factors such as age, sex, smoking, family history and physical activity levels, all of which are associated with higher cardiovascular risk [76]. For MetS to be a putative risk factor for both CVD and type 2 diabetes, all other possible confounding factors need to be controlled for in order to tease out the exact effect of the MetS construct on the risk for future CVD and diabetes events.

1.10 EPIDEMIOLOGY OF METABOLIC SYNDROME IN MIDLIFE WOMEN

The prevalence of MetS increases with age [98]. This observation has been made in all races and ethnic groups around the world with varying levels with regards to gender. Using data from (NHANES) III, Ford et al found the overall prevalence of MetS in an adult population to be 24%, with the prevalence increasing from 6.7% among those 20-29 years of age to 43.3% among those 60-69 years of age [99]. Among US adults, no significant gender difference was observed with respect to prevalence of MetS (23.7 % in women and 24.0% in men) [99]. Among racial and ethnic groups in the US, the highest prevalence of MetS was found in Hispanics (32%) as compared to Whites (22%) and Blacks (22%) [99]. In women, the prevalence was lower among Whites than among Blacks or Mexican American women [100].

The epidemiology of MetS among midlife women varies depending on the definition that is used to characterize the prevalence. In a study conducted in Sweden, the prevalence of the MetS varied with the definition used and ranged from 10 to 15% among midlife women [29]. In a Korean study, using NCEP-ATP III criteria, the age-adjusted prevalence of MetS in midlife women was 30.0%, nearly twice the levels found among men. Furthermore, the findings also showed a rapid increase in the prevalence of MetS from the age of 50 through 59 [22]. In a cross-sectional study conducted in an urban Iranian city, the prevalence of MetS among middle aged women was 31% [43]. While there are a number of prevalence studies of the MetS spanning many countries across the world and incorporating various definitions of MetS, no study has evaluated different definitions of MetS in midlife women in the United States.

Table 1-1 Metabolic syndrome definitions

	WHO	NCEP ATP III	AHA/NHLBI	IDF
	WHO requires a person to have type 2 diabetes mellitus or impaired glucose tolerance and ≥ 2 of the following:	NCEP requires any three of the five criteria to be met	AHA/NHLBI requires any three of the five criteria to be met	IDF requires a person to have central obesity as defined by waist criterion below (with various ethnicity specification) and ≥ 2 of the following:
Obesity	Waist-hip ratio >0.90 in men >0.85 in women and/or BMI >30 kg/m^2	Waist (≥ 102 cm or ≥ 40 inches) in men (≥ 88 cm or ≥35 inches) in women	Waist (≥ 102 cm or ≥ 40 inches) in men (≥ 88 cm or ≥35 inches) in women	Waist ≥ 94 cm for European men ≥ 80 cm in European women; ethnicity-specific values for other group
Blood pressure	≥ 140/90 mmHg or on antihypertensive medication	≥130/85mmHg or on medication	≥130/85mmHg or on medication	≥130/85 mmHg or antihypertensive medication
Triglycerides	≥150 mg/dL	≥150 mg/dL on triglycerides-lowering medication	≥150 mg/dL on triglycerides-lowering medication	>150 mg/dL or triglycerides-lowering medication
HDL-cholesterol	<35 mg/dL in men <39 mg/dL in women	< 40 mg/dL in men < 50 mg/dL in women or HDL-raising medication	< 40 mg/dL in men < 50 mg/dL in women or HDL-raising medication	<40 mg/dL in men <50 mg/dL in women or HDL-raising medication
Fasting		≥110 mg/dL or on	≥100 mg/dL or on anti-	≥ 100 mg/dL or previously diagnosed type 2

Table 1 Continued

	WHO	NCEP ATP III	AHA/NHLBI	IDF
plasma glucose		anti-diabetic therapy	diabetic therapy	diabetes
Micro albuminuria	Overnight urinary albumin excretion rate >20 mg/min			

WHO, World Health Organization; NCEP, National Cholesterol Education Program; AHA/NHLBI, American Heart Association / National Heart, Lung, and Blood Institute; IDF, International Diabetes Federation; *, Drug treatment is an alternative.

Table 1-2 Studies of the Metabolic Syndrome (MetS) Associated with the risk of Cardiovascular Disease

Study Name and Author	Study population	Definition of MetS	Prevalence of the MetS at baseline	Duration of follow-up	Variables controlled for in the study	Endpoint or measurable outcome	Results or findings
Health ABC, Holvoet et al[101]	3033 men and women aged 70-79 years in the US	ATP III	38%	Questionnaire every 6 months	Sex, age, ethnicity, smoking	CHD incidence	MetS is a risk factor for CHD
Framingham Offspring Study, Rutter et al[102]	3037 men and women aged 26-82. No history of diabetes or family CVD	ATP III	23.8%	7 years	Age, sex	CVD incidence	MetS is independent predictor of CVD events
San Antonio Heart Study, Hunt et al[103]	2815 men and women age 25-64 years in the US	ATP III	25.2%	12.7 years; Questionnaire, telephone interviews	Age, sex, race	CVD - all cause mortality	MetS predictive of CVD in the study
ARIC Study, McNeill et al[104]	12089 men and women aged 45-64 years in US. Participants with diabetes and family history of CVD are excluded	ATP III	23.5%	11 years, Physical examination	Race, age, site, smoking, LDL-cholesterol	CHD-Stroke incidences	Participants with MetS were at increased risk of long term CVD outcome
Botnia Study, Isomaa et al[78]	4483 men and women age 35-70 years in Sweden and Finland	WHO	Not available	Median follow-up 6.9	Age, Sex, smoking, LDL-cholesterol	CVD morbidity and mortality	MetS identified participants with increased CVD morbidity and mortality
Bruneck Study, Bonora et al[105]	888 men and women aged 40-79 years in Italy	WHO	34.1%	5 years	Age, sex, smoking, alcohol, physical activity, history of CVD, LDL-cholesterol	CHD incidence	Participants with MetS are at increased risk for CHD
British Women's	Women aged 60-	IDF	48%	15778 woman-	Age, smoking,	CVD- all-cause	MetS is modestly

Table 1-2 Continued

Study Name and Author	Study population	Definition of MetS	Prevalence of the MetS at baseline	Duration of follow-up	Variables controlled for in the study	Endpoint or measurable outcome	Results or findings
Heart and Health Study, Lawlor et al [106]	79 years, free of CHD at baseline in United Kingdom			years	inactivity and life-course socioeconomic position	mortality	associated with CHD risk in older women
Kuopio Ischemic Heart Disease, Wang et al[107]	1025 men and women aged 65-74 years in Finland	IDF	Not available	13.5 years	Age, gender, tobacco, current smoking, consumption of alcohol and physical activity at leisure and total cholesterol	CVD-mortality	MetS is a marker of CVD risk
The Malmo Diet and Cancer study , Nilsson et al[108]	5047 men and women, middle-aged, non-diabetic participant in Sweden	IDF/ ATP/EGIR	21.9%	11 years	Age, gender, LDL-cholesterol, life-style factors	CVD events	IDF was not superior to ATP and EGIR for prediction of event events

CVD, Cardiovascular disease; CHD, Coronary Heart Disease; IDF, International diabetes Federation; WHO, World Health Organization; ATP III, Adult Treatment Panel III; EGIR, European Group for the Study of Insulin Resistance; US, United States

Table 1-3 Studies of the Metabolic Syndrome (MetS) Associated with subclinical vascular measures

Authors	Study Design	Objective	Study Population	Subclinical CVD measures	Metabolic syndrome (MetS)	Results/Findings	Strengths/Limitations
Skilton et al[109]	Cross-sectional	Examine the associations between early carotid atherosclerosis and MetS definitions	Men and women participants at risk for CVD and dyslipidemia	Carotid IMT; Carotid plaque	IDF AHA/NHLBI NCEP-ATP III	MetS independently associated with increased atherosclerosis supporting screening for MetS among people at risk of CVD	Participants were at risk for CVD compared to the broader general French population
Ahluwalia et al[110]	Cross-sectional	Examine the association of MetS definitions with carotid and femoral plaques	Random sample of N= 11543 French adults aged (35-65 years)	Carotid and femoral plaque	WHO NCEP-ATP III	Risk of subclinical atherosclerosis (plaque) associated with MetS regardless of the definitions used	First study to include inflammatory factors in assessing the relationship between MetS and subclinical CVD
Ma et al[111]	Cross-sectional	Compare the relationship between Subclinical atherosclerosis and MetS	140 non-diabetic participants aged (38-50) years	Carotid IMT	IDF AHA/NHLBI NCEP-ATP III WHO	No association between carotid IMT and MetS defined by NCEP-ATP III or WHO. MetS definitions by IDF and AHA/NHLBI criteria are the best among four definition in detecting subclinical atherosclerosis in non-diabetic Chinese subjects	Small sample size
Tzou et al[112]	Longitudinal	Investigate the association of MetS with subclinical	507 non-diabetic subjects from Bogalusa Heart	Common carotid IMT; Internal and	NCEP-ATP III, WHO	MetS associated with increased atherosclerotic	Multi-ethnic sample and findings can easily be generalized to the

Table 1-3 Continued

Authors	Study Design	Objective	Study Population	Subclinical CVD measures	Metabolic syndrome (MetS)	Results/Findings	Strengths/Limitations
		atherosclerosis	Study	bulb IMT		burden and increased cardiovascular risk	broader population
Herder et al[113]	Longitudinal	Assesses MetS and progression of atherosclerosis	1442 men and 1532 women from Tromso study	Carotid IMT; Total Plaque area	NCEP- ATP III	Participants with MetS had higher levels of IMT and Total plaque area at follow up. MetS predicted progression of IMT and TPA in those < 50 years of age.	High attrition rate Selection bias due to higher mortality in those without MetS
Bonora et al[105]	Longitudinal	Prospectively evaluating carotid atherosclerosis and coronary heart disease in subjects with the MetS	888 subjects with MetS aged 40-79 years	Common carotid artery; Carotid plaque	WHO NCEP-ATP III	Subjects with the MetS are at increased risk for both progressive carotid atherosclerosis and CHD	Population-based study participants First study to evaluate atherosclerosis in participants with MetS prospectively
Hassinen et al[114]	Longitudinal	Investigate association of MetS and progression of carotid IMT	101 elderly women		NCEP-ATP III	MetS associated with progression of carotid IMT in women	Small sample size
Koskinen et al[92]	Longitudinal	Evaluate conventional risk factors and MetS progression of IMT in young adults	1809 young adults aged (32±5 years)	Carotid IMT	NCEP-ATP III EGIR IDF	MetS via all definitions identified young adults with accelerated IMT progression	High attrition rate Homogenous population therefore cannot generalized the findings to other ethnicities

CVD, Cardiovascular disease; CHD, Coronary Heart Disease; IDF, International diabetes Federation; WHO, World Health Organization; NCEP- ATP III, National Cholesterol Education Program Adult Treatment Panel III; US, United States; EGIR, The European Group for the Study of Insulin Resistance; AHA/NHLBI, American Heart Association/ National Heart, Lung and Blood Institute;

2.0 ARTERIAL REMODELING IN HEALTHY MIDLIFE WOMEN

2.1 Structure of Arterial Wall

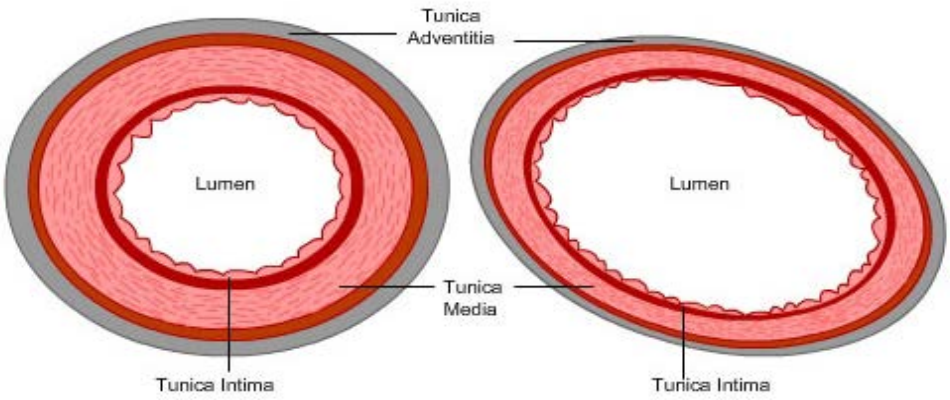


Figure 2-1 Structure of Arterial Wall

Adapted from Vascular Concepts http://www.vascularconcepts.com

The arterial wall is composed of three distinct layers (Figure 2-1). The most interior of the layers is the tunica intima, also known as the intima, and is mainly composed of an elastic membrane lining and an endothelium that is covered by elastic tissues. The middle layer, tunica medial, consists of smooth muscle cells and elastic tissue. The outermost layer, tunica adventitia also known as the adventitia is comprised up of connective tissue [115-117]

2.2 Pathophysiology of Arterial Remodeling

Arterial remodeling (AR) refers to a number of structural and functional changes of the vascular wall that occur in response to disease, injury, and aging [118], and can be divided into

atherosclerotic and arteriosclerotic processes. Atherosclerosis is initiated by inflammation in the intima by the accumulation of lipids in plaques, whereas arteriosclerosis is characterized by more diffuse changes of the medial arterial vascular wall [119]. The processes central to AR (Figure 2-2) are migration and proliferation of vascular smooth muscles cells, degradation and fracture of elastin fibers, and calcification and deposition of extracellular matrix (ECM) material [118].

Endothelial cells, elastic tissue and smooth muscle cells are subject to constant stimuli and mechanical forces, and given this, adaptations take place over time. The atherogenic factors such as lipid oxidation products response to injury and hemodynamic stimuli potentially induce arterial damage [120-122]. Given that basal levels of tensile stress are sustained based on Laplace's law, which states that the larger the vessel radius, the larger the wall tension required to withstand a given internal fluid pressure, thickening of the vessel wall via proliferation and migration of smooth muscles cells occurs [121, 123]. Endothelial cells are important because they ensure normal vascular adaption to chronic changes in blood flow and blood pressure [124]. Endothelial dysfunction, a feature of arterial aging, is suspected to be caused by nitric oxide deficiency or the development of oxidative stress, both of which help in inducing the remodeling response [124].

Different patterns of remodeling are suggested in the literature (Figure 2-3). Outward remodeling refers to an increase in flow, and it is dependent on shear induced endothelial production of nitric oxide [120, 125] and the gelatinase matrix metalloproteinase (MMPs) MMP-2 and MMP-9 [126]. Nitric oxide is at the core of this process largely because it is believed to mediate vessel wall remodeling by regulating expression of MMPs [127]. Inward remodeling occurs in the low-flow state, where an increase in production of mitogenic and fibrogenic growth factors along with their potential factors mediate to increase smooth muscle cell proliferation

and collagen deposition to reorganize vessel structure [125, 128, 129]. AR coupled with changes in circumferential wall tension and circumferential wall stress is termed maladaptive AR [130-132], whereas AR without changes in transmural pressure is considered compensatory adaptive enlargement of the arterial wall [133].

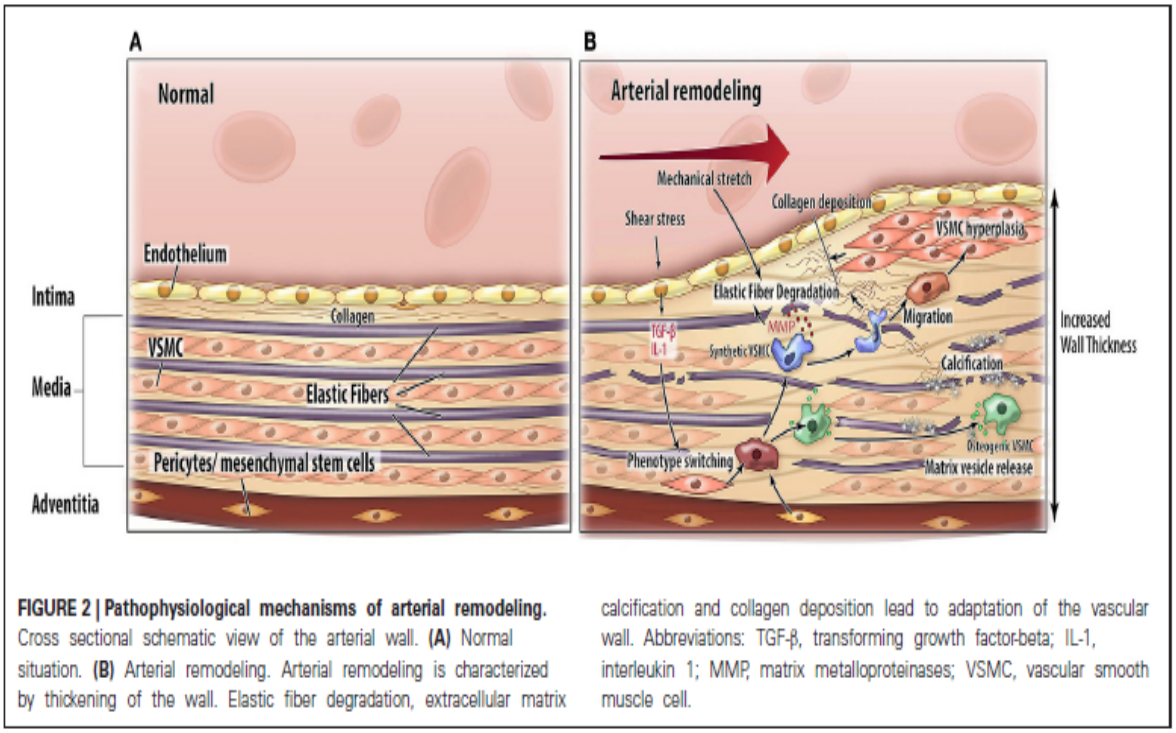


FIGURE 2 | Pathophysiological mechanisms of arterial remodeling. Cross sectional schematic view of the arterial wall. **(A)** Normal situation. **(B)** Arterial remodeling. Arterial remodeling is characterized by thickening of the wall. Elastic fiber degradation, extracellular matrix calcification and collagen deposition lead to adaptation of the vascular wall. Abbreviations: TGF-β, transforming growth factor-beta; IL-1, interleukin 1; MMP, matrix metalloproteinases; VSMC, vascular smooth muscle cell.

Figure 2-2 Pathophysiological Mechanisms of Arterial Remodeling

Adapted from Varik et al[134]

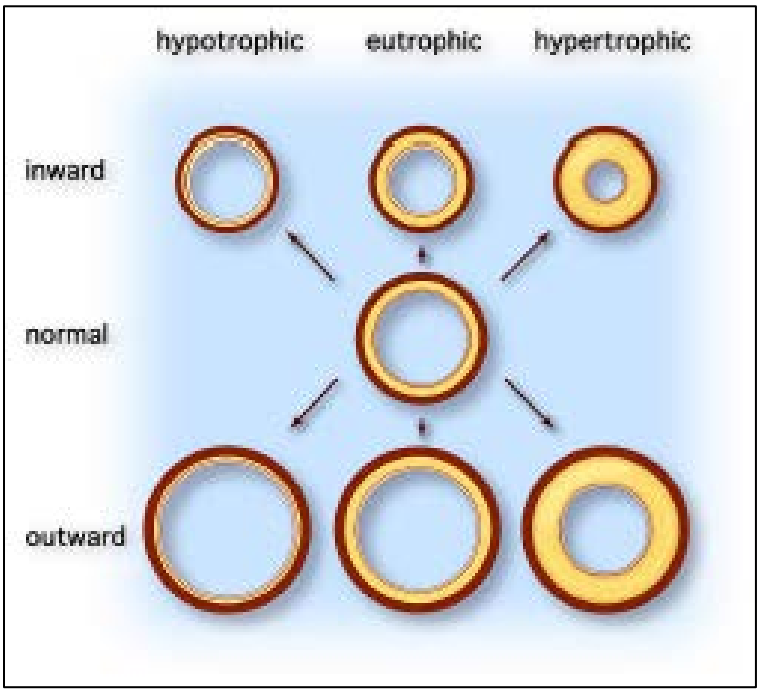


Figure 2-3 Types of Vascular Remodeling

Adapted from Mulvany et al [135]

3.0 METHODS OF ASSESSING ARTERIAL REMODELING

There is tremendous interest in identifying asymptomatic individuals at high risk of CVD who might be candidates for more intense and evidence-based medical intervention that may help to reduce CVD risk. Measurements of carotid intima-media thickness (IMT), carotid plaque, adventitial diameter (AD), and lumen diameter (LD) are markers of arterial health. These markers may be measured with B-mode ultrasound, which is a noninvasive, sensitive, and reproducible methods for identifying and quantifying subclinical atherosclerosis [136].

3.1 Carotid intima-media thickness

Carotid IMT is a measurement of the thickening of the tunica intima and the tunica media of the arterial wall. The measurement is usually made by B-mode ultrasound, which is noninvasive, sensitive and reproducible [137]. Measures of carotid IMT are associated with CVD risk factors, as well as prevalent and incident CVD [136]. Given these features, carotid IMT is considered as a surrogate marker of atherosclerosis.

In diverse study populations, carotid IMT has been found to be associated with atherosclerotic and CVD risk factors [138]. In a recent systematic review, carotid IMT (relative risk (RR), 1.26)) was found to be associated with future CVD events, as evidenced by a one standard deviation increase in carotid IMT being predictive for myocardial infarction and stroke [139].

MetS has been shown to be significantly associated with higher mean carotid IMT (Table 1-3) and the presence of coronary heart disease (CHD) [104]. Both cross-sectional and

prospective studies have found an association between MetS and carotid IMT [85, 94, 110]. Among US middle-aged adults, MetS was associated with progression of carotid IMT after adjusting for traditional CVD risk factors [140]. The components of MetS that either attenuate or accentuate the association between MetS and carotid IMT appear to vary by gender. HDL-c and glucose had varying impact in men and women, respectively. It was also shown that the association between MetS and subclinical atherosclerosis measures, such as carotid IMT, varied by gender with females with MetS having greater mean carotid IMT than men with MetS [141, 142]. However, among postmenopausal women, limited data regarding the association between MetS and subclinical atherosclerosis exist.

3.2 Carotid plaque

Carotid plaque refers to atherosclerotic lesion characterized by focal thickening in intimal layer and typically composed of lipid core and connective tissues. Carotid plaque tend to develop in arterial regions subjected to low wall shear stress and turbulent flow, such as carotid bulb [143]. It is also defined as a distinct area protruding into the vessel lumen that is at least 50% thicker than the adjacent IMT [144]. Carotid plaque is associated with traditional CVD risk factors, coronary ischemia and angiographic coronary artery disease [145]. The presence of carotid plaque is associated with larger mean values of carotid IMT, and has been shown to predict future CVD events [146]. In some instances, carotid plaque was found to be a stronger predictor of incident CVD events than that of carotid IMT [74] therefore the presence of carotid plaque is a useful screening tool for predicting future CVD[147]. MetS is independently associated with calcified and non-calcified plaques [148] but has not been shown to be

consistently associated with plaque. In a Japanese study, MetS was not found to be an independent risk factor for carotid plaque or carotid IMT [149]. In a prospective study over a 13 year period, participants with MetS had a higher total plaque area (TPA) compared to those without MetS [113]. However, the presence of MetS only predicted progression of total plaque area among those below 50 years of age, suggesting that MetS may play a significant role in the processes involved in the early atherosclerotic formation.

3.3 Adventitial diameter

Adventitial diameter (AD) is a marker of vascular health and [144] is the measured distance from the adventitial-medial interface on the near wall to the medial-adventitial interfaces on the far wall. The measure of AD is reliable and reproducible [37]. AD is associated with CVD risk factors and overt CVD. Individuals with pre-existing atherosclerosis or atherosclerosis risk factors have larger mean AD than individuals without those characteristics [150].

MetS is associated with greater AD [151, 152]. Several components of MetS are also positively associated with AD. In a cross-sectional study of middle-aged women, those with MetS were found to have significantly greater values of AD compared to those without MetS [152]. In a population-based cohort of healthy participants, steeper increases in AD were observed over time among participants with persistent MetS compared to those who were never classified as having MetS while adjusting for other CVD risk factors [131]. In a cross sectional

study of older healthy participants without diabetes, MetS was found to be associated with greater AD after adjusting for low-grade inflammation and hemodynamic factors [130].

3.4 Lumen diameter

Lumen diameter (LD) can be measured noninvasively using carotid ultrasound imaging technique. It is a reliable and reproducible measure, if measured non-invasively [75]. Greater LD is independently associated with higher systolic blood pressure, BMI, mean arterial pressure, total cholesterol and carotid IMT and with pre-existing coronary disease [153].

Mets is independently associated with greater LD after adjusting for traditional CVD risk factors and prior CVD. The association was attenuated slightly but remained statistically significant after additional adjustment for important metabolic, inflammatory and hemodynamic variables [130]. In the Women's Angiographic Vitamin and Estrogen trial (WAVE), the annual LD measurement decreased among participants with MetS compared to those free of MetS, but the change was not statistically significant. In a multivariable analysis, MetS was not independently associated with a reduction in mean LD over time [154].

3.5 Circumferential wall tension (CWT)

Circumferential wall tension measures the transmural pressure in the blood vessel. CWT is estimated according to Laplace's law [130, 155, 156]. It is determined using LD and mean arterial pressure (MAP) and is calculated as: CWT = MAP*(Lumen diameter/2). Higher mean

CWT has been shown to be associated with strokes as evidenced by higher carotid CWT measured on the affected side of stroke patients [132].

In a cross-sectional study among non-diabetic participants, MetS was significantly associated with higher mean CWT [130]. In population-based study, higher mean? levels of CWT were associated with both higher levels of waist circumference and blood pressure [131].

3.6 Circumferential wall stress (CWS)

Circumferential wall stress measures blood vessels respond to changes in transmural pressure. By the Laplace's law, CWS is computed as CWS = CWT/ IMT, where IMT = carotid IMT, and CWT = Circumferential wall tension [130, 132].

CWS is associated with MetS. Beijers et al have reported that non-diabetic individuals with MetS had greater CWS compared to those without MetS. Even among those with MetS, higher levels of CWS were significantly associated with a larger waist circumference and higher mean blood pressure [131].

3.7 Cross-sectional Area (CSA)

Arterial wall cross-sectional (CSA) is a measure of vascular volume or mass, and represent arterial wall thickening associated with atherosclerosis[157]. CSA is calculated as π*IMT*(IMT+LD), where LD is Lumen diameter [131, 157].

In a population-based cohort study, increases in mean CSA were significantly associated with changes in systolic blood pressure. Individuals with persistent MetS were found to have significant and steeper increases in mean CSA even after adjusting for blood pressure over 6 years period [131].

4.0 EPIDEMIOLOGY OF ARTERIAL REMODELING IN MIDLIFE WOMEN

Arterial remodeling (AR) is fundamental to many arterial diseases and in particular AR is one of the major determinants of clinical manifestations of coronary disease such as myocardial infarction and stroke [158]. The relationships between traditional CVD risk factors and AR are not fully understood. Thus far, the evidence shows that CVD risk factors such as hypertension and hypercholesterolemia are associated with both positive and negative remodeling of the artery [159]. Carotid plaque, hypertension and coronary flow reserve, after adjustment for other traditional CVD risk factors, have been shown to be independent predictors of AR [159, 160]. Among non-obese postmenopausal women, waist-to-hip ratio, a marker for central adiposity, was associated with AR after adjusting for body mass index, age and lipid profile [161].

Variations in AR have been reported in the literature. Among middle-aged women transitioning through the menopause in the SWAN study, Woodard et al found different levels of carotid plaque among White women compared to African American women [162]. Whether this racial difference explains incident CVD morbidity or mortality is not known. The presence and burden of carotid plaque also differed by sex, and at any given age men tend to have more plaque

than women. Sex hormones are thought to be the driving force behind the difference in term of carotid plaque [139].

AR has been shown to be associated with MetS [130, 152, 163]. In a population-based cohort, MetS was significantly associated with maladaptive remodeling of the carotid artery, resulting in higher changes in LD, AD and carotid IMT, independent of hemodynamic variables. An outward remodeling pattern was noted along with greater mean circumferential wall tension and circumferential wall stress [130]. In a cross-sectional study, Iannuzzi et al reported a positive association between MetS and changes in carotid structure among middle-aged women [152]. In a population based study of elderly men and women, MetS was significantly associated with alterations in the structure of the carotid structure of the carotid arteries after adjustment for conventional CVD risk factors [163].

5.0 SPECIFIC AIMS

The metabolic syndrome (MetS) is a collection of risk factors associated with higher risk of heart disease, stroke and diabetes [15]. Various definitions and criteria exist for the classification of MetS and nearly all consist of the following factors: elevated blood pressure, central obesity, dyslipidemia, and impaired glucose [10]. The components of MetS are interrelated and share underlying factors, mechanisms and pathways leading to their development [17]. This dissertation uses data from the Study of Women's Health Across the Nation (SWAN) to examine MetS and its association with subclinical atherosclerosis, common carotid artery remodeling and related risk factors. Furthermore, the effects of MetS status measured over time on carotid remodeling in women of midlife will be examined.

The major aims of this dissertation are as follow:

1. To compare the association between IDF, NCEP-ATP III, and WHO definitions of MetS and subclinical atherosclerosis among middle-aged women, as well as examine individual components of MetS and its association with subclinical atherosclerosis.

2. To examine the relationship between MetS and common carotid artery remodeling and the pattern of remodeling associated with it in non-diabetic midlife women.

3. To assess the effects of MetS status and its individual components changes on common carotid artery parameters over time in midlife women.

6.0 MANUSCRIPT 1: COMPARISON OF METABOLIC SYNDROME DEFINITIONS AND SUBCLINICAL ATHEROSCLEROSIS: THE STUDY OF WOMEN'S HEALTH ACROSS THE NATION

Julius Asubonteng, [1] Emma Barinas-Mitchell, [1] Stephen Wisniewski, [1] Rebecca Thurston, [1, 2] Suresh Mulukutla, [3] Kristine Ruppert, [1] Faith Selzer[1]

[1] Department of Epidemiology, University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA

[2] Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA

[3] Cardiovascular Institute, University of Pittsburgh Medical Center, Pittsburgh, PA

(This manuscript is in preparation to be submitted to Atherosclerosis)

6.1 ABSTRACT

Objective: The aim of this study was to compare the association between subclinical atherosclerosis and metabolic syndrome defined using three well-recognized definitions among older middle-aged women to determine which of the definitions is associated with worse subclinical atherosclerosis profile.

Methods: Participants from 6 sites of the Study of Women's Health Across the Nation (SWAN) free of clinical cardiovascular disease and who had measures of carotid intima-media thickness (IMT) and carotid plaque (CP) at the 12th annual visit were analyzed. Women were identified as having MetS if they met the criteria defined by the International Diabetes Federation (IDF), National Cholesterol Education Program Adults Treatment Panel III (NCEP-ATP III) and World Health Organization (WHO) criteria. Multivariable linear and logistic regression models were used to investigate the association between the presence of MetS with IMT and CP while adjusting for age, study site, race/ethnicity, BMI, LDL-C, smoking status, menopausal status, hormone use and education level.

Results: The presence of MetS was significantly and positively associated with IMT for all three definitions (all $p<.0001$). After adjusting for covariates, MetS remained positively and significantly associated with IMT (IDF β = 0.0303 ($p < .0001$), NCEP-ATP III β =0.0274 ($p<.0001$), WHO β =0.0570 ($p<.0001$)). The WHO construct was more strongly associated with IMT compared to both the IDF and the NCEP- ATP III definitions. MetS was also significantly associated with the presence of CP (IDF Odds Ratio [*OR*] =1.61 [95% Confidence Interval [CI] 1.30-2.01], NCEP-ATP III *OR*=1.68 [95% CI 1.35-2.10], WHO *OR* =1.68 [95% CI 1.27-2.24). After controlling for covariates, MetS remained significantly associated with a 70%

to 98% higher risk in the presence of CP compared to those without MetS with the WHO definition conferring the highest risk.

Conclusions: The presence of MetS using three definitions was significantly associated with greater burden of subclinical atherosclerosis measures in older middle-aged women. The WHO definition was the best in identifying older middle-aged women with a worse subclinical atherosclerosis profile, followed by IDF, and then NCEP-ATP III.

6.2 INTRODUCTION

Metabolic syndrome (MetS), a clustering of cardiovascular disease (CVD) related risk factors consisting of abdominal obesity, dyslipidemia, hypertension and hyperglycemia [164, 165], is associated with both incident type 2 diabetes mellitus and CVD events [82] and is one of the significant public health challenges faced by both developed and developing countries [165]. While several definitions are used to classify MetS status, most incorporate similar criteria. The key diagnostic criteria were first put forth by the World Health Organization (WHO) in 1998, followed by the European Group for the study of Insulin Resistance (EGIR) in 1999, the National Cholesterol Education Program's Adult Treatment Panel III (NCEP-ATP III) in 2001, and the International Diabetes Federation (IDF) in 2005. The main differences among the various definitions are (1) the inclusion/exclusion of features that define criteria such as use of pharmacological treatments, (2) specific cut points that determine criteria like fasting glucose ≥ 110 mg/dL or ≥ 100 mg/dL and (3) the compulsory inclusion of central obesity and diabetes. Despite the various options in definitions, the NCEP-ATP III definition is most commonly used in epidemiological and clinical practice worldwide for its ease of assessment [166].

Beyond overt CVD events, MetS, as defined by NCEP-ATP III [167], IDF and AHA/NHLBI[109], and WHO[164], has been shown to be significantly associated with markers of subclinical atherosclerosis including higher mean carotid intima-media thickness (IMT), arterial stiffness and the presence of carotid plaque. It is believed that measures of subclinical atherosclerosis are surrogate markers of pre-clinical CVD, and over time such measures are associated with CVD events [139]. While MetS is associated with the presence of subclinical atherosclerosis in many epidemiological studies [110, 168], other reports have found no

association between MetS and subclinical atherosclerosis after adjustment for individual MetS components [164, 169].

Various MetS definitions are linked to subclinical atherosclerosis in middle-aged adults. In a prospective study, Hassinen et al. reported that incident MetS was associated with accelerated progression of carotid IMT in elderly women [170]. In a population - based study conducted in Korea among participants 50 years and older, the presence of MetS was associated with subclinical atherosclerosis, and the association was more pronounced among women compared to men [171]. The published findings show an association between MetS and subclinical atherosclerosis, yet questions remain regarding the clinical utility of the various constructs of MetS. Moreover, findings from The Study of Women's Health Across the Nation (SWAN) indicate that the prevalence of MetS increases through the menopausal transition and is independent of age, potentially implicating changes in hormone [172]. Data is lacking in women, and it is, therefore, important to assess the performance of various definitions of MetS in identifying the risk for CVD based on subclinical atherosclerosis measures.

We therefore sought to compare the association between the IDF, NCEP-ATP II and WHO definitions of MetS and subclinical atherosclerosis among older middle-aged women. We also examined individual components of MetS and its association with subclinical atherosclerosis to determine which of the definitions is associated with worse subclinical atherosclerosis profile.

6.3 METHODS

6.3.1 Study Population

The Study of Women's Health Across the Nation (SWAN) is a multiethnic, community-based, longitudinal study of the natural history of the menopausal transition in a cohort of 3302 women enrolled at 7 field sites throughout the United States (Boston, Massachusetts; Chicago, Illinois; Detroit, Michigan; Los Angeles, California; Oakland, California; Newark, New Jersey; and Pittsburgh, Pennsylvania). The design of the study has been described previously [173]. The cohort, at the baseline, consisted of non-pregnant White, Black, Chinese, Japanese and Hispanic women, aged 42 to 52 years, with an intact uterus and at least one ovary, having had at least one menstrual period in the preceding 3 months, and not using hormone therapy in the preceding 3 months.

The sample size of the current analysis consisted of participants who had a carotid ultrasound examination during the 12^{th} follow-up clinic visit. The University of California at Los Angeles site did not participate in the carotid ultrasound protocol and is therefore not included in this analysis. Of 3302 women enrolled at the baseline, 1552 underwent a carotid artery ultrasound examination. Among participants who participated in the carotid ultrasound protocol, 45 women were removed from the analysis due to missing IMT data. An additional 66 participants were excluded due to missing data pertaining to MetS criteria, leaving a final sample size of 1441 participants (Figure 6-1). The institutional review board at each participating site and at the Data Coordinating Center located at the University of Pittsburgh approved the study protocol.

6.3.2 Assessment of cardiovascular and metabolic risk factors

All study participants underwent annual or biannual study visits consisting of interviewer-administered questionnaires to ascertain medication use, medical history, lifestyle characteristics and menopausal status, physical measures, and a fasting blood draw for assessment of cardiovascular risk factors and reproductive hormone levels. Race or ethnicity was self-reported.

Blood pressure was measured in the right arm, while participants were seated with feet flat on floor following at least 5 minutes of sitting quietly before measurements were taken. A standard mercury sphygmomanometer was used to measure systolic and diastolic pressures at first and fifth korotkoff sounds. The average of two sequential readings was used in the analyses. Height was measured without shoes using a stadiometer. Weight was measured with light indoor clothing using calibrated scales. Waist circumference was measured with participants in light undergarments.

Lipids, glucose, and insulin measured using a Siemens ADVIA 2400 automated chemistry analyzer utilizing Siemens ADVIA chemistry system reagents (Siemens Healthcare Diagnostics, Deerfield IL) at the University of Michigan Pathology Laboratory, which is Clinical Laboratory Improvement Amendments (CLIA) certified and accredited by the College of American Pathologists. Triglycerides, high-density lipoprotein cholesterol (HDL-C) and directly measured low density lipoprotein cholesterol (LDL-C) [174] were analyzed using a coupled enzymatic methods that utilized lipase, glycerol kinase, glycerol-3-phosphate oxidase (G3PO), and peroxidase (for triglycerides) and cholesterol esterase, cholesterol oxidase, and peroxidase

(for HDL-C and direct LDL-C). Serum insulin was measured by a two-site sandwich immunoassay using direct chemiluminescent technology that used constant amounts of two antibodies. Glucose was measured using a two-step enzymatic reaction that utilized hexokinase and glucose-6-phosphate dehydrogenase (G6PDH) enzymes. Diabetes was defined as either fasting glucose ≥ 126 mg/dL, a diagnosis of diabetes by physicians or anti-diabetic medication treatment.

6.3.3 Metabolic syndrome definitions

NCEP-ATP III metabolic syndrome definition

The NCEP-ATP III definition of the MetS consists of the following five factors: central obesity (waist circumference > 102 cm for men, > 88 cm for women), elevated triglycerides (≥ 150 mg/dL), elevated blood pressure (systolic blood pressure ≥ 130 mmHg/diastolic blood pressure ≥85) or medication for hypertension, fasting plasma glucose (≥ 100 mg/dL) and reduced HDL cholesterol (< 40 mg/dL for men, < 50 mg/dL for women) [175]. An individual with three or more of the above factors was classified as having MetS.

IDF metabolic syndrome definition

The IDF definition of MetS consists of the same factors as NCEP-ATP III definitions. Within the IDF definition, central obesity is required to be a component of the criteria, plus two

or more of the other factors. The components of IDF are as follows: waist circumference ≥ 94 cm for European men, and ≥80 cm for European women and other ethnicity-specific values for other racial/ethnic groups; triglycerides ≥150 mg/dL; systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or treatment of previously diagnosed hypertension; HDL <40 mg/dL in men and < 50 mg/dL in women; fasting glucose ≥ 100 mg/dL [176].

WHO metabolic syndrome definition

The WHO definition consists of the same factors that comprise the other definitions with the exception of the requirement of insulin resistance (abnormal glucose regulation or type 2 diabetes, or fasting plasma glucose ≥110 mg/dL). Two or more of the following components are also required: triglycerides ≥150 mg/dL; systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or current use of antihypertensive; HDL <35 mg/dL in men and < 39 mg/dL in women; body mass index (BMI) > 30 or waist-to-hip ratio (WHR) >0.9 in men or > 0.85 in women; urinary albumin creatinine ratio ≥ 30 mg/g after overnight fast [18].

6.3.4 Carotid intima-media thickness and plaque

Centrally trained and certified sonographers obtained carotid ultrasound images using a Terason t3000 Ultrasound System (Teratech[177] Corp, Burlington, MA) equipped with a variable frequency 5-12 Mhz linear array transducer. Two digitized images were obtained of each of the left and right distal common carotid artery (CCA). From these 4 images and using the Artery Measurement System (AMS) semi-automated edge detection software [178], near

and far wall CCA intima-media thickness (IMT) measures were obtained by electronically tracing the lumen-intima interface and the media-adventitia interface across a 1-cm segment proximal to the carotid bulb. The average and maximal values for these measures were recorded, with the mean of the average and maximal readings of all 4 images used in analyses. All carotid scan images were read centrally at the SWAN Ultrasound Reading Center (University of Pittsburgh Ultrasound Research Lab) by two trained readers. Clinic site sonographers evaluated the presence and extent of atherosclerotic plaque in each of 5 segments of the left and right carotid artery (distal and proximal common carotid artery, carotid bulb, and proximal internal and external carotid arteries) [179]. Plaque was defined as a distinct area protruding into the vessel lumen that was at least 50% thicker than the adjacent IMT and summarized as the presence or absence of any plaque. Reproducibility of IMT measures was good to excellent with an intraclass correlation coefficient between sonographers of ≥ 0.77, and between readers of > 0.90. The assessment of atherosclerotic plaque was found to be a valid and reproducible measure of carotid atherosclerosis in a number of populations based studies, with intraclass correlations ranging from 0.86 to 0.93 [180].

6.3.5 Statistical analyses

The MetS status for each participant was classified based on each of the 3 definitions described above. Descriptive statistics were summarized as means or medians for continuous variables and percentages for categorical variables. Normality for all continuous variables was assessed and comparisons between those with and without MetS were made by the Wilcoxon-

rank sum test or Student's t-test. The Chi-square test was used to compare nominal variables between MetS and non-MetS groups.

Multivariable linear and logistic regression analyses were used to evaluate the association between each of the MetS definitions and its individual components and measures of subclinical atherosclerosis (carotid IMT and carotid plaque presence (yes/no), respectively). The unadjusted models assessed the univariate relationship between MetS status and both carotid IMT and plaque. All models were then adjusted for age, race/ethnicity, study site, menopausal status, education, smoking, body mass index, LDL-c, and use of hormone therapy medications. This set of variables was selected due to the design of the SWAN study and based on known risk factors with subclinical atherosclerosis in the literature. To assess the relationship between individual components of MetS and carotid IMT and plaque, separate models were developed that included the individual components of each MetS definitions while adjusting for standard set of covariates.

To explore which of the MetS definition correlated better with measures of subclinical atherosclerosis, model diagnostics were evaluated. Unadjusted and adjusted R-squared of each model were used to examine for outcomes of IMT and receiver operating curves (ROC) were used to examine the performance of each of the MetS models for carotid plaque. All statistical analyses were performed with the use of SAS software, version 9.3, and a two-sided *P*-value of 0.05 or less was considered to indicate statistical significance.

6.4 RESULTS

The 1441 participants in this study were comprised of 30.5% (n = 439) Blacks, 51.1% (n = 736) Whites, 12.8% (n = 185) Chinese and 5.6% (n = 81) Hispanic women. The average age of participants was 59.6 ±2.7 years (Table 6-1). In all, 36.4% of the study participants fulfilled at least one of the three MetS definitions considered in the study. Classifying participants by MetS definition, 34.6% met IDF criteria, 32.2 % met NCEP-ATP III criteria and 15.9% met the WHO definition (figure 6-2). Among participants with MetS, 204 (14.2%) fulfilled all three definitions for Mets.

In each of the MetS definitions, the prevalence of MetS was higher among Hispanic women (Table 6-2). As expected, participants with MetS had higher mean body mass index, waist circumference, waist-to hip ratio, systolic blood pressure, diastolic blood pressure, fasting plasma glucose, and triglycerides compared to those without MetS. With respect to total cholesterol, participants without MetS had higher mean levels compared to those with MetS in all definitions likely due to the higher use of cholesterol modifying medications among those with MetS. Across all definitions, participants with MetS had a significantly greater average carotid IMT and a higher prevalence of carotid plaque compared to those without MetS.

MetS was significantly and positively associated with carotid IMT in all three definitions (all $p<.0001$) (table 6-3). Even with adjustment, all MetS definitions remained significantly and positively associated with carotid IMT (IDF β = 0.0303 ($p < .0001$), NCEP-ATP III β =0.0274 ($p<.0001$), WHO β =0.0570 ($p<.0001$)) (Table 6-3). The WHO construct was more strongly associated with carotid IMT compared to the IDF and the NCEP- ATP III definitions as assessed

by the higher r-squared and adjusted r-squared (Table6-4). The difference, however, between the IDF and NCEP-ATP III definition was minimal. With the removal of participants with diabetes, the findings were nearly the same between IDF and NCEP-ATP III constructs in correlating with carotid IMT.

All MetS definitions were significantly associated with the presence of carotid plaque (IDF Odds Ratio [*OR*] =1.61 [95% Confidence Interval [CI] 1.30-2.01], NCEP-ATP III *OR*=1.68 [95% CI 1.35-2.10], WHO *OR* =1.69 [95% CI 1.27-2.24). Even after adjusting for age, race/ethnicity, clinic site, menopausal status, education, smoking status, LDL, body mass index, and hormone therapy use, all MetS definitions remained significantly associated with a 70% to 98% higher risk in the presence of carotid plaque compared to those without MetS. The area under the curve analysis for each of the MetS definitions was significant, but there was no difference with respect to their performance in discriminating the presence of carotid plaque in both unadjusted and adjusted models (Table 6-5) and (FIGURE 6-3). When removing participants with diabetes, no significant differences were observed with respect to the performance of the MetS constructs in relation to the presence of carotid plaque.

To examine the relationship between each of the individual components of MetS definitions and subclinical atherosclerosis, a series of unadjusted and adjusted multivariable regression models were performed. Using the IDF definition, higher blood pressure, waist circumference and fasting glucose were independently associated with carotid IMT, $\beta = 0.0273$ $p < 0.0001$, $\beta = 0.0293$, $p = 0.0009$ and $\beta = 0.0264$, $p = 0.0002$, respectively (table 5). Similarly, blood pressure, waist circumference and fasting glucose were the individual components of the

NCEP-ATP III definition that were significantly associated with carotid IMT, β = 0.0276, p <0.0001, β = 0.0182, p = 0.0330 and β= 0.0272, p= 0.0001, respectively. The components of the WHO definition significantly associated with IMT included blood pressure (β = 0.0293, p <.0001) and fasting glucose (β = 0.0211, p =.0098) (Table 6-6). For carotid plaque, higher fasting glucose and blood pressure were the individual components significantly associated with presence of carotid plaque in all three definitions (table 6-7). Additionally, body mass index was also independently associated with presence of carotid plaque in the WHO definition.

6.5 DISCUSSION

The present study investigated the association between three commonly used definitions of MetS, namely IDF, NCEP-ATP III and WHO, and measures of subclinical atherosclerosis among older middle-aged women. We found that MetS, via all definitions, was significantly associated with measures of subclinical atherosclerosis. The WHO definition was more strongly associated with carotid IMT and carotid plaque presence compared to either the NCEP-ATP III or the IDF definitions. The MetS components most strongly and consistently associated with carotid IMT and plaque were blood pressure and fasting glucose across all definitions considered in the current study.

This current study found the MetS construct to be significantly associated with a greater burden of subclinical atherosclerosis in middle-aged women. Our results suggest that the WHO definition was the best in identifying middle-aged women with a worse subclinical atherosclerosis profile, followed by IDF, and then NCEP-ATP III. In our sensitivity analysis, where participants with diabetes were excluded, similar findings were observed. We also found that the overall MetS construct was useful for assessing the burden of subclinical atherosclerosis, although not independent of individual components of the MetS definitions. Some studies have reported no association between MetS and subclinical atherosclerosis [180, 181], whereas, others have raised questions about the clinical utility of the MetS construct regardless of the definition [177]. A number of other studies have shown that the association between MetS and subclinical atherosclerosis is more pronounced in women than men [101, 109, 182-184]. This finding has led some to suggest that the protective effect of the female sex against atherosclerosis is lost in

the presence of MetS [184]. However, Skilton et al reported no sex difference with respect to the effect of MetS on subclinical atherosclerosis[109].

We observed differences in strength of association with respective to MetS definitions and burden of subclinical atherosclerosis. Of the MetS definitions considered in this analysis, the WHO definition identified the fewest number of participants with MetS largely due to its requirement of either existing diabetes or the higher levels of fasting glucose. However, participants classified as having MetS according to the WHO definition, had a higher mean carotid IMT compared to those with MetS by the other definitions. Still, all three of the MetS definitions considered in the current study were significantly associated with carotid plaque presence. Again, the strongest of the associations was observed with the WHO definition, followed by NCEP-ATP III, and then IDF. Similar to our findings, MetS, as defined by WHO and NCEP-ATP III definitions, was strongly associated with the presence of subclinical atherosclerosis in middle-aged adults in a study conducted in France[110]. In the Northern Manhattan study comprised of White, Black, and Hispanics men and women, MetS, as defined by NCEP-ATP III, was significantly associated with subclinical atherosclerosis [185]. The Atherosclerosis Risk in Communities (ARIC) study, a cohort of over 14,000 middle-aged adults, also reported an association between MetS and higher mean carotid IMT [104]. The IDF definition was found to be a better predictor of carotid atherosclerosis in middle-aged women by Skilton and colleagues compared to the NCEP-ATP III definition. The hypothesized reason for this finding was the inclusion of abdominal obesity in IDF definition[109]; however, we did not observe that in our study.

We also examined the relationship of individual components of MetS definitions and subclinical atherosclerosis. Across each MetS definition included in this study, higher blood pressure and fasting plasma glucose were positively and significantly associated with carotid IMT, and the presence of plaque. Elevated waist circumference was associated with carotid IMT but not with presence of carotid plaque in both the IDF and NCEP-ATP III definitions. These findings are consistent with what has been reported in the literature. Among middle-aged adults, Iglseder et al reported that fasting glucose was the most strongly associated of the individual MetS components with carotid IMT[182]. In the Bogalusa Heart Study, higher blood pressure was a significant predictor of carotid IMT [167]. In The Rancho Bernardo study, hypertension was the only component of the MetS associated with coronary artery calcium progression, while hyperglycemia was a significant risk factor among the subset of participants under 65 years of age [102]. In the Muscatine study, carotid IMT was positively and significantly associated with systolic blood pressure only in women [103]. Sipila et al reported significant associations between both blood pressure and waist circumference and carotid IMT[94]. There are, however, differences between the current study and previous studies. Despite differences in the MetS definitions and the ages of the cohorts in the Bogalusa Heart study and the Rancho Bernardo Study as compared to our study, the consistent findings lend credence to the adverse role played by blood pressure and glucose in development of atherosclerosis.

The current study has a number of strengths, but also several limitations. The sample consisted of community - dwelling women in whom subclinical atherosclerosis burden was assessed by centrally trained vascular sonographers with no knowledge of participants' CVD risk factors. The study sample was multi-racial and multi-ethnic and comprised of White, Black,

Chinese and Hispanic women. To our knowledge, this is the first study to assess three commonly used MetS definitions and their individual components in relation to subclinical atherosclerosis in a racially/ethnically diverse group of middle-aged women. However, given that this is a cross-sectional study and we can only speculate about cause and effect, and therefore caution must be taken in the interpretation of these findings.

In conclusion, the MetS is associated with a greater burden of subclinical atherosclerosis in older middle-aged women. Of the individual MetS components, blood pressure and fasting plasma glucose were positively and independently associated with carotid IMT and presence of carotid plaque in this study whereas dyslipidemia was related to neither measure of subclinical CVD. Finally, there were differences in the strength of associations between MetS definitions and subclinical atherosclerosis with the WHO definition being the most strongly associated, largely due to its requirement for the inclusion of diabetes, followed by IDF definition, and then NCEP-ATP III. Our findings suggest that, irrespective of the MetS definition used, the presence of MetS is associated with subclinical atherosclerosis. The identification of middle-aged women with MetS and treating their risk factors, especially blood pressure and blood glucose may aid in efforts to reduce the development of subclinical atherosclerosis.

6.6 TABLES AND FIGURES

Table 6-1 Participant characteristics

Variables	N = 1441*	Value
Age (years)		59.6±2.73
Race/Ethnicity (n, %)		
Blacks		439 (30.5)
White		736 (51.1)
Chinese		185 (12.8)
Hispanic		81 (5.6)
Metabolic syndrome traits		
BMI(kg/m^2)		30.0±7.2
Waist circumference (cm)		93.0±15.9
SBP(mmHg)		122.1±16.9
DBP(mmHg)		74.2±10.0
Glucose(mg/dL)		93(86-101)
Triglycerides(mg/dL)		102(75-141)
HDL-c(mg/dL)		61.8±16.5
T2DM		
Yes		187(13.0)
No		1254(87.0)
Other CVD risk factors		
Waist-Hip Ratio		0.84± 0.07
Total cholesterol(mg/dL)		204.6±38.2
LDL-c(mg/dL)		119.7±32.3
BP medication use (n, %)		
Yes		593(41.2)
No		848(58.8)
Cholesterol medication		
Yes		449(31.2)
No		992(68.8)
Smoking		
Yes		130(9.1)
No		1298(90.9)
Subclinical Atherosclerosis		
Carotid IMT (mm)		0.79±0.12
Carotid plaque (n, %)		
Yes		629(43.7)
No		811(56.3)

BMI, Body mass index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; HDL-C, high-density lipoprotein-cholesterol; LDL-C, Low density lipoprotein cholesterol; T2DM, Type II diabetes mellitus; BP, Blood pressure medication; Carotid IMT, Carotid Intima-media thickness

Table 6-2 Participants characteristics by metabolic syndrome definitions

	IDF		NCEP-ATP III		WHO	
	Yes (N=499)	No (N= 942)	Yes (N=464)	No (N=977)	Yes (N=229)	No (N=1212)
Age (years)	59.7±2.9	59.5±2.6	59.7±2.8	59.5±2.7	59.9±2.9	59.6±2.7
Race/Ethnicity (n, %)						
Black	197(38.4%)	246(26.3%)	172(37.1%)	267(27.3%)	84(38.0%)	359(29.3%)
White	233(45.4%)	505(54.1%)	216(46.5%)	520(53.2%)	93(41.2%)	647(52.8%)
Chinese	44(8.6%)	141(15.1%)	35(7.5%)	150(15.4%)	22(10.0%)	163(13.3%)
Hispanic	39(7.6%)	42(4.9%)	41(8.8%)	40(4.1%)	24(10.9%)	57(4.7%)
Traits of MetS						
BMI(kg/m^2)	33.8±6.7	28.1±6.6[a]	34.4±6.6	28.0±6.5[a]	35.5±7.1	29.0±6.8[a]
WC(cm)	103.2±14.3	87.6±13.9[a]	104.9±13.9	87.2±13.5[a]	107.1±13.5	90.4±14.9[a]
SBP(mmHg)	128.6±17.2	118.6±15.6[a]	128.7±17.2	118.9±15.7[a]	130.1±18.7	120.5±16.0[a]
DBP(mmHg)	76.2±10.1	73.2±9.7[a]	76.3±10.2	73.3±9.7[a]	75.5±11.0	74.0±9.8[a]
Glucose(mg/dL)	104(95-118)	89(84-95)[a]	105(96-121)	89(84-95)[a]	118(110-145)	91(85-97)[a]
Triglycerides(mg/dL)	143(101-193)	89(68-116)[a]	147(107-194)	90(68-116)[a]	149(104-200)	96(72-129)[a]
HDL-C(mg/dL)	50.9±12.0	67.6±15.6[a]	50.0±11.2	67.4±15.6[a]	50.8±12.3	63.9±16.3[a]

[a] P<.0001; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; HDL-C, High density lipoprotein; WC, Waist Circumference; T2DM, Type II Diabetes Mellitus; IDF, International Diabetes Federation; NCEP-ATP, National Cholesterol of Education Program's Adult Treatment Panel III; WHO, World Health Organization

Table 6-2 Continued

	IDF		NCEP-ATP III		WHO	
	Yes (N=499)	**No (N= 942)**	**Yes (N=465)**	**No (N=976)**	**Yes (N=229)**	**No (N=1212)**
Other risk factors						
T2DM (n, %)	148(29.7%)	39(4.1%)[a]	148(31.8%)	39(4.0%)[a]	155(67.7%)	32(2.6%)[a]
Waist-Hip Ratio	0.88±0.07	0.82±0.06[a]	0.88±0.07	0.82±0.06[a]	0.89±0.07	0.83±0.07[a]
Total cholesterol (mg/dL)	194.0±40.3	210.3±35.9[a]	193.7±40.5	209.9±36.0[a]	187.3±38.1	208.6±37.2[a]
LDL-C (mg/dL)	113.4±33.3	122.9±31.2[a]	113.1±33.4	122.7±31.2[a]	105.7±34.4	122.3±31.2[a]
BP medication	363(70.7%)	235(25.2%)[a]	345(71.4%)	253(26.2%)[a]	192(86.9%)	406(33.1%)[a]
Cholesterol medication	253(50.7%)	196(20.8%)[a]	240(51.6%)	209(21.4%)[a]	151(65.9%)	298(24.6%)[a]
Smoking	66(13.4%)	64(6.8%)[a]	62(13.6%)	68(7.0%)[a]	32(14.1%)	98(8.2%)[a]
Subclinical						
Atherosclerosis						
Carotid IMT(mm)	0.83±0.13	0.77±0.11[a]	0.83±0.13	0.78±0.11[a]	0.85±0.14	0.78±0.11[a]
Carotid plaque (n, %)	256(51.4%)	373(39.6%)[a]	242(52.3%)	387(39.6%)[a]	125(54.6%)	504(41.6%)[a]

[a] P <.0001; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; BMI, Body Mass Index; WC, Waist Circumference; T2DM, Type II Diabetes Mellitus; IDF, International Diabetes Federation; NCEP-ATP, National Cholesterol of Education Program's Adult Treatment Panel III; WHO, World Health Organization

Table 6-3 Association between metabolic syndrome and carotid IMT in middle-aged women

	IDF		NCEP-ATP III		WHO	
	β(SE)	**R^2**	**β(SE)**	**R^2**	**β(SE)**	**R^2**
All women						
Unadjusted	0.0545(0.006)*	0.0472	0.0552(0.006)*	0.0467	0.0712(0.008)*	0.0480
Adjusted	0.0303(0.007)*	0.1466	0.0274(0.007)*	0.1438	0.0570(0.009)*	0.1501
No DM						
Unadjusted	0.0426(0.007)*	0.0279	0.0429(0.007)*	0.0266	--	--
Adjusted	0.0187(0.007)*	0.1228	0.0168(0.008)*	0.1216	--	--

* p <.0001; Carotid IMT, Carotid Intima-Media Thickness; IDF, International Diabetes Federation; NCEP-ATP, National Cholesterol of Education Program's Adult Treatment Panel III; WHO, World Health Organization; DM, Diabetes Mellitus; Adjusted for: age, race/ethnicity, site, MENOPAUSAL STATUS, education, smoking , BMI, Body Mass Index; LDL-C and hormone use

Table 6-4 Association of metabolic syndrome with carotid plaque in middle-aged women

	IDF			NCEP-ATP III			WHO		
	OR	**95% CI**	**AUC**	**OR**	**95% CI**	**AUC**	**OR**	**95% CI**	**AUC**
All Women									
Unadjusted	1.61	(1.30, 2.01)	0.554	1.68	(1.35, 2.10)	0.557	1.69	(1.27, 2.24)	0.535
Adjusted	1.70	(1.30, 2.18)	0.661	1.71	(1.31, 2.23)	0.660	1.98	(1.46, 2.75)	0.648
No DM									
Unadjusted	1.54	(1.20, 1.97)	0.543	1.60	(1.24, 2.06)	0.545	--	--	--
Adjusted	1.57	(1.18, 2.08)	0.659	1.61	(1.20, 2.17)	0.661	--	--	--

* p<.0001; Carotid IMT, Carotid Intima-Media Thickness; IDF, International Diabetes Federation; NCEP-ATP, National Cholesterol of Education Program's Adult Treatment Panel III; WHO, World Health Organization; DM, Diabetes Mellitus; Adjusted for: Adjusted for: age, race/ethnicity, site, MENOPAUSAL STATUS, education, smoking , BMI, Body Mass Index; LDL-C and hormone use

Table 6-5 Association of Individual components of metabolic syndrome with Carotid IMT in middle-aged women

	IDF		NCEP-ATP III		WHO	
	β(SE)	***P***	**β(SE)**	***P***	**β(SE)**	***P***
Hypertension	**0.0273 (0.007)**	**<.0001**	**0.0276(0.007)**	**<.0001**	**0.0293(0.006)**	**<.0001**
HDL-c	-0.0008 (0.008)	0.9122	-0.0003(0.008)	0.9647	0.0172(0.016)	0.2977
Glucose	**0.0264 (0.007)**	**0.0002**	**0.0272(0.007)**	**0.0001**	**0.0211(0.008)**	**0.0098**
WC	**0.0293 (0.009)**	**0.0009**	**0.0182(0.008)**	**0.0330**	---	---
Triglycerides	0.00858 (0.008)	0.2911	0.0090(0.0081)	0.2684	0.0096(0.008)	0.2271
BMI	---	---	---	---	0.0139(0.008)	0.0848

* p<.0001; Carotid IMT, BP, Blood Pressure; WC, waist Circumference; Carotid Intima-Media Thickness; IDF, International Diabetes Federation; NCEP-ATP, National Cholesterol of Education Program's Adult Treatment Panel III; WHO, World Health Organization; Adjusted for: age, race/ethnicity, site, MENOPAUSAL STATUS, education, smoking , BMI, Body Mass Index; LDL-C and hormone use

Table 6-6 Association of Individual components of metabolic syndrome with Carotid plaque in middle-aged women

	IDF			NCEP-ATP III			WHO		
	OR	**95% CI**	***P***	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Hypertension	**1.65**	**(1.28, 2.13)**	**0.0001**	**1.62**	**(1.26, 2.09)**	**0.0002**	**1.75**	**(1.36, 2.25)**	**<.0001**
HDL-C	1.30	(0.97, 1.73)	0.0841	1.27	(0.95, 1.69)	0.1063	1.60	(0.84, 2.98)	0.1607
Glucose	**1.48**	**(1.14, 1.95)**	**0.0035**	**1.48**	**(1.13, 1.93)**	**0.0043**	**1.32**	**(1.05, 1.98)**	**0.0235**
WC	1.01	(0.72, 1.42)	0.9441	1.27	(0.91, 1.75)	0.1527	---	---	
Triglycerides	1.11	(0.82, 1.51)	0.4919	1.09	(0.80, 1.48)	0.5794	1.13	(0.84, 1.53)	0.4612
BMI	---	---	---	---	---	---	**1.40**	**(1.03, 1.90)**	**0.0319**

BP, Blood Pressure; WC, waist Circumference; OR, odds ratio; CI, Confidence interval; P, p-value; Carotid IMT, Carotid Intima-Media Thickness; IDF, International Diabetes Federation; NCEP-ATP, National Cholesterol of Education Program's Adult Treatment Panel III; WHO, World Health Organization; Adjusted for: age, race/ethnicity, site, MENOPAUSAL STATUS, education, smoking , BMI, Body Mass Index; LDL-C and hormone use

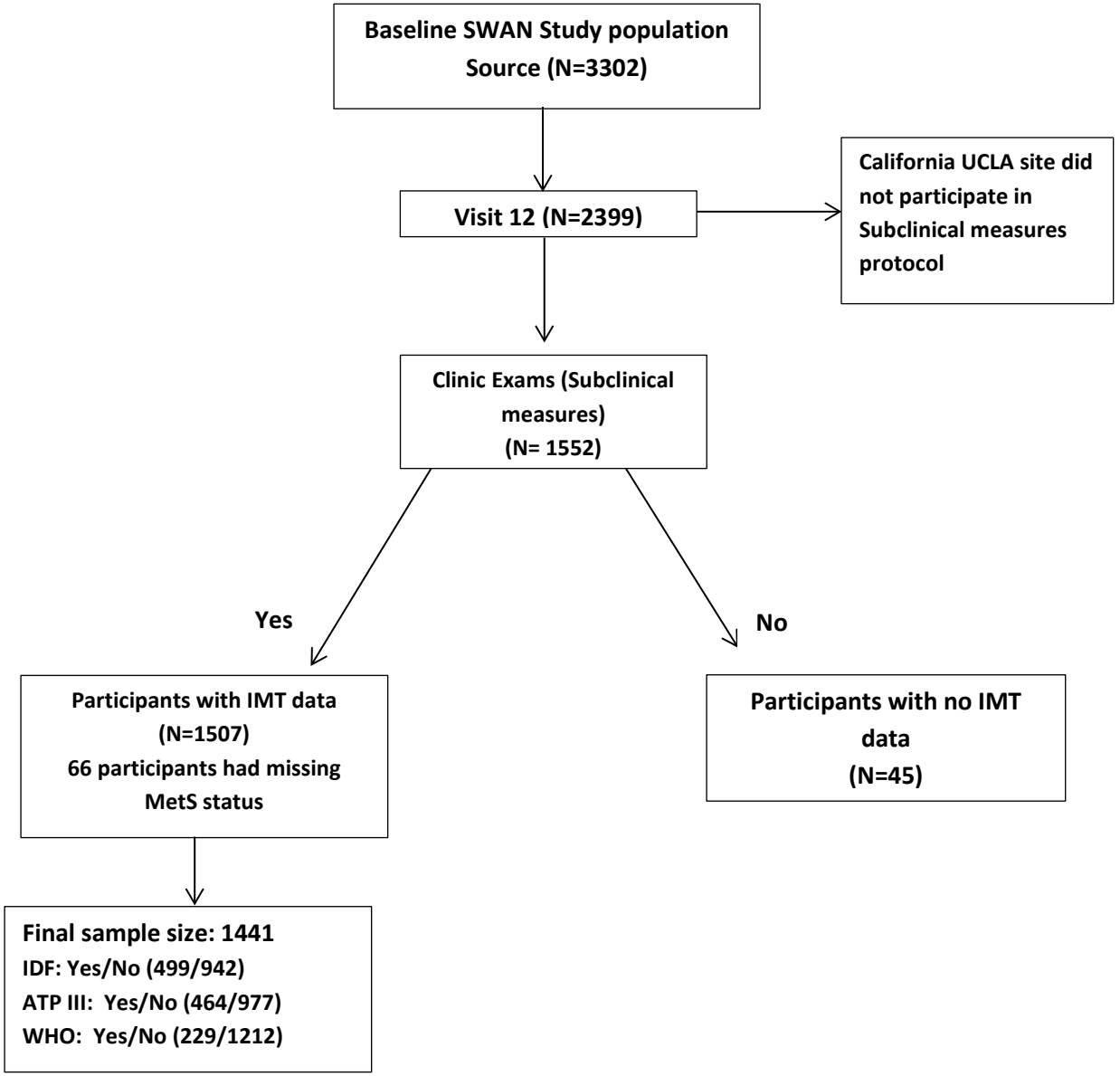
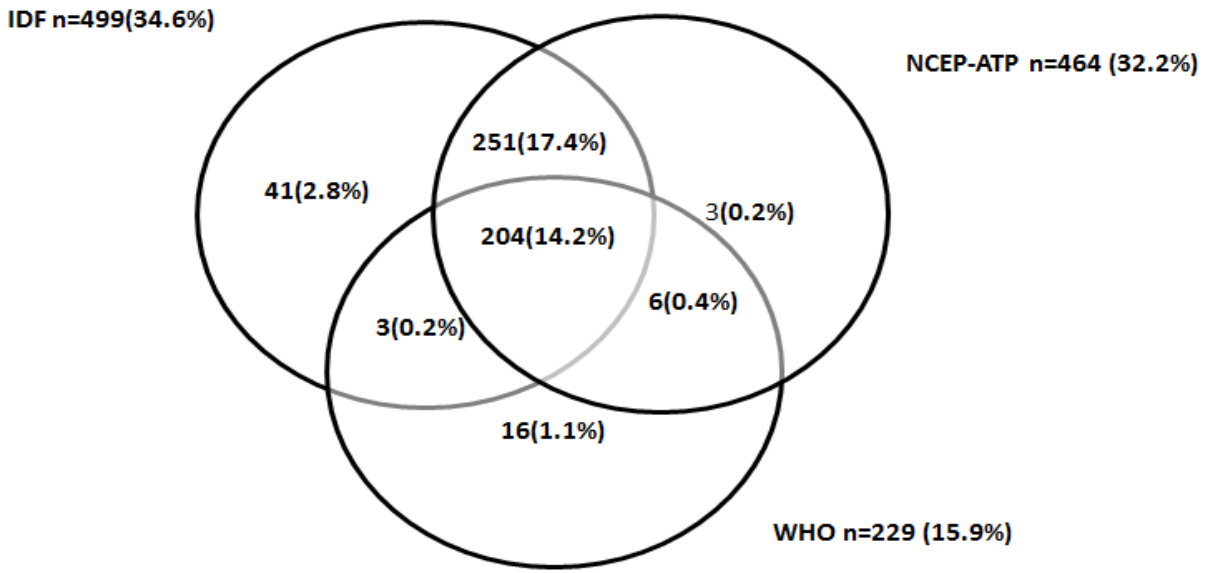


Figure 6-1 The flowchart of participants included in this study



Graphical presentation of participants fulfilling International Diabetes Federation(IDF), The National Cholesterol Education Program Expert Panel- Adult Treatment Panel (NCEP-ATP) and World Health Organizations (WHO) definitions for metabolic syndrome. Presented as counts and percentages of the study

Figure 6-2 Prevalence of Metabolic Syndrome by definitions used in the study

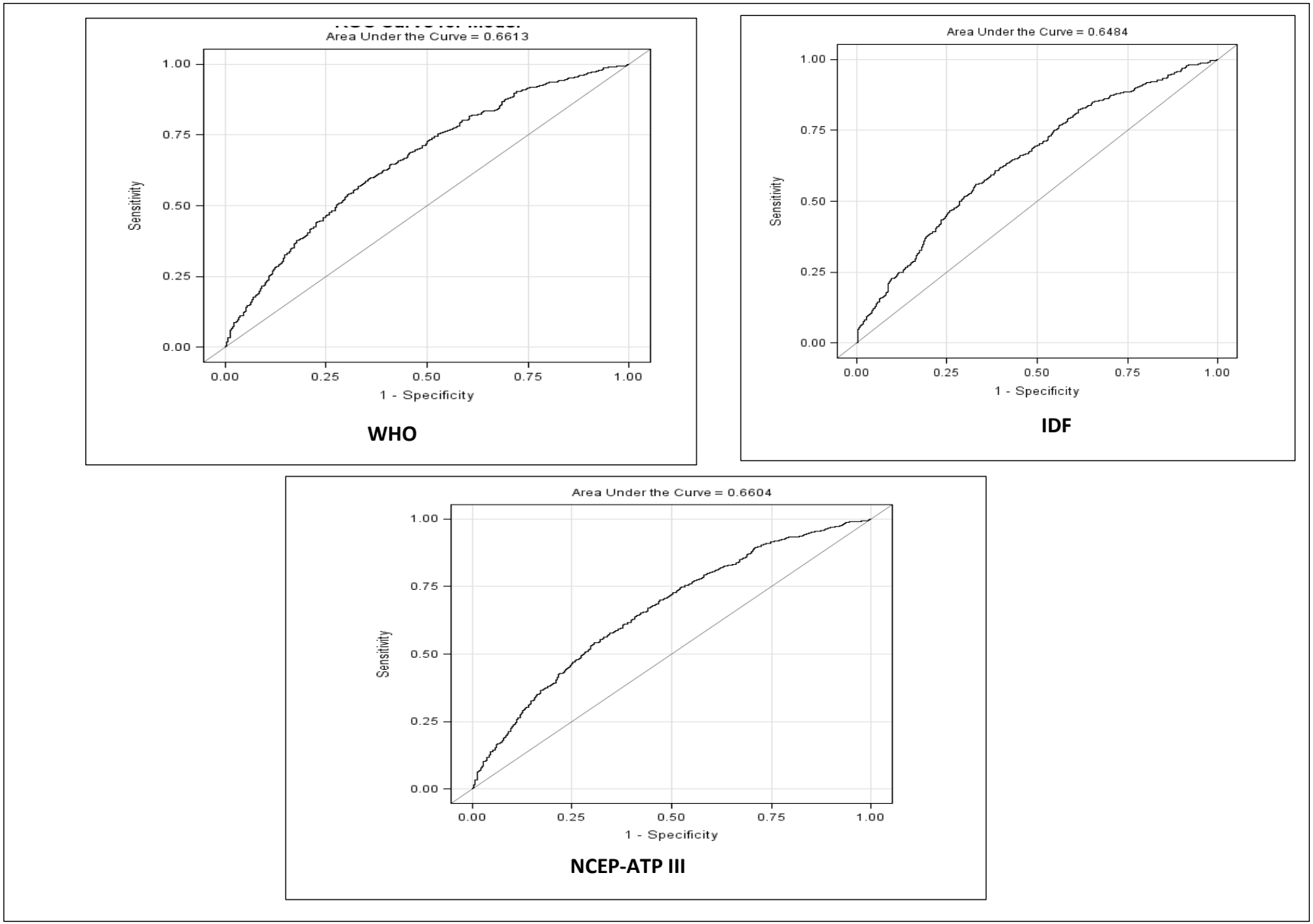


Figure 6-3 Area under receiver-operator characteristic curve by metabolic syndrome definition

7.0 MANUSCRIPT 2: METABOLIC SYNDROME AND CAROTID REMODELING IN NON-DIABETIC MIDDLE-AGED WOMEN: THE STUDY OF WOMEN'S HEALTH ACROSS THE NATION

Julius Asubonteng, [1] Emma Barinas-Mitchell, [1] Stephen Wisniewski, [1] Rebecca Thurston, [1, 2] Suresh Mulukutla, [3] Faith Selzer [1]

[1] Department of Epidemiology, University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA

[2] Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA

[3] Cardiovascular Institute, University of Pittsburgh Medical Center, Pittsburgh, PA

(This manuscript is in preparation to be submitted to the Journal of the American College of Cardiology)

7.1 ABSTRACT

Background and Objective: The metabolic syndrome (MetS) is linked to higher risk of cardiovascular disease (CVD) events, including stroke. However, few studies have assessed MetS and maladaptive remodeling in relation to subclinical CVD. The aim of this study was to examine whether MetS was associated with maladaptive remodeling of the common carotid artery, and if the association was independent of select inflammation, metabolic and hemodynamic factors.

Methods: Participants from 6 sites of the Study of Women's Health Across the Nation (SWAN) free of diabetics and who had B-mode ultrasound images at the 12th annual visit were analyzed. Women were classified as having MetS if they met the criteria defined by National Cholesterol Education Program Adults Treatment Panel III (NCEP-ATP III). Multivariable linear regression was used to investigate the association between the presence of MetS and carotid remodeling while adjusting for potential confounders.

Results: MetS was significantly and positively associated with LD (β (95 % confidence interval)), 0.218 mm (0.149, 0.288)), AD (0.281 mm (0.201, 0.362)), IMT (0.032 mm (0.017, 0.046)), CWT (5.48 kPa (4.16, 6.79)) and CWS (4.14 kPa (2.14, 6.13)) after adjustment for age, height, education, site, use of hormone therapy, menopausal status, low-density lipoprotein-cholesterol and smoking. These associations were slightly lessened when inflammation, metabolic and hemodynamic variables were further adjusted for. The Hispanic by MetS interaction term was significantly associated with IMT. The Black by MetS interaction was negatively associated with CWT. Both Black and Hispanic ethnicities by MetS interaction terms

were negatively associated with CWS after adjustment for inflammatory, metabolic and hemodynamic factors.

Conclusion: The presence of MetS is associated with maladaptive remodeling of the common carotid artery in non-diabetic middle-aged women independent of select inflammatory, metabolic, and hemodynamic risk factors. Different patterns of remodeling were observed by race/ethnicity, and how these patterns of remodeling could potentially be related to the variation in risk of stroke warrant further examination.

7.2 INTRODUCTION

The presence of metabolic syndrome (MetS), defined as a cluster of risk factors including central obesity, dyslipidemia, elevated blood pressure and impaired glucose, is associated with incident ischemic stroke [186-188]. While the association between MetS and the risk of stroke is not clearly understood, it has been postulated that both structural and functional arterial changes such as the remodeling of large arteries located in the head and neck may play an important role in this association [189], however, there is paucity of data on the role of MetS on arterial remodeling (AR).

Arterial remodeling occurs in response to inflammatory, metabolic, and hemodynamic alterations within the arterial environment [189, 190] and is considered to occur naturally with aging. Early arterial remodeling is significantly associated with hemodynamic changes, as well as cardiovascular morbidity and mortality [118]. Arterial remodeling consists of intimal-medial arterial thickening or dilation. These processes can be evaluated non-invasively by using ultrasound to measure intima-media thickness (IMT) [191] and adventitial diameter (AD), respectively, of the common carotid artery. Thicker IMT and wider AD have been shown to be risk factors for overt cardiovascular disease (CVD) and in particular, incident stroke[192]. Furthermore, AR that occurs in concert with increases in circumferential wall tension (CWT) and circumferential wall stress (CWS) is considered maladaptive [189, 193]. Maladaptive AR is also associated with the risk of stroke, as evidenced by higher carotid CWT among patients who have had stroke [194].

The association between MetS and carotid artery remodeling has been investigated in population-based studies. Several epidemiological studies have reported an association between MetS and carotid artery remodeling in non-diabetic individuals [189], in young to middle-aged women [152], and in older adults independent of traditional CVD risk factors [163]. However, few studies have sought to characterize the association between MetS and arterial remodeling in combination with CWT and CWS. Moreover, the published findings to date on MetS and carotid remodeling are limited to small samples of primarily white study participants. Whether or not the MetS and common carotid artery remodeling relationship is applicable to women of older middle-aged and other ethnicities needs to be studied further.

To address several of the gaps, our study examined the relationship between MetS and common carotid artery remodeling as measured by lumen diameter, AD, carotid IMT, CWT, CWS and the associated pattern of remodeling in a cohort of older middle-aged women of mixed races/ethnicities. Furthermore, we assessed the role of inflammatory, metabolic and hemodynamic factors on the relationship between MetS and common carotid artery remodeling because the effect of these factors on the association between MetS and common carotid artery parameters have not been fully established. Finally, we examined the relationship between race/ethnicity, MetS, and common carotid artery remodeling to evaluate differential effect by race/ethnicity via interactions between MetS and racial/ethnic groups.

7.3 METHODS

7.3.1 Study Population

The study sample consisted of women enrolled in the Study of Women's Health Across the Nation (SWAN) who were pre/peri-menopausal or postmenopausal by their 12th follow-up visit. SWAN is a multiethnic, community-based, longitudinal cohort of the natural history of 3302 women enrolled at 7 sites throughout the United States (Boston, Massachusetts; Chicago, Illinois; Detroit, Michigan; Los Angeles, California; Oakland, California; Newark, New Jersey; and Pittsburgh, Pennsylvania). The cohort at baseline was composed of White, Black, Chinese, Japanese and Hispanic women, aged 42 to 52 years, who had an intact uterus and at least one ovary, had at least one menstrual period in the preceding 3 months, had not used sex steroid hormone therapy in the preceding 3 months and were not pregnant. Of the initial 3302 women at baseline, 2399 participants were seen at 12^{th} visit, and 1552 (64.7%) underwent a carotid artery ultrasound examination as part of the study visit. The University of California at Los Angeles site did not participate in the carotid ultrasound protocol and is therefore not included in this analysis. Among participants who participated in the carotid ultrasound protocol, 45 women were removed from the analysis due to missing IMT data. An additional 60 participants were excluded due to missing data pertaining to MetS criteria, and 193 diabetic participants were excluded because of compromised arterial function in type 2 diabetics, leaving a final sample size of 1254 (80.8%) participants (Figure 7-1). The institutional review board at each site approved the protocol and all women provided written informed consent.

7.3.2 Assessment of cardiovascular and metabolic risk factors

All study participants underwent annual or biannual study visits consisting of interviewer-administered questionnaires to ascertain medication use, medical history, lifestyle characteristics and menopausal status, physical measures, and a fasting blood draw and for assessment of cardiovascular risk factors and reproductive hormone levels. Race or ethnicity was self-reported.

Blood pressure was measured in the right arm, while participants were seated with feet flat on floor following at least 5 minutes of sitting quietly before measurements were taken. A standard mercury sphygmomanometer was used to measure systolic and diastolic pressures at first and fifth korotkoff sounds. The average of two sequential readings was used in the analyses. Pulse pressure was defined as difference between systolic and diastolic blood pressure. Height was measured without shoes using a stadiometer. Weight was measured without shoes, and with light indoor clothing using calibrated scales. Waist circumference was measured with participants in light undergarments.

Lipids, glucose and insulin were measured on a Siemens ADVIA 2400 automated chemistry analyzer utilizing Siemens ADVIA chemistry system reagents (Siemens Healthcare Diagnostics, Deerfield IL) at the University of Michigan Pathology Laboratory, a Clinical Laboratory Improvements Amendments (CLIA) certified and accredited laboratory. Triglycerides, high-density lipoprotein cholesterol (HDL-C) and directly-measured low density lipoprotein cholesterol (LDL-C) [174] were analyzed using a coupled enzymatic methods that utilized lipase, glycerol kinase, glycerol-3-phosphate oxidase (G3PO), and peroxidase (for

triglycerides) and cholesterol esterase, cholesterol oxidase, and peroxidase (for HDL-C and direct LDL-C). Serum insulin was measured by a two-site sandwich immunoassay using direct chemiluminescent technology that uses constant amounts of two antibodies. High sensitivity C-reactive protein (CRP) levels were measured using an ultra-sensitive rate immunonephelometric method (BN 100, Dade-Behring, Marburg, Germany). Adiponectin was measured via the quantitative sandwich enzyme immunoassay technique. Glucose was measured using a two-step enzymatic reaction that utilized hexokinase and glucose-6-phosphate dehydrogenase (G6PDH) enzymes. Diabetes was defined as either fasting glucose ≥ 126 mg/dL, diagnosis of diabetes by a physician or use of anti-diabetic medications.

7.3.3 NCEP-ATP III metabolic syndrome definition

The NCEP-ATP III criterion was used to identify MetS. This definition consists of meeting at least three of the following five factors: central obesity (waist circumference > 102 cm for men, > 88 cm for women), raised triglycerides (≥ 150 mg/dL), elevated blood pressure (systolic blood pressure ≥130 mmHg / diastolic blood pressure ≥ 85 or use of anti-hypertensive medications), fasting plasma glucose (≥110 mg/dL) and reduced HDL cholesterol (< 40 mg/dL for men, < 50 mg/dL for women) [175]. An individual with three or more of the above factors was classified as having MetS.

7.3.4 Carotid Arterial Properties

At each site, centrally trained and certified sonographers obtained carotid ultrasound images using a Terason t3000 Ultrasound System (Teratech Corp, Burlington, MA) equipped with a variable frequency 5-12 MHz linear array transducer. Two digitized images for later reading by 2 trained readers at the SWAN Ultrasound Reading Center (University of Pittsburgh Ultrasound Research Lab) were obtained for each of the left and right distal common carotid artery (CCA). From each of these 4 images, using the Artery Measurement System (AMS) semi-automated edge detection software [178], near and far wall CCA intima-media thickness (IMT) measures were obtained by electronically tracing the lumen-intima interface and the media-adventitia interface across a 1-cm segment proximal to the carotid bulb. The average and maximal values were recorded for each image, with the mean of the average and maximal readings of all images used in analyses. Common carotid artery (CCA) inter-adventitial diameters were measured directly as the distance from the adventitial-medial interface on the near wall to the medial-adventitial interface on the far wall at end-diastole across the same CCA segments used for IMT measurement. Lumen diameter (LD) was directly measured, and defined as the distance from the intima-lumen interface of the near wall to the lumen-intima interface of the far wall. Mean circumferential wall tension (CWT) and circumferential wall stress (CWS) were calculated according to Laplace's law[194]. Mean CWS and CWT were calculated as CWT (kPa) = MAP (LD/2) and CWS (kPa) = mean CWT/IMT [189], where MAP is the mean arterial pressure. MAP was approximated as [(2* diastolic blood pressure) + systolic blood pressure]/3. Reproducibility of IMT measures was good to excellent with an intraclass correlation coefficient between sonographers of ≥ 0.77, and between readers of > 0.90. The scanning and reading protocols have been used in numerous studies [180, 181, 195].

7.3.5 Statistical analyses

Demographic characteristics, cardiovascular disease risk factors, and measures of carotid artery properties were compared between participants with and without MetS using the chi-square test for categorical variables, and either t-tests or Wilcoxon test for continuous variables depending on the distribution of the variable.

Multivariable linear regression was used to examine the relationship between MetS and carotid artery properties, as measured by lumen diameter, adventitial diameter, carotid IMT, mean circumferential wall stress and circumferential wall tension. A series of models were fit: model 1 adjusted for age, height, education, site, hormone use, menopausal status, LDL-cholesterol and smoking. These variables were controlled for based on previous studies, as well as the design of the SWAN Study. To assess the additional effect of inflammation on the association between MetS and common carotid artery parameters, high sensitivity C- reactive protein (CRP), a non-specific marker of inflammation, was added to model 1. The effect of the metabolic factor adiponectin and the hemodynamic factor pulse pressure were also assessed in relation to MetS and common carotid artery parameters by adding each to model 1.

The relationship between MetS and common carotid artery remodeling was assessed whether it differed by race and ethnicity. The White participants were used as the reference group. To test whether remodeling differed by race/ethnicity and MetS, interaction terms were included to the models specified above that also included the main effects for MetS and race/ethnicity. In the regression model, the association between MetS and carotid properties was reported as coefficient (betas) along with the 95 % confidence intervals. Regression assumptions

were assessed in each model fit. A two-sided p-value (<0.05) was considered statistically significant.

7.4 RESULTS

Clinical characteristics by MetS status

Selected clinical characteristics measured at the 12th study visit according to the presence or absence of MetS is described on Table 7-1. The prevalence of MetS was 25.7% with the prevalence of MetS among the racial group as follows: Blacks (31.8%), White (24.4%), Chinese (13.6%) and Hispanic (36.7%), $p<0.001$. Higher levels of hsCRP and fasting insulin were observed among participants with MetS. Participants without MetS had higher mean total cholesterol levels, were less likely to report use of lipid modifying medications and also had higher mean adiponectin levels than those with MetS.

Participants with MetS had greater mean carotid IMT, LD and AD compared to participants without MetS (Table 7-2). Furthermore, participants with MetS had greater mean CWS and CWT compared to participants without MetS.

MetS and Arterial remodeling

MetS was significantly associated with both LD and AD even after adjustment for age, height, education, site, hormone use, menopausal status, low-density lipoprotein-cholesterol and smoking (Table 7-3, model 1). With the inclusion of the inflammatory marker hsCRP, both LD and AD remained significantly associated with MetS, but the strength of the associations slightly lessened (Table 7-3, model 2). Further adjustment for the metabolic factor adiponectin and the hemodynamic factor pulse pressure did not change the relationship between MetS and both LD

and AD (Table 7-3, model 3 and 4). Similar to measures of lumen diameter, MetS was significantly associated with carotid IMT after adjustment for age, height, education, site, hormone use and menopausal status, low-density lipoprotein-cholesterol and smoking (Table 7-3, model 1). After adjusting individually for inflammatory, metabolic, and hemodynamic risk factors, the presence of MetS was significantly and positively associated with carotid IMT (Table 7-3, model 2-4). The presence of MetS was significantly associated with higher mean CWT and CWS after controlling for age, height, education, site, hormone use and menopausal status, low-density lipoprotein-cholesterol and smoking (Table 7-3, model 1). Adjusting for hsCRP did not alter the association between MetS and mean CWT and CWS (Table 7-3, model 2). Again, adjusting for metabolic and hemodynamic factors did not change the associations between MetS and mean CWT and CWS (Table 7-3, Model 3 and 4).

Mets and carotid arterial properties by race/ethnicity

To assess a differential effect of race/ethnicity and metabolic status on carotid remodeling, the overall effect of racial/ethnic, main effects and interaction terms for each racial/ethnic group were tested. The overall effect of race was significantly associated with LD, AD, IMT, CWT and CWS after adjusting for potential confounders. The main effects of Black and Chinese ethnicities were significantly associated with LD (Table 7-4). Only the main effect of Black ethnicity was significantly associated with AD (Table 7-5), carotid IMT (Table 7-6), CWT (Table 7-7) and CWS (Table 7-8) after adjusting for potential confounders.

None of the race and ethnicity by MetS interaction terms was significant with respect to LD (Table 7-4). However, the interaction term for Hispanic participants by MetS was close to being significantly associated with AD after adjustment for pulse pressure (Table 7-4, model 4).

The Hispanic by MetS interaction term was significantly associated with carotid IMT after controlling for age, height, education, site, hormone use, menopausal status, low-density lipoprotein-cholesterol and smoking (Table 7-6, model 1). Including hsCRP in the model, there was a marginal association between Hispanic by MetS interaction term and carotid IMT (Table 7-6, model 2). The Hispanic by MetS interaction term remained significantly associated with carotid IMT after further adjustment for metabolic and hemodynamic factors (Table 7-6, model 3 and 4).

The Black by MetS interaction term was negatively associated with circumferential wall tension (CWT) and independent of inflammatory, metabolic and hemodynamics factors (Table 7-7). Similar patterns were observed for the interaction terms between Hispanic ethnicity and MetS but statistical significance was not reached. Both Black and Hispanic ethnicities by MetS interaction terms were negatively associated with circumferential wall stress (CWS) independent of inflammatory, metabolic and hemodynamic factors. In race-specific model, we found variations of association between MetS and IMT. Among Chinese, Black ethnicities, significant associations between MetS and IMT were observed independent of metabolic and hemodynamic factors. No significant association was observed between MetS and IMT among Whites while adjusting for inflammatory, metabolic and hemodynamic factors. CWT and CWS were significantly associated with MetS in each of the race-specific model for Black, Whites, Chinese and Hispanic ethnicities independent of inflammatory and metabolic factors.

7.5 DISCUSSION

This study assessed the association between MetS and remodeling of the common carotid artery among non-diabetic older middle-aged women. Our findings showed that MetS is significantly associated with maladaptive remodeling of the common carotid artery as indicated by greater mean adventitial diameter, lumen diameter and carotid IMT. Moreover, an outward pattern of remodeling was observed as evidenced by greater mean circumferential wall tension and circumferential wall stress in women with MetS. Our findings also indicated that the associations between MetS and carotid artery remodeling are independent of inflammatory, hemodynamic, and metabolic risk factors. Finally, we observed differential maladaptive remodeling patterns of the common carotid artery with MetS status by race/ethnicity. Specifically, Black and Hispanic women with MetS experienced more extreme remodeling of the common carotid artery than their White counterparts.

In this study, we assessed the impact of inflammatory, metabolic and hemodynamic factors on the relationship between MetS and carotid artery remodeling. While the roles of these factors on the relationship between MetS and carotid artery remodeling are still not clear [196-198], we found a significant difference in the non-specific marker of inflammation hsCRP among those with MetS compared to those without MetS. However, hsCRP did not explain the association between MetS and carotid artery remodeling. In our study, we also observed lower levels of adiponectin among participants with MetS compared to those without MetS, and yet, the association between MetS and carotid artery remodeling was not explained by hypo-adiponectinemia. Hypoadiponectinemia has been shown to be associated with ischemic stroke [199, 200], and in line with this association, it has been suggested that adiponectin levels be

incorporated in the criteria that define MetS [196]. However we found no evidence to support such a proposition. Furthermore, the assessment of the hemodynamic factor pulse pressure did not explain the relationship between MetS and carotid artery remodeling, although the strength of the association was lessened slightly with the addition of pulse pressure to the models. These findings suggest that there are other potential factors at play in the association between MetS and carotid artery remodeling other than those that have been explored in this study.

The findings from our study are in an agreement with what others have reported regarding the association between MetS and carotid artery remodeling [152, 163, 189]. In a French study, Empana et al reported significant association between MetS and carotid artery structure along with the outward pattern of remodeling of the carotid artery [163]. Iannuzzi et al also observed a significant association between MetS and carotid remodeling in middle-aged women, as well as an outward pattern of remodeling [152]. However, none of these two previous studies evaluated either CWT or CWS, which are measures used to determine whether or not observed remodeling patterns are maladaptive. In a small study of older white adults, Beijers et al reported that MetS was associated with maladaptive remodeling of the carotid artery as depicted by changes in carotid artery measures along with increases in mean CWT and CWS (4). As an extension to the findings of Beijers et al, we found significant associations between MetS and carotid IMT independent of inflammatory, hemodynamic and metabolic factors, along with significant changes in CWT and CWS in a multiethnic study population.

The findings from this study showed that not only was race/ethnicity associated with measures of remodeling of the carotid artery independent of MetS but that there was a differential effect by race/ethnicity and MetS status. We observed significant interactions between Hispanic ethnicity by MetS and carotid IMT independent of confounding factors

including age, height, education, site, hormone use, menopausal status, low-density lipoprotein-cholesterol and smoking, as well as select inflammatory, metabolic and hemodynamic factors. Hispanic ethnicity by MetS was marginally associated with AD. A significant association was observed between Black ethnicity and CWT. We also observed significant interaction terms by Black and Hispanic ethnicities on the association between MetS and CWS independent of the inflammatory, metabolic and hemodynamic factors evaluated in our analyses. Taken together, these findings point to a pattern of maladaptive remodeling that differed by race/ethnicity, which is important because there are evidence that it is associated with greater risk of stroke[194]. The study participants are in midlife, which is very important phase of life for women, where changes in lipids [201] and vascular measures such as IMT [202]are reported to occur. Given these changes that are known to occur in midlife, the variations in associations observed in this study clearly have clinical implication in light of the known differences in morbidity and mortality in CVD.

Several epidemiological studies have linked the MetS and vascular remodeling, as well as greater risk for incidence of stroke. Data from the National Health and Nutrition Examination Survey (NHANES) established a significant association between MetS and ischemic stroke [77], as well as a higher number of prevalent vascular risk factors among ethnic women as compared to white women[203]. Several prospective studies have also shown a link between MetS and stroke [186, 204]. In a multiethnic Northern Manhattan Study (NOMAS) cohort, Boden-Albala et al [205] reported that the presence of MetS was strongly associated with vascular disease and stroke in women, and that the association was strongest among Hispanic participants. In the Cardiovascular Health Study (CHS) cohort, O'Leary et al showed that increases in carotid IMT were directly associated with greater risk of stroke in older adults without a history of CVD

[206]. Bots et al reported a significant association between carotid IMT and stroke in the Rotterdam Elderly Study [191]. In spite of the findings from these studies, there were limitations that our current study sought to address. CHS did not assess the effect of race and ethnicity on the association between risk of stroke and increases on carotid IMT, as well as evaluated measures to characterize the extent of the carotid remodeling. The Rotterdam Elderly Study included participants with symptomatic cardiovascular disease and the authors concluded that incorporating such participants affected the magnitude of the association between carotid remodeling and stroke. In our study, a potential explanation for the differential pattern of maladaptive remodeling of the carotid artery by race/ethnicity could be due largely to some unmeasured risk factors. There are ethnic and racial variations in some subclinical CVD measures [207, 208] . Black ethnicity is reported to have a greater mean IMT compared to South Asians [207], and non-Hispanic White [209] when CVD risk factors are adjusted for. In vein of these ethnic and racial variations, it remains to be seen if the ethnic comparisons in this study are valid or not; however, if appropriate set of covariates are adjusted for then the comparisons in this study should be deemed to be right. Given the entirety of the evidence, it is possible that variations in stroke risk could be as a result of the underlying vascular risk factors and their association with surrogate measures of subclinical atherosclerosis all of which vary by the race/ethnicity.

The current study has some strengths as well as limitations. This is the first study to assess carotid artery remodeling in a multi-ethnic cohort focused on examining the association between MetS and carotid remodeling in non-diabetic older middle-aged women. As a cross-sectional study, inferences regarding causality must be made with caution. There was paucity of data in Hispanic ethnicity therefore the importance of comparisons made in this study must be

carefully interpreted. No three dimensional images of the carotid artery image were made, therefore vascular measurements such as CWT and CWS might have either underestimated or overestimated the association between MetS and carotid artery remodeling.

In conclusion, the presence of MetS is associated with maladaptive remodeling of the common carotid artery in non-diabetic older middle-aged women independent of select inflammatory, metabolic, and hemodynamic risk factors. Different patterns of remodeling were observed by race/ethnicity, and how these patterns of remodeling could potentially be related to the variation in risk of stroke warrant further examination. The findings suggest that targeting metabolic syndrome in midlife women would subsequently help to prevent CVD among multiethnic women.

7.6 TABLES AND FIGURES

Table 7-1 Baseline characteristics according to metabolic syndrome status

Characteristics	Metabolic Syndrome		
	Absent (N=932)	**Present(N=322)**	P value
Age(years)	59.6±2.7	59.6±2.7	0.50
Race (n, %)			
Black	247(26.5)	115(35.7)	<.0001
White	501(53.8)	162(50.3)	
Chinese	146(15.7)	23(7.1)	
Hispanic	38(4.1)	22(6.8)	
MetS Traits			
Systolic blood pressure(mm Hg)	118.8±15.8	127.7±16.0	---
Diastolic blood pressure(mm Hg)	73.3±9.8	77.1± 9.8	---
Antihypertensive medication use n (%)	233(25.0)	208(64.6)	---
HDL-cholesterol (mg/dl)	67.5±15.6	51.4±11.9	---
Triglycerides(mg/dl)	90(68-116)	145.5(107-190)	---
Fasting glucose(mg/dl)	89(84-95)	101(93-110)	---
Waist(cm)	86.9±13.2	103.4±13.7	---
Other characteristics			
Smoking n (%)	61(6.7)	44(13.8)	<.0001
BMI(kg/m^2)	27.7±6.3	34.1±6.5	<.0001
Total cholesterol (mg/dl)	210.1±35.9	203.5±38.7	<.0001
LDL-cholesterol(mg/dl)	123.3±29.0	121.2±31.4	<.0001
Treatment with lipid-lowering medications n (%)	180(19.3)	132(41.0)	<.0001
Fasting Insulin (uIU /ml)	7.1(4.8-11.0)	15.6(11.3-22.7)	<0.001
$HOMA_{IR}$	1.6(1.02-2.48)	3.88(1.88-5.82)	<.0001
Heart rate(bpm)	66.0±8.2	68.6±9.7	0.0001
Hs-CRP(mg/l)	1.16(0.47-1.16)	3.14(1.26-7.27)	<.0001
Adiponectin (mg/mL)	15.4±9.7	8.4±5.2	<.0001
Hormone use n (%)	46(4.9)	15(4.7)	0.84

Data are presented as mean ± s.d or median (interquartile range); BMI, body mass index; HDL, high-density lipoprotein; $HOMA_{IR}$, homeostasis model assessment for insulin resistance; LDL, low-density lipoprotein; MetS, metabolic syndrome; WHR, waist-to-hip ratio; Hs-CRP, high sensitivity C-reactive protein.

Table 7-2 Carotid arterial properties according to metabolic syndrome status

Carotid Arterial Properties	Metabolic syndrome		
	Absent (n=932)	**Present (n=322)**	***P value***
Mean Adventitial diameter (mm)	7.07 ±0.61	7.39±0.66	<.0001
Mean Intima-media thickness (mm)	0.77 ±0.11	0.82±0.13	<.0001
Mean Lumen diameter (mm)	5.5±0.53	5.8±0.56	<.0001
Mean circumferential wall tension (kPa)	32.6±5.5	36.1±5.6	<.0001
Mean circumferential wall stress (kPa)	42.7±7.9	45.0±8.5	<.0001

Results are expressed as means ± s.d; adjusted for age, race and site; mm, millimeter

Table 7-3 Carotid remodeling according to the presence or absence of MetS

Model	LD(mm)		AD(mm)		IMT(mm)		CWT(kPa)		CWS(kPa)	
	β	95% CI	β	95% CI	β	95% CI	β	95% CI	β	95% CI
1	0.218	0.149, 0.288*	0.281	0.201, 0.362*	0.032	0.017, 0.046*	5.48	4.16, 6.79*	4.14	2.14, 6.13*
2	0.206	0.132, 0.279*	0.258	0.173, 0.343*	0.026	0.011, 0.042*	5.20	3.81, 6.59*	4.30	2.21, 6.39*
3	0.200	0.127, 0.273*	0.255	0.171, 0.339*	0.028	0.013, 0.043*	4.99	3.60, 6.37*	3.87	1.77, 5.97*
4	0.188	0.119, 0.257*	0.236	0.157, 0.315*	0.024	0.009, 0.0381*	4.10	2.89, 5.31*	3.12	1.15, 5.09*

Results are expressed as regression coefficients (beta) and respective 95% CI. The regression coefficient beta indicates the difference in arterial property (in units) between individuals with vs. without MetS. LDL-c, Low-density lipoprotein cholesterol; hsCRP, high sensitivity C - reactive protein; ln, logarithm; *P<0.001.

Model1, adjusted for age, height, education, site, hormone use, menopausal status, LDL-cholesterol + smoking
Model2, adjusted for model 1 + In –hsCRP
Model3, adjusted for model 1 + Adiponectin
Model4, adjusted for model 1 + pulse pressure

Table 7-4 Carotid remodeling according to the presence or absence of MetS by race/ethnicity: LD

	LD							
	Model 1		Model 2		Model 3		Model 4	
	β (SE)	*P*	β (SE)	*P*	β (SE)	*P*	β (SE)	*P*
MetS	0.23(0.05)	<.0001	0.19(0.05)	0.0002	0.22(0.05)	<.0001	0.19(0.05)	<.0001
Ethnicity								
Black	0.15(0.04)	0.0011	0.11(0.05)	0.0208	0.13(0.05)	0.0050	0.11(0.04)	0.0122
Chinese	0.25(0.07)	0.0002	0.25(0.07)	0.0006	0.25(0.07)	0.0002	0.26(0.063)	<.0001
Hispanic	-0.04(0.12)	0.7372	-0.07(0.13)	0.5904	-0.049(0.12)	0.6917	-0.049(0.12)	0.6812
Black*MetS	-0.038(0.08)	0.0767	-0.001(0.08)	0.9851	-0.028(0.08)	0.7139	-0.027(0.08)	0.7167
Chinese*MetS	-0.067(0.13)	0.1298	-0.056(0.13)	0.6712	-0.062(0.13)	0.6310	-0.07(0.13)	0.5888
Hispanic*MetS	0.14(0.15)	0.1490	0.19(0.15)	0.2122	0.15(0.14)	0.3181	0.17(0.14)	0.2354

Results are expressed as regression coefficients (beta) and respective standard error; p-value. The regression coefficient beta indicates the difference in arterial property (in units) between individuals with vs without MetS; LD, Lumen Diameter; LDL-c, Low-density lipoprotein cholesterol; hsCRP, high sensitivity C - reactive protein; ln, logarithm; Reference group: white women

Model1, adjusted for age, height, education, site, hormone use, menopausal status, LDL-cholesterol, smoking;
Model2, adjusted for model 1 + In – hsCRP
Model3, adjusted for model 1 + Adiponectin
Model4, adjusted for model 1 + pulse pressure

Table 7-5 Carotid remodeling according to the presence or absence of MetS by race/ethnicity: AD

	AD							
	Model 1		Model 2		Model 3		Model 4	
	β (SE)	P	β (SE)	P	β (SE)	P	β (SE)	P
MetS	0.26(0.06)	<.0001	0.22(0.06)	0.0002	0.25(0.06)	<.0001	0.21(0.05)	0.0002
Ethnicity								
Black	0.22(0.05)	<.0001	0.19(0.05)	0.0006	0.19(0.05)	0.0002	0.17(0.05)	0.0010
Chinese	0.27(0.08)	0.0004	0.27(0.08)	0.0010	0.27(0.08)	0.0006	0.29(0.08)	0.0001
Hispanic	-0.06(0.14)	0.6991	-0.09(0.15)	0.5617	-0.06(0.14)	0.6477	-0.07(0.14)	0.6094
Black*MetS	0.004(0.09)	0.9669	0.023(0.09)	0.8014	0.008(0.08)	0.9258	0.020(0.09)	0.8170
Chinese*MetS	0.026(0.15)	0.8610	0.030(0.15)	0.8426	0.032(0.15)	0.8291	0.025(0.15)	0.8648
Hispanic*MetS	0.27(0.17)	0.1160	0.313(0.18)	0.0763	0.28(0.17)	0.1066	0.32(0.17)	0.0599

Results are expressed as regression coefficients (beta) and respective standard error; p-value. The regression coefficient beta indicates the difference in arterial property (in units) between individuals with vs. without MetS; AD, Adventitial diameter; LDL-c, Low-density lipoprotein cholesterol; hsCRP, high sensitivity C - reactive protein, ln, logarithm; Reference group: white women

Model1, adjusted for age, height, education, site, hormone use, menopausal status, LDL-cholesterol, smoking
Model2, adjusted for model 1 + In – hsCRP
Model3, adjusted for model 1 + Adiponectin
Model4, adjusted for model 1 + pulse pressure

Table 7-6 Carotid remodeling according to the presence or absence of MetS by race/ethnicity: IMT

	IMT							
	Model 1		Model 2		Model 3		Model 4	
	β (SE)	P	β (SE)	P	β (SE)	P	β (SE)	P
MetS	0.016(0.01))	0.1101	0.014(0.01)	0.1934	-0.004(0.01)	0.7121	0.008(0.009)	0.4488
Ethnicity								
Black	0.035(0.009)	0.0001	0.037(0.009)	<.0001	0.028(0.009)	0.0018	0.028(0.009)	0.0022
Chinese	0.010(0.014)	0.4678	0.013(0.014)	0.3950	0.009(0.014)	0.4701	0.013(0.014)	0.3467
Hispanic	-0.007(0.03)	0.7905	-0.008(0.03)	0.7558	-0.014(0.03)	0.5832	-0.011(0.02)	0.6742
Black*MetS	0.021(0.02)	0.1844	0.012(0.02)	0.4510	0.022(0.01)	0.1138	0.024(0.016)	0.1292
Chinese*MetS	0.047(0.03)	0.0826	0.043(0.3)	0.1147	0.049(0.03)	0.0671	0.047(0.03)	0.0759
Hispanic*MetS	**0.064(0.03)**	**0.0394**	0.061(0.03)	0.0566	**0.062(0.3)**	**0.0443**	**0.071(0.3)**	**0.0196**

Results are expressed as regression coefficients (beta) and respective standard error, p-value. The regression coefficient beta indicates the difference in arterial property (in units) between individuals with vs. without MetS; IMT, Intima-media thickness; LDL-c, Low-density lipoprotein cholesterol; hsCRP, high sensitivity C - reactive protein, ln, logarithm; Reference group: white women

Model1, adjusted for age, height, education, site, hormone use, menopausal status, LDL-cholesterol, smoking;
Model2, adjusted for model 1 + In – hsCRP
Model3, adjusted for model 1 + Adiponectin
Model4, adjusted for model 1 + pulse pressure

Table 7-7 Carotid remodeling according to the presence or absence of MetS by race/ethnicity: CWT

	CWT							
	Model 1		Model 2		Model 3		Model 4	
	β (SE)	*P*	β (SE)	*P*	β (SE)	*P*	β (SE)	*P*
MetS	6.8(0.91)	<.0001	6.27(0.96)	<.0001	6.54(0.95)	<.0001	5.15(0.84)	<.0001
Ethnicity								
Black	5.52(0.83)	<.0001	4.99(0.88)	<.0001	5.12(0.87)	<.0001	4.04(0.77)	<.0001
Chinese	1.74(1.25)	0.1681	2.34(1.34)	0.0812	1.65(1.27)	0.1949	2.26(1.15)	0.0494
Hispanic	1.69(2.32)	0.4655	0.62(2.42)	0.7986	1.49(2.32)	0.5207	1.09(1.94)	0.6057
Black*MetS	**-4.09(1.45)**	**0.0048**	**-3.38(1.49)**	**0.0215**	**-3.81(1.46)**	**0.0092**	**-3.33(1.32)**	**0.0122**
Chinese*MetS	2.06(2.44)	0.3990	1.85(2.48)	0.4552	2.09(2.44)	0.3924	2.05(2.23)	0.3580
Hispanic*MetS	-3.38(2.79)	0.2279	-2.62(2.88)	0.3626	-3.37(2.80)	0.2288	-1.94(2.56)	0.4487

Results are expressed as regression coefficients (beta) and respective standard error, p-value. The regression coefficient beta indicates the difference in arterial property (in units) between individuals with vs without MetS. CWT, Circumferential Wall Tension; LDL-c, Low-density lipoprotein cholesterol; hsCRP, high sensitivity C - reactive protein; ln, logarithm; Reference group: white women

Model1, adjusted for age, height, education, site, hormone use, menopausal status, LDL-cholesterol, smoking;
Model2, adjusted for model 1 + In – hsCRP
Model3, adjusted for model 1 + Adiponectin
Model4, adjusted for model 1 + pulse pressure

Table 7-8 Carotid remodeling according to the presence or absence of MetS by race/ethnicity: CWS

	CWS							
	Model 1		Model 2		Model 3		Model 4	
	β (SE)	*P*	β (SE)	*P*	β (SE)	*P*	β (SE)	*P*
MetS	7.24(1.39)	<.0001	6.76(1.46)	<.0001	6.97(1.45)	<.0001	6.03(1.38)	<.0001
Ethnicity								
Black	3.76(1.28)	0.0034	2.62(1.34)	0.0519	3.41(1.33)	0.0108	2.66(1.27)	0.0358
Chinese	1.49(1.93)	0.4407	2.22(2.04)	0.2765	1.42(1.95)	0.4664	1.88(1.82)	0.3197
Hispanic	2.69(3.55)	0.4499	1.16(3.67)	0.7521	2.53(3.56)	0.4782	2.24(3.48)	0.5205
Black*MetS	**-7.24(2.21)**	**0.0011**	**-5.42(2.28)**	**0.0176**	**-6.69(2.24)**	**0.0028**	**-6.67(2.18)**	**0.0022**
Chinese*MetS	-1.31(3.74)	0.7260	-1.36(3.77)	0.7192	-1.32(3.74)	0.7242	-1.31(3.67)	0.7203
Hispanic*MetS	**-10.26(4.29)**	**0.0170**	**-8.64(4.38)**	**0.0488**	**-10.2(4.29)**	**0.0173**	**-9.19(4.21)**	**0.0294**

Results are expressed as regression coefficients (beta) and respective standard error; p-value. The regression coefficient beta indicates the difference in arterial property (in units) between individuals with vs without MetS. CWS, Circumferential Wall Stress; LDL-c, Low-density lipoprotein cholesterol; hsCRP, high sensitivity C - reactive protein, ln, logarithm; Reference group: white women

Model1, adjusted for age, height, education, site, hormone use, menopausal status, LDL-cholesterol, smoking;
Model2, adjusted for model 1 + ln – hsCRP
Model3, adjusted for model 1 + Adiponectin
Model4, adjusted for model 1 + pulse pressure

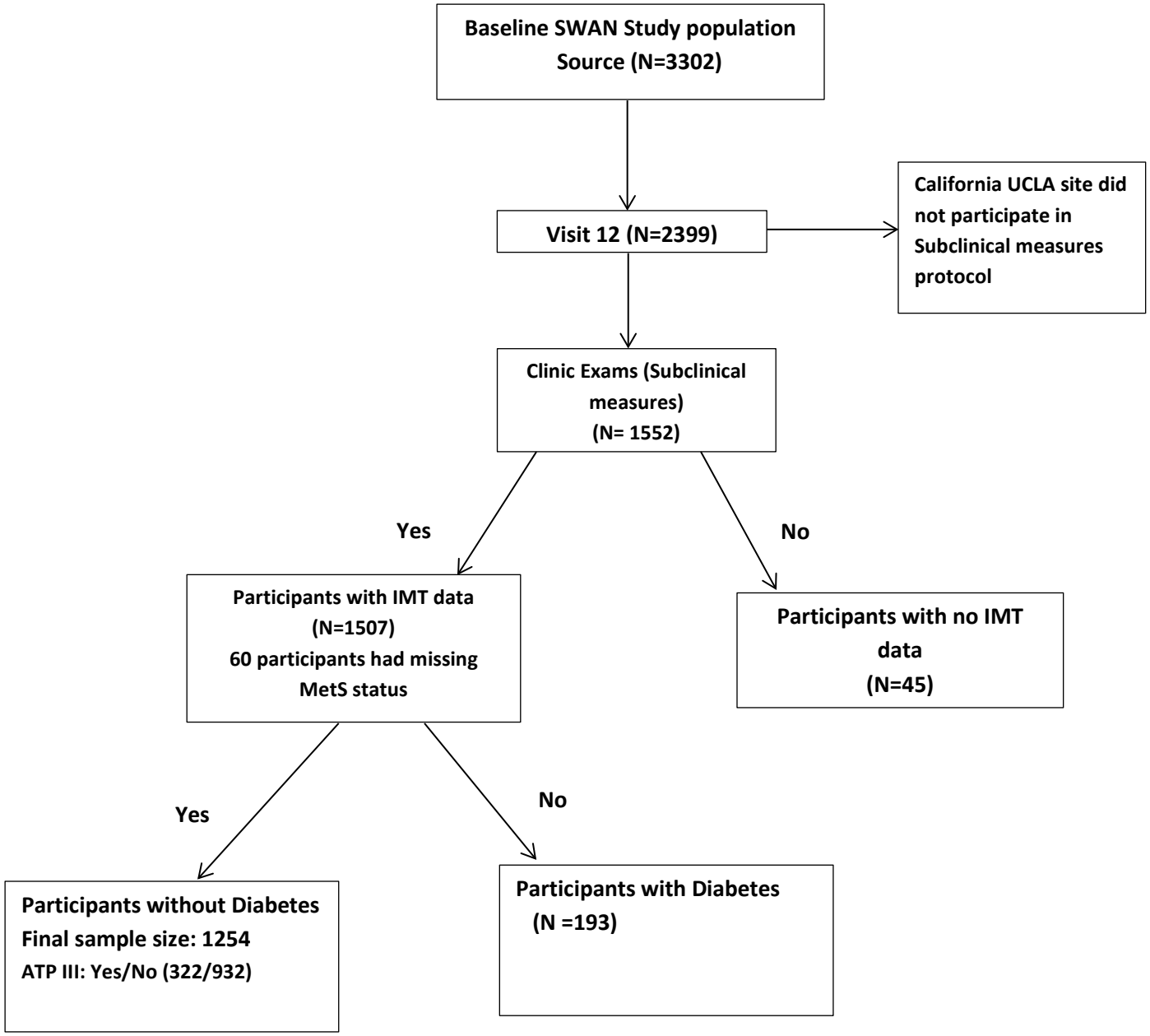


Figure 7-1 The flowchart of participants included in this study

8.0 MANUSCRIPT 3: THE EFFECTS OF METABOLIC SYNDROME STATUS CHANGES ON CAROTID ARTERY REMODELING: STUDY OF WOMEN'S HEALTH ACROSS THE NATION

Julius Asubonteng,[1] Emma Barinas-Mitchell,[1] Stephen Wisniewski,[1] Rebecca Thurston,[1,2] Suresh Mulukutla,[3] Faith Selzer [1]

[1] Department of Epidemiology, University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA

[2] Departments of Psychiatry, University of Pittsburgh, Pittsburgh, PA

[3] Cardiovascular Institute, University of Pittsburgh Medical Center, Pittsburgh, PA

8.1 ABSTRACT

Background: Metabolic syndrome (MetS) is associated with a higher risk for cardiovascular disease (CVD) events, including stroke. While the association between MetS and the risk of stroke is poorly understood; changes in structural and functional arteries parameters are posited to play a role in this association given the varying effects of MetS status changes. We aimed to examine changes in carotid artery structural and functional parameters in relation to changes in MetS status and its components in midlife women.

Methods: Data for current study are from the Study of Women's Across the Nation (SWAN) Heart Study, an ancillary study designed to examine natural history of subclinical atherosclerosis during the menopausal transition from two sites. The Pittsburgh and Chicago sites both recruited and followed Black and White Women. Baseline and follow-up visits occurred between 2001 and 2004. Participants were classified as having MetS or not at baseline and follow-up visits if they met the criteria defined by International Diabetes Federation (IDF). Participants were then assigned into one of the 4 groups: never, incident, recovery and persistent. Generalized estimating equations (GEE) were used to assess differences in carotid parameters at baseline and at follow-up visits, and their changes over time between the four MetS groups. All analyses were adjusted for age, education, smoking, LDL-c, cholesterol lowering medication, and menopausal status.

Results: At baseline and follow-up, the women in the persistent MetS group had larger mean IMT (β±SE: 0.76±0.12), and the recovery MetS group had larger mean AD (7.2±0.07), LD (5.6±0.67), CSA (15.2±2.4), CWT (34.1±4.4), CWS (53.3±7.8) as compared to other MetS

groups. During the follow-up, the persistent MetS group experienced a steeper increase in carotid IMT compared to those who never developed MetS (0.02 versus 0.012 mm/y). The recovery MetS group showed a negative rate of change on LD (-0.1 versus 0.0 mm/y), whereas other MetS categories did not differ in comparison to the reference group. CWT increased in both the incident (0.45 versus -0.3 kPa/y) and persistent (0.05 versus -0.3 kPa/y) MetS groups and decreased in the recovery MetS group (-1.55 versus -0.3 kPa/y) as compared to the never group.

Conclusion: Midlife women with persistent MetS over the course of 2-years of follow-up were more likely to experience carotid artery remodeling compared to those who never developed MetS. The reversibility of maladaptive remodeling of the carotid artery parameters among women in the recovery MetS group suggests that MetS risk factor modification measures could have a significant and positive impact on subclinical cardiovascular disease risk.

8.2 INTRODUCTION

Metabolic syndrome (MetS) is a risk factor for cardiovascular disease (CVD), especially stroke [210], that incorporates central obesity, dyslipidemia, elevated blood pressure (BP), and elevated plasma glucose. While the relationship between MetS and the risk of stroke is poorly understood, it has been hypothesized that changes in structural and functional arterial properties play a role in this relationship given the varying effects of MetS status changes [211, 212].

Arterial remodeling (AR) refers to changes in structural and functional properties of arteries over time, and it occurs largely in response to metabolic, inflammatory and hemodynamic changes within the arterial environment [211, 213, 214]. AR can either be adaptive or maladaptive. Maladaptive remodeling occurs with adverse changes in both circumferential wall stress (CWS) and circumferential wall tension (CWT) [132, 211, 215], whereas adaptive remodeling occurs without changes in CWS and CWT [216]. Maladaptive remodeling has been shown to be associated with the risk of stroke, as evidenced by higher mean carotid CWT among patients who have had stroke [132, 212].

Several epidemiological studies have linked the presence of MetS to carotid artery remodeling in diverse study populations in terms of age as well as CVD risk factors [170, 211, 212, 217-219]. Compared to participants without MetS, young adults with MetS have been observed with a higher mean IMT [220], and an accelerated IMT progression over time [92, 170]. MetS has also been shown to be associated with carotid remodeling in non-diabetic individuals [211], middle-aged women [218], and older adults independent of CVD risk factors [221]. Significant changes in CVD risk factors are reported to have a corresponding and

favorable change in markers of subclinical atherosclerosis. Change in MetS status, however, is posited to have varying effects on the vasculature based on the handful of published articles. In longitudinal studies examining the effect of MetS status change on the vasculature, specifically the carotid artery, recovery from MetS was found to be significantly associated with a reduction in carotid artery properties such as lumen diameter (LD), IMT and adventitial diameter(AD) among young adults [212, 219] compared to those without a change in their metabolic status. To date, however, carotid artery properties of only young adults have been studied in relation to change in MetS status and thus carotid artery properties in relation to change in MetS status in midlife and elderly women and men are unknown.

Adding to our understanding of MetS status change on the vasculature among midlife women is important because prevalence of the MetS increases during menopause transition independent of aging and other known CVD risk factors [79]. We sought to assess the effects of MetS status changes on carotid artery parameters changes over time. In addition, we examined changes in circumferential wall tension and circumferential wall stress to characterize the pattern of remodeling over time. Given these goals, we examined changes in carotid artery structural and functional parameters in relation to changes in MetS status and its components in the Study of Women's Across the Nation (SWAN) Heart Study.

8.3 METHODS

8.3.1 Study Population

The study sample included women enrolled in the Study of Women's Health Across the Nation (SWAN). SWAN is a multiethnic, community-based, longitudinal cohort of the natural history of 3302 women enrolled at 7 sites throughout the United States (Boston, Massachusetts; Chicago, Illinois; Detroit, Michigan; Los Angeles, California; Oakland, California; Newark, New Jersey; and Pittsburgh, Pennsylvania). The cohort at baseline was composed of White, Black, Chinese, Japanese and Hispanic women, aged 42 to 52 years, who had an intact uterus and at least one ovary, had at least one menstrual period in the preceding 3 months, had not used sex steroid hormone therapy in the preceding 3 months and were not pregnant.

The data for current study are from the SWAN Heart study, an ancillary study designed to examine natural history of subclinical atherosclerosis during the menopausal transition from two sites. The Pittsburgh and Chicago sites both recruited and followed Black and White women. At the baseline (N =425) and follow-up (N=343) participants were recruited and followed. The final sample size consisted of 252 participants had data on both baseline and follow-up visits, and data to ascertain MetS status of the participants. Baseline and follow-up visits occurred between 2001 and 2004. The mean follow-up was approximately 2 years. The institutional review board at each site approved the protocol and all women provided written informed consent.

8.3.2 Covariates Measures

At the baseline and follow-up visits, interviewer-administered questionnaires were used to assess medication use, lifestyle characteristics, menopausal status, and physical measures. Fasting blood samples were drawn for assessments of cardiovascular risk factors and included triglycerides, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol and fasting glucose. Fasting blood samples were analyzed at the Medical Research Laboratories (Lexington, KY). EDTA-treated plasma was used to analyze lipids. Isolation of high-density lipoprotein – cholesterol (HDL-C) (mg/dL) was done with heparin-2 M manganese chloride, and low density lipoprotein (LDL-c) (mg/dL) was estimated with the Friedewald equation [222].

8.3.3 International Diabetes Federation (IDF) metabolic syndrome definition

The criterion for the determination of the MetS using the IDF definition is sex-specific and we only describe the components as they pertain to women. Within the IDF definition for MetS, central obesity is required to be a component of the criteria, plus two or more of the other factors. The components of IDF are as follows: waist circumference (WC) ≥80 cm for those self-identified as White or Black; triglycerides ≥150 mg/dL; systolic blood pressure (SBP) ≥130 mmHg or diastolic blood pressure (DBP) ≥85 mmHg or on antihypertensive medication; HDL-c < 50 mg/dL; fasting glucose ≥ 100 mg/dL [176].

Participants were classified as having MetS or not at baseline and follow-up visits. Participants were then assigned into one of the following 4 groups of MetS status based on two

assessments: never (no MetS at both baseline and follow-up), incident (MetS at follow-up but not at baseline), recovery (MetS at baseline but not at follow-up) and persistent (MetS at both visits).

8.3.4 Subclinical Measures

At baseline and follow-up, carotid intima-media thickness (IMT) and adventitial diameter were assessed using B-mode ultrasound (Pittsburgh site: Toshiba American Medical Systems, Tustin, CA; and Chicago site: Hewlett Packard, Andover, MA) by centrally trained and certified sonographers. Right and left carotid arteries were scanned to obtain a total of eight images: near and far wall of the common carotid (1 cm proximal to the bulb), far wall of the common bulb (starting from point where the common carotid walls are no longer parallel and ending at the flow divider), and far wall of the internal carotid artery (distal 1 cm from the flow divider). IMT was measured by using the Artery Measurement Systems (AMS), a semi-automated edge detection software [177], by tracing the lumen-intima interface and the media-adventitia interface across a 1-cm segment. A total of 140 measures for each segment were generated, and the mean value of the averaged readings at all 8 locations was used. For AD, the distance from the adventitial-medial interface on the near wall to the medial-adventitial interface on the far wall at end-diastole was measured for both right and left common carotid artery. Lumen diameter (LD) was measured directly, and defined as the distance from the intima-lumen interface of the near wall to the lumen-intima interface of the far wall. Mean circumferential wall tension (CWT) and circumferential wall stress (CWS) were calculated according to Laplace's law [194] and mean CWT (kPa) = MAP (LD/2) and CWS (kPa) = mean CWT/IMT [189], where MAP is the mean arterial pressure. MAP was approximated as [(2* diastolic blood pressure) + systolic

blood pressure]/3. To assess the reproducibility of subclinical measures, 20 scans were performed to examine the inter-reader reproducibility of the measures, with an intra-class correlation of 0.98 and 0.99 for carotid IMT and AD, respectively [202].

8.3.5 Statistical Analyses

Baseline demographic and cardiovascular disease risk factor characteristics were compared by the four categories of change in MetS status (never, incident, recovery and persistent groups) using the chi-square test for categorical variables, and either t-test or Wilcoxon tests for continuous variables depending on normality.

Generalized estimating equations (GEE) were used to assess differences in carotid artery parameters at baseline and at follow up, and their changes over time between the four MetS status groups. MetS groups were included in these analyses as dummy variables and differences were tested relative to the reference group (never) and the differences in changes were tested by MetS group x time interaction terms. The individual components that comprise MetS were assessed in their continuous form in relation to carotid artery parameters at the baseline, follow up and their changes over time. All analyses were adjusted for age, site, education, smoking, LDL-c, cholesterol lowering medication, and menopausal status. For the regression models, the associations between MetS status changes and carotid artery properties were reported in Beta coefficients and 95% confidence intervals. All analyses were conducted using SAS version 9.3 and STATA version 12.

8.4 RESULTS

Baseline demographic and clinical characteristics of the study participants by the four MetS groups are shown in Table 8-1. The participants in the MetS recovery group were slightly older at baseline compared to the other three groups. In aggregate, the majority of participants were either premenopausal or peri-menopausal, reported receiving at least some college education and 67.5% of the study participants were White. From baseline to follow up, mean body mass index (BMI) increased in the incident group, and decreased in the recovery group. As expected, there were changes in individual components that comprised the MetS in relation to the four MetS groups, particularly among the women in the incident and recovery groups. Among the incident group, mean SBP, DPB, WC and triglycerides were higher at the follow-up visit compared to baseline, whereas mean HDL-c values declined. The women in the recovery group experienced declines in mean SBP, DBP, WC and triglyceride values from baseline to follow-up and HDL-c levels increased slightly during follow-up. From baseline to follow-up, mean SBP, DBP and HDL-c decreased slightly and mean WC increased in both the persistent and the never MetS groups.

Significant differences in carotid artery properties and changes in MetS status from baseline to follow-up visits were found. The overall MetS status changes were associated with subclinical measures in each period. At baseline and follow-up, the women in the persistent MetS group had larger mean IMT (0.76±0.12), and the recovery MetS group had larger mean AD (7.2±0.07), LD (5.6 ± 0.67), CSA (15.2±2.4), CWT (34.1±4.4), and CWS(53.3±7.8) as compared to other MetS groups. At baseline, participants with persistent MetS had significantly

higher levels of mean IMT, CSA and CWT, but not of AD, LD and CWS compared to participants who never developed MetS (Table 8-1).

During the follow-up, the persistent MetS group experienced a steeper increase in carotid IMT compared to those who never developed MetS (0.02 versus 0.012 mm/y) (Table 8-2 and Figure 8-1). The recovery women showed a negative rate of change on LD (-0.1 versus 0.0 mm/y), whereas other MetS categories did not differ in comparison to the reference group. The women in the recovery MetS experienced substantial increases in CSA (0.45 versus 0.35 mm/y). CWT increased in both the incident (0.45 versus -0.3 kPa/y) and persistent (0.05 versus -0.3 kPa/y) MetS groups and decreased in the recovery MetS group (-1.55 versus -0.3 kPa/y) as compared to the never group.

The associations between the four MetS status groups and changes in carotid artery parameters are shown in Table 8-3. At baseline, higher levels of AD, IMT, LD, CSA, CWT and CWS were significantly related to SBP and waist circumference. At the follow-up visit, higher levels of AD, LD, CSA, CWT and CWS were significantly and positively associated with SBP and waist circumference. Carotid IMT at follow-up was significantly associated with SBP, but not with waist circumference. Finally, positive changes in SBP were positively associated with changes in LD, CWT and CWS from baseline to follow-up.

8.5 DISCUSSION

The current study assessed the effect of longitudinal MetS status changes on carotid artery remodeling in an established cohort of midlife women participating in SWAN heart study. Among women with persistent MetS, we found significant increases in mean AD, IMT, LD and CWT over the follow-up period and also higher mean baseline values of IMT, CSA and CWT as compared to those who never developed MetS (Figure 8-1). Moreover, women with persistent MetS experienced increases in IMT and CSA in the course of follow-up, along with an increase in CWT. Women in Recovery MetS group experienced a decrease in LD and CWT, and a significant decline in CWS over the follow-up period. Higher systolic blood pressure and larger waist circumference were significant and consistent determinants of adverse carotid artery remodeling in our current study.

In the present study, we observed varying effects of MetS status changes on the carotid artery remodeling in midlife women. The arterial remodeling among women with persistent MetS was considered maladaptive because we found increases in IMT, AD and CSA, along with an increase in CWT. This finding suggests that among midlife women without CVD, persistent MetS is associated with the thickening of the carotid artery wall independent of confounding risk factors such as age, smoking, education, menopausal status, LDL-c and race. While the carotid artery properties of women in the recovery MetS group profile improved in relation to the factors related to the nature and pattern of the remodeling, slight increases were observed in mean AD and IMT, suggesting an adaptive vascular response [216]. Similar observations had been made in The Cardiovascular Risk in Young Finns Study [219] , and the Amsterdam Growth and Health Longitudinal Study [212]. In lieu of these findings, it has been suggested that there is the likely reversibility of a pathobiological process in young adults, which if not caught in time, could

progress into overt cardiovascular or cerebrovascular disease, such as a stroke or myocardial infarction.

In our study, participants in the recovery MetS group were observed to have significantly different carotid artery properties as compared to those who never developed MetS. This finding shows that favorable changes in MetS are likely to have a corresponding favorable effect on the carotid artery. Although artery remodeling occurred in all four MetS groups over time, those in the recovery group were not considered maladaptive because there was a reduction in mean transmural pressure in the carotid artery. Lifestyle and medical therapy interventions targeted to alter or treat or manage CVD risk factors, such as hypertension, diabetes mellitus, dyslipidemia and obesity, have been shown to slow or delay the progression of atherosclerosis or in some instances regression of atherosclerosis has been reported [92, 219, 223-225]. Atherosclerosis is initiated through oxidized LDL particles and macrophages activation, which leads to the formation of foam cells [143, 226]. The foam cells trigger fatty streak formation in atherosclerosis [143, 227]. On the other hand, modified LDL particles are also able to clear the artery wall of foam cell lesions through the liver via HDL-c [228]. In the Young Finn cohort study, a 6-year change in HDL-c was inversely associated with carotid IMT progression. In light of these findings, Koskinen et al hypothesized that reversing foam cell lesions could explain the favorable changes in carotid artery properties or measures among participants whose MetS status improved from baseline to follow-up [219].

In evaluating the individual components of MetS, systolic blood pressure was significantly associated with carotid artery remodeling. Increases in LD, CWT and CWS were positively associated with SBP even after adjusting for covariates such as age, smoking status, LDL-c, education and menopausal status. This finding is a potential indication of the effects of

pulsatile components of blood pressure on arterial remodeling. Another competing explanation for this observation is that transmural pressure exerts excess force on load-bearing features of arterial wall, such as elastin and collagen, which in turn leads to changes and fractures in the extracellular matrix and eventually results in arterial enlargements [229]. Larger waist circumference was associated with AD, LD, CWT and CWS in both the baseline and the follow-up period alone, but in the longitudinal models, WC was not significantly related to measures of arterial remodeling. These observations suggest that blood pressure and abdominal obesity are likely the two MetS criteria most strongly related with adverse effects on carotid arterial properties. Our findings, in these contexts, are in agreement with what others have been reported in the literature [211, 217, 218, 221]. In adults, Ferreira et al made a similar observation regarding the effects of blood pressure and abdominal obesity on carotid remodeling [212], however, they used a revised MetS definition completely different the criteria recommended by IDF.

Our study has strengths and limitations. The follow-up period was approximately 2 years, which might not be long enough to truly evaluate the effect of MetS and its individual components on carotid artery remodeling. The sample size of the four MetS groups was relatively small, especially in the incident, persistent and recovery categories, but our sample size was comparable to the few studies that have investigated MetS status changes on carotid artery remodeling. Women in recovery MetS group experienced reduction in LD, CWT and CWS but given the sample size in that category much emphasis could not be placed on it. Moreover, SWAN Heart study was not designed to examine the very question we sought to understand in this study. Mean arterial pressure measures were estimated versus directly measuring them in the arteries. Brachial artery blood pressure was used to derive CWT and CWS in place of

blood pressure measurements taken directly in the carotid arteries, therefore there is the likelihood of underestimation or overestimation of these measures in our analyses. Our study has a number of strengths. This is the first study to have investigated MetS and potential changes and carotid artery parameters in midlife women over time. The mean carotid artery IMT across carotid segments was used because it captures early atherosclerosis better among young women than simply using means in other segments alone. The artery measurement system was used to directly measure lumen diameter in this study compared to deriving it based on other measures of the carotid artery.

In conclusion, midlife women with persistent MetS over the course of 2-years of follow-up were more likely to experience carotid artery remodeling compared to those who never developed MetS. Furthermore, the type of arterial remodeling among those with persistent MetS appeared to be maladaptive, which might put these women at higher risk factor for cardiovascular disease, and in particular stroke. The reversibility of maladaptive remodeling of the carotid artery parameters among women in the recovery MetS group suggests that MetS risk factor modification measures could have a significant and positive impact on subclinical cardiovascular disease risk.

8.6 TABLES AND FIGURES

Table 8-1 Characteristic of Study population at Baseline and follow-up by Metabolic Syndrome Status Changes

Characteristics	Time	Metabolic Syndrome Status			
		Never(n=170)	Incident(n=21)	Recovery(n=16)	Persistent(n=45)
Age (years)	Baseline	50.5±2.6	49.4±2.5	52.1±2.9	50.5±3.0
	Follow-up	52.5±2.6	51.5±2.5	54.3±2.9	52.9±3.0
Ethnicity n (%)					
Black		50(29.4)	7(33.3)	7(43.7)	18(40.0)
White		120(70.6)	14(66.7)	9(56.3)	27(60.0)
Menopausal status n (%)					
Post-menopausal		46(30.5)	4(19.0)	7(53.8)	14(28.6)
Late /Early Premenopausal		105(69.5)	17(80.8)	6(46.1)	31(68.9)
Education n (%)					
High School		29(17.1)	3(14.3)	2(12.5)	8(17.8)
Some College		88(51.8)	11(52.4)	10(62.5)	23(51.1)
Post Grad. School		53(31.2)	7(33.3)	4(25.0)	14(31.1)
Individual components of MetS					
Systolic Blood Pressure (mm Hg)	Baseline	114.1±14.9	119.1±11.7	128.9±20.3	125.4±18.7
	Follow-up	113.3±14.6	121.2±15.7	121.5±12.5	124.0±15.7
Diastolic Blood Pressure (mm Hg)	Baseline	73.9±9.5	75.3±8.9	81.3±10.8	77.8±9.3
	Follow-up	72.4±8.5	78.2±9.3	75.6±9.9	77.3±11.7
Waist Circumference (cm)	Baseline	84.9±13.3	92.3±12.0	94.8±11.1	101.7±13.0
	Follow-up	85.4±13.1	95.1±12.7	93.5±10.9	103.1±13.5
HDL cholesterol	Baseline	61.6±13.0	49.8±7.5	51.4±11.4	44.4±8.8
	Follow-up	61.7±13.3	43.8±6.0	52.8±9.1	44.3±7.9

Table 8-1 Continued

Characteristics	Time	Metabolic Syndrome Status			
		Never(n=170)	Incident(n=21)	Recovery(n=16)	Persistent(n=45)
Triglycerides	Baseline	97.0±32.0	131.2±61.9	159.7±65.9	209.0±175.4
	Follow-up	101.8±46.2	158.0±47.2	117.9±38.1	201.7±106.2
Other risk factors					
Body mass index (kg/m^2)	Baseline	27.7±5.9	29.8±5.1	30.4±4.1	34.1±6.4
	Follow-up	27.9±5.7	30.9±5.3	29.3±3.6	34.2±6.0
Current smoking, n (%)	Baseline	20 (12.2)	1 (5)	3 (20)	5 (11.4)
	Follow-up	20 (12.9)	1 (5)	3 (18.8)	6 (13.6)
LDL cholesterol	Baseline	117.3±32.2	120.6±37.5	137.9±40.8	128.6±37.6
	Follow-up	122.6±30.5	126.6±33.7	128.6±32.1	132.5±38.6
Blood pressure lowering medication, n (%)	Baseline	20 (11.8)	2 (9.5)	6 (37.5)	16 (35.6)
	Follow-up	24 (14)	4 (19)	7 (43.7)	19 (42.2)
Cholesterol lowering medication, n (%)	Baseline	6 (3.5)	0 (0.0)	2 (12.5)	5 (11.1)
	Follow-up	13 (7.7)	2 (9.5)	5 (31.3)	11 (24.4)
Carotid Artery parameters					
Carotid IMT(mm)	Baseline	0.67±0.09	0.66±0.09	0.70±0.07	0.73±0.11
	Follow-up	0.71±0.09	0.68±0.09	0.75±0.07	0.76±0.12
Adventitial diameter(mm)	Baseline	6.6±0.53	6.5±0.72	7.2±0.7	6.8±0.52
	Follow-up	6.7±0.54	6.6±0.7	7.2±0.7	6.9±0.54
Lumen diameter (mm)	Baseline	5.3±0.44	5.2±0.56	5.8±0.51	5.4±0.50
	Follow-up	5.3±0.45	5.2±0.51	5.6±0.67	5.4±0.53
Wall cross-sectional area (mm^2)	Baseline	12.6±2.2	12.3±2.5	14.3±2.2	14.1±2.5
	Follow-up	13.3±2.3	12.7±2.9	15.2±2.4	14.7±2.6
Circumferential wall tension(kPa)	Baseline	30.9±5.4	31.2±5.2	37.2±5.5	33.6±2.1

Table 8-1 Continued

Characteristics	Time	Metabolic Syndrome Status			
		Never(n=170)	Incident(n=21)	Recovery(n=16)	Persistent(n=45)
	Follow-up	30.3±5.1	32.1±5.8	34.1±4.4	33.7±5.8
Circumferential wall stress(kPa)	Baseline	46.6±8.6	47.4±7.4	53.3±7.8	46.7±9.2
	Follow-up	43.3±8.3	47.3±7.6	45.8±8.5	45.6±10.3

Table 8-2 Comparison of Carotid Artery measures across categories of Changes in Metabolic Syndrome Status

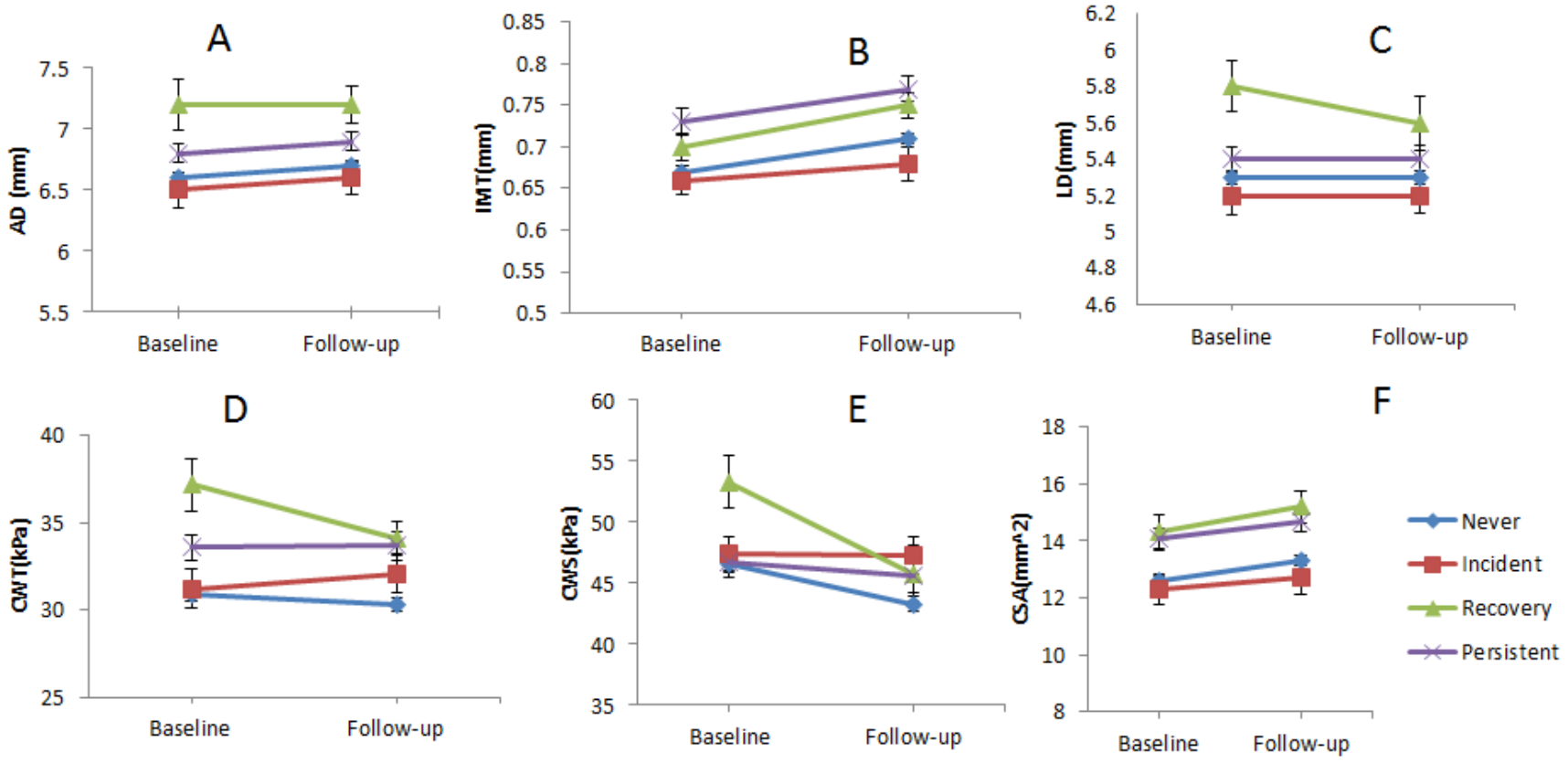
		Baseline		Follow-up		2-year changes	
Dependent variable	Changes in MetS status	β	95% CI	β	95% CI	β	95% CI
Adventitial Diameter (mm)	Incident	0.048	-0.216, 0.313	0.050	-0.202, 0.303	0.004	-0.128, 0.135
	Recovery	0.404	-0.064, 0.744	0.313	-0.008, 0.634	-0.036	-0.202, 0.131
	Persistent	0.174	-0.018, 0.367	0.247	0.066, 0.429**	0.054	-0.041, 0.148
Carotid IMT (mm)	Incident	0.0023	-0.036, 0.041	-0.017	-0.059, 0.025	-0.022	-0.051, 0.008
	Recovery	0.0149	-0.035, 0.065	0.0458	-0.007, 0.099	0.023	-0.015, 0.061
	Persistent	0.0485	0.019, 0.077**	0.026	0.010, 0.070**	-0.016	-0.038, 0.005
Lumen Diameter (mm)	Incident	-0.034	-0.242, 0.174	0.177	-0.196, 0.247	0.048	-0.083, 0.179
	Recovery	0.311	0.047, 0.575*	0.352	-0.105, 0.459	-0.092	-0.256, 0.072
	Persistent	0.133	-0.021, 0.287	0.193	0.034, 0.353*	0.083	-0.013, 0.180
Wall cross-sectional area (mm^2)	Incident	-0.018	-1.03, 0.99	-0.274	-1.33, 0.785	-0.238	-0.891, 0.413
	Recovery	1.02	-0.269, 2.31	1.39	0.041, 2.74*	0.309	-0.506, 1.12
	Persistent	1.24	0.485, 1.99**	1.29	0.533, 2.05**	-0.024	-0.505, 0.456
Circumferential wall tension (kPa)	Incident	0.87	-1.53, 3.18	2.34	0.10, 4.58*	1.27	-0.66, 3.05
	Recovery	4.8	1.89, 8.28**	1.90	-0.95, 4.74	-2.08	-0.52, 3.06
	Persistent	2.54	0.85, 7.67**	3.08	1.47, 4.68**	0.44	-0.88, 1.76
Circumferential wall stress (kPa)	Incident	0.99	-2.85, 4.84	4.23	0.36, 4.64	2.84	-0.49, 6.17
	Recovery	5.7	0.85, 10.6*	-0.03	-4.95, 4.89	-4.17	-8.3, -0.009*
	Persistent	0.72	-2.14, 3.57	2.25	-0.53, 5.03	1.63	-0.82, 4.08

Adjusted for age, smoking, education, race, LDL-c, cholesterol lowering medication, menopausal status as well as changes in the adjusted covariates in the 2-year change model;* *p <0.001; *p <0.05

Table 8-3 The associations between changes in each metabolic syndrome characteristic and changes in Carotid Artery parameters

		Dependent Variable					
Independent Variable	Time	AD	IMT	LD	CSA	CWT	CWS
Systolic blood pressure	Baseline	0.295***	0.342***	0.213**	0.369**	0.801***	0.586***
	Follow-up	0.312***	0.354***	0.200**	0.381***	0.759***	0.491***
	2 year change	0.107	-0.059	0.141*	0.016	0.767***	0.582***
Waist circumference	Baseline	0.297***	0.239***	0.276***	0.291	0.267***	0.118
	Follow-up	0.262***	0.110	0.253***	0.192***	0.239***	0.148
	2 year change	0.007	-0.053	0.037	-0.049	0.103	0.106
HDL cholesterol	Baseline	-0.027	-0.099	-0.0129	-0.058	-0.019	0.038
	Follow-up	-0.093	-0.061	-0.050	-0.072	-0.066	-0.035
	2 year change	-0.029	0.109	-0.117	0.064	-0.046	-0.117
Triglycerides	Baseline	-0.019	-0.056	0.0050	-0.059	0.028	0.081
	Follow-up	0.075	0.047	0.049	0.055	0.115	0.077
	2 year change	0.173*	-0.071	0.173**	-0.005	0.161*	0.163*
Glucose	Baseline	0.102	0.093	0.095	0.107	0.129	0.066
	Follow-up	0.061	0.114	0.019	0.096	0.073	0.001
	2 year change	-0.045	0.019	-0.075	-0.001	-0.039	-0.046

Adjusted for age, smoking, education, LDL-c, cholesterol lowering medication, menopausal status as well as changes in the adjusted covariates in the 2-year change model * **p <0.0001** p <0.001 *p <0.05



A. AD, adventitial diameter; B. IMT, intima-media thickness; C. LD, lumen diameter; D. CWT, circumferential wall tension; E. CWS, circumferential wall stress; F. CSA, cross-sectional area. All data adjusted for age, smoking, education, Low-density lipoprotein cholesterol, as well as changes in the covariates

Figure 8-1 Changes in carotid artery parameters by changes in metabolic syndrome status

9.0 GENERAL DISCUSSION

9.1 SUMMARY OF FINDINGS

This dissertation sought to examine the MetS and its association with subclinical atherosclerosis, carotid artery remodeling and its related risk factors, as well as the longitudinal effect of MetS status changes on carotid artery remodeling in midlife women. The summary of the findings for chapter 6, 7 and 8 are presented below.

In chapter 6, the MetS, via all definitions, was significantly associated with measures of subclinical atherosclerosis. The WHO definition was more strongly associated with carotid IMT and carotid plaque presence compared to either the NCEP-ATP III or the IDF definitions. The MetS components most strongly and consistently associated with carotid IMT and plaque were higher blood pressure and greater fasting glucose across all definitions considered in the current study.

In chapter 7, the MetS was significantly associated with maladaptive remodeling of the common carotid artery as indicated by greater mean adventitial diameter, lumen diameter and carotid IMT. Moreover, an outward pattern of remodeling was observed as evidenced by greater mean circumferential wall tension and circumferential wall stress in women with MetS. Our findings also indicated that the associations between MetS and carotid artery remodeling are independent of inflammatory, hemodynamic, and metabolic risk factors. Finally, we observed differential maladaptive remodeling patterns of the common carotid artery with MetS status by

race/ethnicity. Specifically, Black and Hispanic women experienced more extreme remodeling of the common carotid artery with MetS than their White counterparts.

In chapter 8, among women with persistent MetS, we found significant increases in mean AD, IMT, LD and CWT over the follow-up period and also higher mean baseline values of IMT, CSA and CWT as compared to those who never developed MetS. Moreover, women with persistent MetS experienced increases in IMT and CSA in the course of follow-up, along with an increase in CWT. Recovery MetS women experienced a decrease in LD and CWT, and a significant decline in CWS over the follow-up period. Higher systolic blood pressure and larger waist circumference were significant and consistent determinants of adverse carotid artery remodeling in our current study.

9.2 STRENGTHS AND LIMITATIONS

In light of the significant findings of the dissertation, strengths and limitations of the manuscript must be enumerated. The strengths and limitations of chapter 6, 7 and 8 are presented below.

In chapter 6, the sample consisted of community - dwelling women in whom subclinical atherosclerosis burden was assessed by centrally trained vascular sonographers with no knowledge of participants' CVD risk factors. The study sample was multi-racial and multi-ethnic and comprised of White, Black, Chinese and Hispanic women. To our knowledge, this was the first study to assess three commonly used MetS definitions and their individual components in relation to subclinical atherosclerosis in a racially/ethnically diverse group of

middle-aged women. However, this was a cross-sectional study; therefore the findings must be interpreted with caution.

In chapter 7, this is the first study to assess carotid artery remodeling in a multi-ethnic cohort focused on examining the association between MetS and carotid remodeling in non-diabetic older middle-aged women. As a cross-sectional study, inferences regarding causality must be made with caution. There was paucity of data in Hispanic ethnicity therefore the importance of comparisons made in this study must be carefully interpreted. No three dimensional images of the carotid artery image were made, therefore vascular measurements such as CWT and CWS might have either underestimated or overestimated the association between MetS and carotid artery remodeling.

In chapter 8, the follow-up period was approximately 2 years, which might not be long enough to truly assess the effect of MetS and its individual components on carotid artery remodeling. The size of the four MetS groups was relatively small, especially the incident, persistent and recovery categories, but our sample size was comparable to the few studies that have investigated MetS status changes on their effects on carotid artery remodeling. Moreover, SWAN Heart study was not designed to examine the very question we sought to examine. This is the first study to have investigated MetS and potential changes and carotid artery parameters in midlife women over time. The mean carotid artery IMT across carotid segments was used because it captures early atherosclerosis better among young women than simply using means in other segments alone.

9.3 PUBLIC HEALTH SIGNIFICANCE

Subclinical atherosclerosis is thought to precede overt clinical cardiovascular events, such as stroke in high-risk populations. The presence of MetS is a strong predictor of incident CVD events. MetS is linked to subclinical atherosclerosis and maladaptive remodeling of the carotid artery. Lifestyle modifications including, a healthy diet, physical activity, cessation of smoking and weight control/loss, and pharmacological intervention targeting specific MetS components can be initiated to mitigate the effects of the MetS, and maybe reduce the risk for subclinical atherosclerosis progression and CVD events. This dissertation has provided evidence that MetS may promote vascular remodeling among midlife women. This finding is very important because targeting MetS via its components may reverse or prevent vascular remodeling, and subsequently reduce risk for the development of cardiovascular events in women.

9.4 FUTURE RESEARCH

Findings from this dissertation have shown the importance of metabolic syndrome and development of subclinical atherosclerosis, which is a precursor to CVD events. Data show that women on average develop CVD ten to fifteen years later in life than men, and this is suggested to be due largely to menopause[230]. With this background, metabolic syndrome and its components must be prospectively studied to understand how they affect the development and progression of atherosclerosis in midlife. Understanding metabolic syndrome and its components and how they are related to the development of subclinical atherosclerosis in women 10 years prior to the menopause transition can potentially help to prevent CVD among women.

9.5 CONCLUSION

In summary, the presence of MetS using three definitions was significantly associated with greater burden of subclinical atherosclerosis in midlife women. MetS is also associated with maladaptive remodeling of the common carotid artery in midlife women independent of select measure of inflammatory, metabolic and hemodynamic risk factors. Midlife women with persistent MetS status over a 2-year period were significantly associated with maladaptive remodeling of the carotid artery after adjusting for potential confounders. These findings suggest that targeting and preventing MetS and its components may potentially reduce subclinical CVD in midlife women.

BIBLIOGRAPHY

1. Bello, N. and L. Mosca, *Epidemiology of coronary heart disease in women.* Prog Cardiovasc Dis, 2004. **46**(4): p. 287-95.
2. Go, A.S., et al., *Heart Disease and Stroke Statistics—2013 Update: A Report From the American Heart Association.* Circulation, 2013. **127**(1): p. e6-e245.
3. Regitz-Zagrosek, V., *Cardiovascular disease in postmenopausal women.* Climacteric, 2003. **3**: p. 13-20.
4. Crawford, S.L. and C.B. Johannes, *The Epidemiology of Cardiovascular Disease in Postmenopausal Women.* Journal of Clinical Endocrinology & Metabolism, 1999. **84**(6): p. 1803-1806.
5. Group, W., et al., *Cardiovascular Disease in Women: A Statement for Healthcare Professionals From the American Heart Association.* Circulation, 1997. **96**(7): p. 2468-2482.
6. Mensah, G.A., et al., *State of disparities in cardiovascular health in the United States.* Circulation, 2005. **111**(10): p. 1233-41.
7. Feinstein, M., et al., *Racial Differences in Risks for First Cardiovascular Events and Noncardiovascular Death: The Atherosclerosis Risk in Communities Study, the Cardiovascular Health Study, and the Multi-Ethnic Study of Atherosclerosis.* Circulation, 2012. **126**(1): p. 50-59.
8. Brown, J.R. and G.T. O'Connor, *Coronary heart disease and prevention in the United States.* N Engl J Med, 2010. **362**(23): p. 2150-3.
9. Kylin, E., *Studien ueber das Hypertonie-Hyperglyka "mie-Hyperurika" miessyndrom.* Zentralblatt fuer Innere Medizin;, 1923. **44**: p. 105-127.
10. Reaven, G.M., *Banting lecture 1988. Role of insulin resistance in human disease.* Diabetes, 1988. **37**(12): p. 1595-607.
11. Ferrannini, E. and P. Iozzo, *Is insulin resistance atherogenic? A review of the evidence.* Atherosclerosis Supplements, 2006. **7**(4): p. 5-10.
12. Gami, A.S., et al., *Metabolic Syndrome and Risk of Incident Cardiovascular Events and Death: A Systematic Review and Meta-Analysis of Longitudinal Studies.* Journal of the American College of Cardiology, 2007. **49**(4): p. 403-414.
13. Cornier, M.-A., et al., *The Metabolic Syndrome.* Endocrine Reviews, 2008. **29**(7): p. 777-822.
14. Reaven, G., *The metabolic syndrome or the insulin resistance syndrome? Different names, different concepts, and different goals.* Endocrinology and Metabolism Clinics of North America, 2004. **33**(2): p. 283-303.
15. Eckel, R.H., S.M. Grundy, and P.Z. Zimmet, *The metabolic syndrome.* The Lancet, 2005. **365**(9468): p. 1415-1428.
16. Grundy, S.M., *Metabolic Syndrome Pandemic.* Arteriosclerosis, Thrombosis, and Vascular Biology, 2008. **28**(4): p. 629-636.
17. Grundy, S.M., et al., *Diagnosis and Management of the Metabolic Syndrome: An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement.* Circulation, 2005. **112**(17): p. 2735-2752.

18. Alberti, K.G. and P.Z. Zimmet, *Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation.* Diabet Med, 1998. **15**(7): p. 539-53.
19. Balkau, B. and M.A. Charles, *Comment on the provisional report from the WHO consultation. European Group for the Study of Insulin Resistance (EGIR).* 1999: Diabet Med. 1999 May;16(5):442-3.
20. Ford, E.S., *Prevalence of the metabolic syndrome in US populations.* Endocrinology and Metabolism Clinics of North America, 2004. **33**(2): p. 333-350.
21. Alberti, K.G.M.M., P. Zimmet, and J. Shaw, *The metabolic syndrome?a new worldwide definition.* The Lancet, 2005. **366**(9491): p. 1059-1062.
22. Alberti, K.G.M.M., et al., *Harmonizing the Metabolic Syndrome: A Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity.* Circulation, 2009. **120**(16): p. 1640-1645.
23. Simmons, R.K., et al., *The metabolic syndrome: useful concept or clinical tool? Report of a WHO Expert Consultation.* Diabetologia, 2010. **53**(4): p. 600-5.
24. Ferrannini, E., et al., *Hyperinsulinaemia: the key feature of a cardiovascular and metabolic syndrome.* Diabetologia, 1991. **34**(6): p. 416-22.
25. Adiels, M., et al., *Overproduction of large VLDL particles is driven by increased liver fat content in man.* Diabetologia, 2006. **49**(4): p. 755-765.
26. Ridker, P.M., et al., *C-Reactive Protein, the Metabolic Syndrome, and Risk of Incident Cardiovascular Events: An 8-Year Follow-Up of 14 719 Initially Healthy American Women.* Circulation, 2003. **107**(3): p. 391-397.
27. Whorwood, C.B., et al., *Increased Glucocorticoid Receptor Expression in Human Skeletal Muscle Cells May Contribute to the Pathogenesis of the Metabolic Syndrome.* Diabetes, 2002. **51**(4): p. 1066-1075.
28. Apridonidze, T., et al., *Prevalence and Characteristics of the Metabolic Syndrome in Women with Polycystic Ovary Syndrome.* Journal of Clinical Endocrinology & Metabolism, 2005. **90**(4): p. 1929-1935.
29. Hu, F.B., *Globalization of Diabetes: The role of diet, lifestyle, and genes.* Diabetes Care, 2011. **34**(6): p. 1249-1257.
30. Grundy, S., *The Metabolic Syndrome,* in *Atlas of Atherosclerosis and Metabolic Syndrome,* S.M. Grundy, Editor. 2011, Springer New York. p. 1-26.
31. Kahn, R., et al., *The Metabolic Syndrome: Time for a Critical Appraisal: Joint statement from the American Diabetes Association and the European Association for the Study of Diabetes.* Diabetes Care, 2005. **28**(9): p. 2289-2304.
32. DeFronzo, R.A., *Insulin resistance, lipotoxicity, type 2 diabetes and atherosclerosis: the missing links. The Claude Bernard Lecture 2009.* Diabetologia, 2010. **53**(7): p. 1270-1287.
33. Wang, C.C.L., M.L. Goalstone, and B. Draznin, *Molecular Mechanisms of Insulin Resistance That Impact Cardiovascular Biology.* Diabetes, 2004. **53**(11): p. 2735-2740.
34. Cusi, K., et al., *Insulin resistance differentially affects the PI 3-kinase- and MAP kinase-mediated signaling in human muscle.* J Clin Invest, 2000. **105**(3): p. 311-20.

35. Katzmarzyk, P.T., et al., *The Importance of Waist Circumference in the Definition of Metabolic Syndrome: Prospective analyses of mortality in men.* Diabetes Care, 2006. **29**(2): p. 404-409.
36. Reaven, G., F. Abbasi, and T. McLaughlin, *Obesity, Insulin Resistance, and Cardiovascular Disease.* Recent Progress in Hormone Research, 2004. **59**(1): p. 207-223.
37. Wajchenberg, B.L., *Subcutaneous and Visceral Adipose Tissue: Their Relation to the Metabolic Syndrome.* Endocrine Reviews, 2000. **21**(6): p. 697-738.
38. Després, J.P., *Is visceral obesity the cause of the metabolic syndrome?* Annals of Medicine, 2006. **38**(1): p. 52-63.
39. Janssen, I., P.T. Katzmarzyk, and R. Ross, *Waist circumference and not body mass index explains obesity-related health risk.* The American Journal of Clinical Nutrition, 2004. **79**(3): p. 379-384.
40. Meigs, J.B., et al., *Body Mass Index, Metabolic Syndrome, and Risk of Type 2 Diabetes or Cardiovascular Disease.* Journal of Clinical Endocrinology & Metabolism, 2006. **91**(8): p. 2906-2912.
41. Canoy, D., et al., *Body Fat Distribution and Risk of Coronary Heart Disease in Men and Women in the European Prospective Investigation Into Cancer and Nutrition in Norfolk Cohort: A Population-Based Prospective Study.* Circulation, 2007. **116**(25): p. 2933-2943.
42. Reaven, G.M., *The metabolic syndrome: time to get off the merry-go-round?* J Intern Med, 2011. **269**(2): p. 127-36.
43. DeFronzo, R.A., *Current issues in the treatment of type 2 diabetes. Overview of newer agents: where treatment is going.* Am J Med, 2010. **123**(3 Suppl): p. 008.
44. Rocha, V.Z. and P. Libby, *Obesity, inflammation, and atherosclerosis.* Nat Rev Cardiol, 2009. **6**(6): p. 399-409.
45. Jensen, M.D., *Is visceral fat involved in the pathogenesis of the metabolic syndrome? Human model.* Obesity, 2006. **14**(1): p. 20S-24S.
46. Despres, J.-P. and I. Lemieux, *Abdominal obesity and metabolic syndrome.* Nature, 2006. **444**(7121): p. 881-887.
47. Ford, E.S., *Factor analysis and defining the metabolic syndrome.* Ethn Dis, 2003. **13**(4): p. 429-37.
48. Rahmouni, K., et al., *Obesity-Associated Hypertension: New Insights Into Mechanisms.* Hypertension, 2005. **45**(1): p. 9-14.
49. Ferrannini, E., et al., *Insulin resistance in essential hypertension.* The New England journal of medicine, 1987. **317**(6): p. 350-357.
50. Rowe, J.W., et al., *Effect of insulin and glucose infusions on sympathetic nervous system activity in normal man.* Diabetes, 1981. **30**(3): p. 219-25.
51. DeFronzo, R.A., *Insulin resistance, hyperinsulinemia, and coronary artery disease: a complex metabolic web.* Journal of cardiovascular pharmacology, 1992. **20 Suppl 11**: p. S1-16.
52. Grundy, S.M., et al., *Definition of Metabolic Syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association Conference on Scientific Issues Related to Definition.* Circulation, 2004. **109**(3): p. 433-438.
53. Lebovitz, H.E., *Insulin resistance: definition and consequences.* Exp Clin Endocrinol Diabetes, 2001. **109**(2): p. S135-48.

54. Reynisdottir, S., et al., *Adipose Tissue Lipoprotein Lipase and Hormone-Sensitive Lipase: Contrasting Findings in Familial Combined Hyperlipidemia and Insulin Resistance Syndrome.* Arteriosclerosis, Thrombosis, and Vascular Biology, 1997. **17**(10): p. 2287-2292.
55. Fisher, E.A. and H.N. Ginsberg, *Complexity in the Secretory Pathway: The Assembly and Secretion of Apolipoprotein B-containing Lipoproteins.* Journal of Biological Chemistry, 2002. **277**(20): p. 17377-17380.
56. Hopkins, G.J. and P.J. Barter, *Role of triglyceride-rich lipoproteins and hepatic lipase in determining the particle size and composition of high density lipoproteins.* Journal of Lipid Research, 1986. **27**(12): p. 1265-77.
57. Pate, R.R., et al., *Physical activity and public health. A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine.* JAMA, 1995. **273**(5): p. 402-7.
58. Hu, G., et al., *Occupational, commuting, and leisure-time physical activity in relation to risk for Type 2 diabetes in middle-aged Finnish men and women.* Diabetologia, 2003. **46**(3): p. 322-329.
59. Yang, X., et al., *The longitudinal effects of physical activity history on metabolic syndrome.* Med Sci Sports Exerc, 2008. **40**(8): p. 1424-31.
60. Crichton, G.E., et al., *Dairy consumption and metabolic syndrome: a systematic review of findings and methodological issues.* Obesity Reviews, 2011. **12**(5): p. e190-e201.
61. Esmaillzadeh, A., P. Mirmiran, and F. Azizi, *Whole-grain consumption and the metabolic syndrome: a favorable association in Tehranian adults.* Eur J Clin Nutr, 2004. **59**(3): p. 353-362.
62. Raisanen, J.P., et al., *Increased daily sodium intake is an independent dietary indicator of the metabolic syndrome in middle-aged subjects.* Ann Med, 2012. **44**(6): p. 627-34.
63. Freiberg, M.S., et al., *Alcohol Consumption and the Prevalence of the Metabolic Syndrome in the U.S.: A cross-sectional analysis of data from the Third National Health and Nutrition Examination Survey.* Diabetes Care, 2004. **27**(12): p. 2954-2959.
64. Fan, A.Z., et al., *Patterns of Alcohol Consumption and the Metabolic Syndrome.* Journal of Clinical Endocrinology & Metabolism, 2008. **93**(10): p. 3833-3838.
65. Baik, I. and C. Shin, *Prospective study of alcohol consumption and metabolic syndrome.* The American Journal of Clinical Nutrition, 2008. **87**(5): p. 1455-1463.
66. Yoon, Y.S., et al., *Alcohol consumption and the metabolic syndrome in Korean adults: the 1998 Korean National Health and Nutrition Examination Survey.* The American Journal of Clinical Nutrition, 2004. **80**(1): p. 217-224.
67. Joy, T., et al., *Genetics of metabolic syndrome.* Current Diabetes Reports, 2008. **8**(2): p. 141-148.
68. Carmelli, D., L.R. Cardon, and R. Fabsitz, *Clustering of hypertension, diabetes, and obesity in adult male twins: same genes or same environments?* Am J Hum Genet, 1994. **55**(3): p. 566-73.
69. Sjögren, M., et al., *The search for putative unifying genetic factors for components of the metabolic syndrome.* Diabetologia, 2008. **51**(12): p. 2242-2251.
70. Kraja, A.T., et al., *A Bivariate Genome-Wide Approach to Metabolic Syndrome: STAMPEED Consortium.* Diabetes, 2011. **60**(4): p. 1329-1339.

71. Mottillo, S., et al., *The Metabolic Syndrome and Cardiovascular RiskA Systematic Review and Meta-Analysis.* Journal of the American College of Cardiology, 2010. **56**(14): p. 1113-1132.
72. Lakka H, L.D.E.L.T.A. and et al., *THe metabolic syndrome and total and cardiovascular disease mortality in middle-aged men.* JAMA, 2002. **288**(21): p. 2709-2716.
73. Laaksonen, D.E., et al., *Metabolic Syndrome and Development of Diabetes Mellitus: Application and Validation of Recently Suggested Definitions of the Metabolic Syndrome in a Prospective Cohort Study.* American Journal of Epidemiology, 2002. **156**(11): p. 1070-1077.
74. Polak, J.F., et al., *The Value of Carotid Artery Plaque and Intima-Media Thickness for Incident Cardiovascular Disease: The Multi-Ethnic Study of Atherosclerosis.* Journal of the American Heart Association, 2013. **2**(2).
75. O'Leary, D.H., et al., *Use of sonography to evaluate carotid atherosclerosis in the elderly. The Cardiovascular Health Study. CHS Collaborative Research Group.* Stroke, 1991. **22**(9): p. 1155-63.
76. Wilson, P.W.F., et al., *Prediction of Coronary Heart Disease Using Risk Factor Categories.* Circulation, 1998. **97**(18): p. 1837-1847.
77. Ninomiya, J.K., et al., *Association of the Metabolic Syndrome With History of Myocardial Infarction and Stroke in the Third National Health and Nutrition Examination Survey.* Circulation, 2004. **109**(1): p. 42-46.
78. Isomaa, B., et al., *Cardiovascular Morbidity and Mortality Associated With the Metabolic Syndrome.* Diabetes Care, 2001. **24**(4): p. 683-689.
79. Janssen, I., et al., *Menopause and the metabolic syndrome: The study of women's health across the nation.* Archives of Internal Medicine, 2008. **168**(14): p. 1568-1575.
80. Cameron, A.J., et al., *The metabolic syndrome as a tool for predicting future diabetes: the AusDiab study.* Journal of Internal Medicine, 2008. **264**(2): p. 177-186.
81. Ford, E., et al., *Metabolic syndrome and risk of incident diabetes: findings from the European Prospective Investigation into Cancer and Nutrition-Potsdam Study.* Cardiovascular Diabetology, 2008. **7**(1): p. 35.
82. Wilson, P.W.F., et al., *Metabolic Syndrome as a Precursor of Cardiovascular Disease and Type 2 Diabetes Mellitus.* Circulation, 2005. **112**(20): p. 3066-3072.
83. Lorenzo, C., et al., *The Metabolic Syndrome as Predictor of Type 2 Diabetes: The San Antonio Heart Study.* Diabetes Care, 2003. **26**(11): p. 3153-3159.
84. Donato, G.B., et al., *Association between menopause status and central adiposity measured at different cutoffs of waist circumference and waist-to-hip ratio.* Menopause, 2006. **13**(2): p. 280-5.
85. Tzou, W.S., et al., *Increased Subclinical Atherosclerosis in Young Adults With Metabolic SyndromeThe Bogalusa Heart Study.* Journal of the American College of Cardiology, 2005. **46**(3): p. 457-463.
86. Ilanne-Parikka, P., et al., *Effect of Lifestyle Intervention on the Occurrence of Metabolic Syndrome and its Components in the Finnish Diabetes Prevention Study.* Diabetes Care, 2008. **31**(4): p. 805-807.
87. Shai, I., et al., *Weight Loss with a Low-Carbohydrate, Mediterranean, or Low-Fat Diet.* New England Journal of Medicine, 2008. **359**(3): p. 229-241.
88. Lakka, T.A. and D.E. Laaksonen, *Physical activity in prevention and treatment of the metabolic syndrome.* Appl Physiol Nutr Metab, 2007. **32**(1): p. 76-88.

89. Ilanne-Parikka, P., et al., *Leisure-Time Physical Activity and the Metabolic Syndrome in the Finnish Diabetes Prevention Study.* Diabetes Care, 2010. **33**(7): p. 1610-1617.
90. LaMonte, M.J., et al., *Cardiorespiratory fitness is inversely associated with the incidence of metabolic syndrome: a prospective study of men and women.* Circulation, 2005. **112**(4): p. 505-12.
91. Hanley, A.J.G., et al., *Factor Analysis of Metabolic Syndrome Using Directly Measured Insulin Sensitivity: The Insulin Resistance Atherosclerosis Study.* Diabetes, 2002. **51**(8): p. 2642-2647.
92. Koskinen, J., et al., *Conventional Cardiovascular Risk Factors and Metabolic Syndrome in Predicting Carotid Intima-Media Thickness Progression in Young Adults: The Cardiovascular Risk in Young Finns Study.* Circulation, 2009. **120**(3): p. 229-236.
93. McNeill, A.M., et al., *The Metabolic Syndrome and 11-Year Risk of Incident Cardiovascular Disease in the Atherosclerosis Risk in Communities Study.* Diabetes Care, 2005. **28**(2): p. 385-390.
94. Sipilä, K., et al., *Metabolic syndrome and carotid intima media thickness in the Health 2000 Survey.* Atherosclerosis, 2009. **204**(1): p. 276-281.
95. Eddy, D.M., L. Schlessinger, and K. Heikes, *The metabolic syndrome and cardiovascular risk: implications for clinical practice.* Int J Obes, 2008. **32**(2): p. 28.
96. Simmons, R.K., et al., *The metabolic syndrome: useful concept or clinical tool? Report of a WHO Expert Consultation.* Diabetologia, 2010. **53**(4): p. 600-605.
97. Sattar, N., et al., *Can metabolic syndrome usefully predict cardiovascular disease and diabetes? Outcome data from two prospective studies.* The Lancet, 2008. **371**(9628): p. 1927-1935.
98. Cameron, A.J., J.E. Shaw, and P.Z. Zimmet, *The metabolic syndrome: prevalence in worldwide populations.* Endocrinology and Metabolism Clinics of North America, 2004. **33**(2): p. 351-375.
99. Ford Es, G.W.H.D.W.H., *Prevalence of the metabolic syndrome among us adults: Findings from the third national health and nutrition examination survey.* JAMA, 2002. **287**(3): p. 356-359.
100. Ford, E.S., C. Li, and G. Zhao, *Prevalence and correlates of metabolic syndrome based on a harmonious definition among adults in the US*.* Journal of Diabetes, 2010. **2**(3): p. 180-193.
101. Holvoet, P., et al., *The Metabolic Syndrome, Circulating Oxidized LDL, and Risk of Myocardial Infarction in Well-Functioning Elderly People in the Health, Aging, and Body Composition Cohort.* Diabetes, 2004. **53**(4): p. 1068-1073.
102. Rutter, M.K., et al., *C-Reactive Protein, the Metabolic Syndrome, and Prediction of Cardiovascular Events in the Framingham Offspring Study.* Circulation, 2004. **110**(4): p. 380-385.
103. Hunt, K.J., et al., *National Cholesterol Education Program Versus World Health Organization Metabolic Syndrome in Relation to All-Cause and Cardiovascular Mortality in the San Antonio Heart Study.* Circulation, 2004. **110**(10): p. 1251-1257.
104. McNeill, A.M., et al., *Prevalence of coronary heart disease and carotid arterial thickening in patients with the metabolic syndrome (The ARIC Study).* The American Journal of Cardiology, 2004. **94**(10): p. 1249-1254.

105. Bonora, E., et al., *Carotid Atherosclerosis and Coronary Heart Disease in the Metabolic Syndrome: Prospective data from the Bruneck Study.* Diabetes Care, 2003. **26**(4): p. 1251-1257.
106. Lawlor, D.A., G.D. Smith, and S. Ebrahim, *Does the new International Diabetes Federation definition of the metabolic syndrome predict CHD any more strongly than older definitions? Findings from the British Women's Heart and Health Study.* Diabetologia, 2006. **49**(1): p. 41-48.
107. Wang, J., et al., *The metabolic syndrome predicts cardiovascular mortality: a 13-year follow-up study in elderly non-diabetic Finns.* European Heart Journal, 2007. **28**(7): p. 857-864.
108. Nilsson, P.M., G. Engström, and B. Hedblad, *The metabolic syndrome and incidence of cardiovascular disease in non-diabetic subjects—a population-based study comparing three different definitions.* Diabetic Medicine, 2007. **24**(5): p. 464-472.
109. Skilton, M.R., et al., *A comparison of the NCEP-ATPIII, IDF and AHA/NHLBI metabolic syndrome definitions with relation to early carotid atherosclerosis in subjects with hypercholesterolemia or at risk of CVD: evidence for sex-specific differences.* Atherosclerosis, 2007. **190**(2): p. 416-22.
110. Ahluwalia, N., et al., *Metabolic syndrome is associated with markers of subclinical atherosclerosis in a French population-based sample.* Atherosclerosis, 2006. **186**(2): p. 345-353.
111. Ma, W.-Y., et al., *Metabolic syndrome defined by IDF and AHA/NHLBI correlates better to carotid intima-media thickness than that defined by NCEP ATP III and WHO.* Diabetes Research and Clinical Practice, 2009. **85**(3): p. 335-341.
112. Tzou, W.S., et al., *Increased Subclinical Atherosclerosis in Young Adults With Metabolic Syndrome: The Bogalusa Heart Study.* Journal of the American College of Cardiology, 2005. **46**(3): p. 457-463.
113. Herder, M., et al., *The metabolic syndrome and progression of carotid atherosclerosis over 13years. The Tromso study.* Cardiovascular Diabetology, 2012. **11**(1): p. 77.
114. Hassinen, M., et al., *Metabolic syndrome and the progression of carotid intima-media thickness in elderly women.* Arch Intern Med, 2006. **166**(4): p. 444.
115. Langille, B.L., *Arterial remodeling: relation to hemodynamics.* Can J Physiol Pharmacol, 1996. **74**(7): p. 834-41.
116. Korshunov, V.A., S.M. Schwartz, and B.C. Berk, *Vascular Remodeling: Hemodynamic and Biochemical Mechanisms Underlying Glagov's Phenomenon.* Arteriosclerosis, Thrombosis, and Vascular Biology, 2007. **27**(8): p. 1722-1728.
117. Pasterkamp, G., D.P.V. de Kleijn, and C. Borst, *Arterial remodeling in atherosclerosis, restenosis and after alteration of blood flow: potential mechanisms and clinical implications.* Cardiovascular Research, 2000. **45**(4): p. 843-852.
118. Van Varik, B., et al., *Mechanisms of arterial remodeling: lessons from genetic diseases.* Frontiers in Genetics, 2012. **3**.
119. Libby, P., *Inflammation in atherosclerosis.* Nature, 2002. **420**(6917): p. 868-874.
120. Ward, M.R., et al., *Arterial Remodeling: Mechanisms and Clinical Implications.* Circulation, 2000. **102**(10): p. 1186-1191.
121. Langille, B.L., *Remodeling of developing and mature arteries: endothelium, smooth muscle, and matrix.* Journal of cardiovascular pharmacology, 1993. **21 Suppl 1**: p. S11-7.

122. Addis, P.B., et al., *Atherogenic and anti-atherogenic factors in the human diet.* Biochem Soc Symp, 1995. **61**: p. 259-71.
123. Levy, B.I., et al., *Microcirculation in hypertension: a new target for treatment?* Circulation, 2001. **104**(6): p. 735-40.
124. Gibbons, G.H. and V.J. Dzau, *The emerging concept of vascular remodeling.* N Engl J Med, 1994. **330**(20): p. 1431-8.
125. Mulvany, M., *Small artery remodelling in hypertension: causes, consequences and therapeutic implications.* Medical & Biological Engineering & Computing, 2008. **46**(5): p. 461-467.
126. Abbruzzese, T.A., et al., *Matrix metalloproteinase inhibition limits arterial enlargement in a rodent arteriovenous fistula model.* Surgery, 1998. **124**(2): p. 328-335.
127. Sasaki, K., et al., *Nitric Oxide Mediates Interleukin-1-Induced Gene Expression of Matrix Metalloproteinases and Basic Fibroblast Growth Factor in Cultured Rabbit Articular Chondrocytes.* Journal of Biochemistry, 1998. **123**(3): p. 431-439.
128. Bassiouny, H.S., et al., *Flow regulation of 72-kD collagenase IV (MMP-2) after experimental arterial injury.* Circulation, 1998. **98**(2): p. 157-63.
129. Eagleton, M.J., et al., *Nitric Oxide Inhibition Increases Aortic Wall Matrix Metalloproteinase-9 Expression.* Journal of Surgical Research, 2002. **104**(1): p. 15-21.
130. Beijers, H.J.B.H., et al., *Metabolic Syndrome in Nondiabetic Individuals Associated With Maladaptive Carotid Remodeling: The Hoorn Study.* American Journal of Hypertension, 2011. **24**(4): p. 429-436.
131. Ferreira, I., et al., *Clustering of Metabolic Syndrome Traits Is Associated With Maladaptive Carotid Remodeling and Stiffening: A 6-Year Longitudinal Study.* Hypertension, 2012. **60**(2): p. 542-549.
132. Carallo, C., et al., *Wall shear stress is lower in the carotid artery responsible for a unilateral ischemic stroke.* Atherosclerosis, 2006. **185**(1): p. 108-113.
133. Reddy, H.K., et al., *Adaptive-Outward and Maladaptive-Inward Arterial Remodeling Measured by Intravascular Ultrasound in Hyperhomocysteinemia and Diabetes.* Journal of Cardiovascular Pharmacology and Therapeutics, 2006. **11**(1): p. 65-77.
134. van Varik, B.J., et al., *Mechanisms of arterial remodeling: lessons from genetic diseases.* Front Genet, 2012. **3**(290).
135. Mulvany, M.J., *Small Artery Remodelling in Hypertension.* Basic & Clinical Pharmacology & Toxicology, 2012. **110**(1): p. 49-55.
136. Stein, J.H., C.E. Korcarz, and W.S. Post, *Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: summary and discussion of the American Society of Echocardiography consensus statement.* Prev Cardiol, 2009. **12**(1): p. 34-8.
137. Sramek, A., et al., *Ultrasound assessment of atherosclerotic vessel wall changes: reproducibility of intima-media thickness measurements in carotid and femoral arteries.* Invest Radiol, 2000. **35**(12): p. 699-706.
138. O'Leary, D.H., et al., *Thickening of the carotid wall. A marker for atherosclerosis in the elderly? Cardiovascular Health Study Collaborative Research Group.* Stroke, 1996. **27**(2): p. 224-31.
139. Lorenz, M.W., et al., *Prediction of Clinical Cardiovascular Events With Carotid Intima-Media Thickness: A Systematic Review and Meta-Analysis.* Circulation, 2007. **115**(4): p. 459-467.

140. Fan, A.Z., *Metabolic syndrome and progression of atherosclerosis among middle-aged US adults.* Journal of atherosclerosis and thrombosis, 2006. **13**(1): p. 46-54.
141. Iglseder, B., et al., *The metabolic syndrome is a stronger risk factor for early carotid atherosclerosis in women than in men.* Stroke, 2005. **36**(6): p. 1212-7.
142. Kawamoto, R., et al., *Metabolic syndrome may be a risk factor for early carotid atherosclerosis in women but not in men.* J Atheroscler Thromb, 2007. **14**(1): p. 36-43.
143. Ross, R., *Atherosclerosis — An Inflammatory Disease.* New England Journal of Medicine, 1999. **340**(2): p. 115-126.
144. Lloyd, K.D., et al., *Common carotid artery diameter and cardiovascular risk factors in overweight or obese postmenopausal women.* Int J Vasc Med, 2012. **169323**(10): p. 21.
145. Zureik, M., et al., *Differential Association of Common Carotid Intima-Media Thickness and Carotid Atherosclerotic Plaques With Parental History of Premature Death From Coronary Heart Disease: The EVA Study.* Arteriosclerosis, Thrombosis, and Vascular Biology, 1999. **19**(2): p. 366-371.
146. Störk, S., et al., *Carotid Artery Plaque Burden, Stiffness, and Mortality Risk in Elderly Men: A Prospective, Population-Based Cohort Study.* Circulation, 2004. **110**(3): p. 344-348.
147. Wyman, R.A., et al., *Ultrasound-detected carotid plaque as a screening tool for advanced subclinical atherosclerosis.* Am Heart J, 2005. **150**(5): p. 1081-5.
148. Butler, J., et al., *Relation of the metabolic syndrome to quantity of coronary atherosclerotic plaque.* Am J Cardiol, 2008. **101**(8): p. 1127-30.
149. Ishizaka, N., et al., *Metabolic syndrome may not associate with carotid plaque in subjects with optimal, normal, or high-normal blood pressure.* Hypertension, 2006. **48**(3): p. 411-7.
150. Eigenbrodt, M.L., et al., *Common carotid arterial interadventitial distance (diameter) as an indicator of the damaging effects of age and atherosclerosis, a cross-sectional study of the Atherosclerosis Risk in Community Cohort Limited Access Data (ARICLAD), 1987-89.* Cardiovasc Ultrasound, 2006. **4**: p. 1.
151. Montalcini, T., et al., *Large Brachial Artery Diameter and Metabolic Syndrome in postmenopausal women.* Atherosclerosis, 2010. **210**(2): p. 458-460.
152. Iannuzzi, A., et al., *Carotid artery remodeling in middle-aged women with the metabolic syndrome (from the "Progetto ATENA" study).* Am J Cardiol, 2005. **96**(8): p. 1162-5.
153. Ruan, L., et al., *Correlates of Common Carotid Artery Lumen Diameter in Black and White Younger Adults: The Bogalusa Heart Study.* Stroke, 2009. **40**(3): p. 702-707.
154. Hsia, J., et al., *Metabolic syndrome and coronary angiographic disease progression: the Women's Angiographic Vitamin & Estrogen trial.* Am Heart J, 2003. **146**(3): p. 439-45.
155. Kelly, R. and D. Fitchett, *Noninvasive determination of aortic input impedance and external left ventricular power output: A validation and repeatability study of a new technique.* Journal of the American College of Cardiology, 1992. **20**(4): p. 952-963.
156. Chironi, G.N., et al., *Correction of carotid intima-media thickness for adaptive dependence on tensile stress: Implication for cardiovascular risk assessment.* Journal of Clinical Ultrasound, 2009. **37**(5): p. 270-275.
157. Roman, M.J., et al., *Vascular Biomarkers in the Prediction of Clinical Cardiovascular Disease: The Strong Heart Study.* Hypertension, 2012. **59**(1): p. 29-35.

158. Sipahi, I., et al., *Static and serial assessments of coronary arterial remodeling are discordant: an intravascular ultrasound analysis from the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial.* Am Heart J, 2006. **152**(3): p. 544-50.
159. Britten, M.B., A.M. Zeiher, and V. Schachinger, *Effects of cardiovascular risk factors on coronary artery remodeling in patients with mild atherosclerosis.* Coron Artery Dis, 2003. **14**(6): p. 415-22.
160. Nixon, A.M., M. Gunel, and B.E. Sumpio, *The critical role of hemodynamics in the development of cerebral vascular disease.* Journal of Neurosurgery, 2010. **112**(6): p. 1240-1253.
161. Montalcini, T., et al., *Artery remodeling and abdominal adiposity in nonobese postmenopausal women.* Eur J Clin Nutr, 2010. **64**(9): p. 1022-4.
162. Woodard, G.A., et al., *Racial differences in the association between carotid plaque and aortic and coronary artery calcification among women transitioning through menopause.* Menopause, 2012. **19**(2): p. 157-63.
163. Empana, J.P., et al., *The metabolic syndrome and the carotid artery structure in noninstitutionalized elderly subjects: the three-city study.* Stroke, 2007. **38**(3): p. 893-9.
164. Paras, E., G.B.J. Mancini, and S.A. Lear, *The relationship of three common definitions of the metabolic syndrome with sub-clinical carotid atherosclerosis.* Atherosclerosis, 2008. **198**(1): p. 228-236.
165. Eckel, R.H., S.M. Grundy, and P.Z. Zimmet, *The metabolic syndrome.* Lancet, 2005. **365**(9468): p. 1415-28.
166. Huang, P.L., *A comprehensive definition for metabolic syndrome.* Disease Models & Mechanisms, 2009. **2**(5-6): p. 231-237.
167. Tzou, W.S., et al., *Increased subclinical atherosclerosis in young adults with metabolic syndrome: the Bogalusa Heart Study.* J Am Coll Cardiol, 2005. **46**(3): p. 457-63.
168. Xu, L., et al., *The Metabolic syndrome is associated with subclinical atherosclerosis independent of insulin resistance: the Guangzhou Biobank Cohort Study-CVD.* Clinical Endocrinology, 2010. **73**(2): p. 181-188.
169. Taniguchi, A., et al., *Metabolic syndrome, insulin resistance, and atherosclerosis in Japanese type 2 diabetic patients.* Metabolism, 2007. **56**(8): p. 1099-103.
170. Hassinen M, K.P.L.T.A. and et al., *MEtabolic syndrome and the progression of carotid intima-media thickness in elderly women.* Archives of Internal Medicine, 2006. **166**(4): p. 444-449.
171. Lee, Y.H., et al., *Metabolic syndrome and carotid artery parameter in Koreans aged 50 years and older.* Circ J, 2010. **74**(3): p. 560-6.
172. Janssen I, P.L.H.C.S.L.B.S.-T.K., *Menopause and the metabolic syndrome: The study of women's health across the nation.* Archives of Internal Medicine, 2008. **168**(14): p. 1568-1575.
173. Sowers MC, S.B., Morganstein D, et al, *SWAN: a multicenter, multiethnic, community-based cohort study of women and the menopausal transition.* Menopause: Biology and Pathobiology, 2000(Academic Press): p. 175-188.
174. Okada, M., et al., *Low-density lipoprotein cholesterol can be chemically measured: A new superior method.* Journal of Laboratory and Clinical Medicine, 1998. **132**(3): p. 195-201.

175. *Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III).* Jama, 2001. **285**(19): p. 2486-97.
176. Alberti, K.G., P. Zimmet, and J. Shaw, *The metabolic syndrome--a new worldwide definition.* Lancet, 2005. **366**(9491): p. 1059-62.
177. Wendelhag, I., et al., *Ultrasound measurement of wall thickness in the carotid artery: fundamental principles and description of a computerized analysing system.* Clin Physiol, 1991. **11**(6): p. 565-77.
178. Wendelhag, I., et al., *Ultrasound measurement of wall thickness in the carotid artery: fundamental principles and description of a computerized analysing system.* Clinical Physiology, 1991. **11**: p. 565-577.
179. Thompson, T., et al., *Progression of carotid intima-media thickness and plaque in women with systemic lupus erythematosus.* Arthritis and rheumatism, 2008. **58**(3): p. 835-42.
180. Sutton-Tyrrell, K., et al., *Subclinical atherosclerosis in multiple vascular beds: an index of atherosclerotic burden evaluated in postmenopausal women.* Atherosclerosis, 2002. **160**(2): p. 407-416.
181. Sekikawa, A., et al., *Intima-media thickness of the carotid artery and the distribution of lipoprotein subclasses in men aged 40 to 49 years between whites in the United States and the Japanese in Japan for the ERA JUMP study.* Metabolism, 2008. **57**(2): p. 177-182.
182. Iglseder, B., et al., *The Metabolic Syndrome Is a Stronger Risk Factor for Early Carotid Atherosclerosis in Women Than in Men.* Stroke, 2005. **36**(6): p. 1212-1217.
183. Thompson, T., K. Sutton-Tyrrell, and R. Wildman, *Continuous Quality Assessment Programs Can Improve Carotid Duplex Scan Quality.* Journal of Vascular Technology, 2001. **25**(1): p. 33-39.
184. Thompson, T., et al., *Progression of carotid intima-media thickness and plaque in women with systemic lupus erythematosus.* Arthritis & Rheumatism, 2008. **58**(3): p. 835-842.
185. Rundek, T., et al., *The metabolic syndrome and subclinical carotid atherosclerosis: the Northern Manhattan Study.* Journal of the cardiometabolic syndrome, 2007. **2**(1): p. 24 - 29.
186. Boden-Albala, B., et al., *Metabolic syndrome and ischemic stroke risk: Northern Manhattan Study.* Stroke, 2008. **39**(1): p. 30-5.
187. Chen, H.J., et al., *Influence of metabolic syndrome and general obesity on the risk of ischemic stroke.* Stroke, 2006. **37**(4): p. 1060-4.
188. Takahashi, K., et al., *Metabolic syndrome increases the risk of ischemic stroke in women.* Intern Med, 2007. **46**(10): p. 643-8.
189. Beijers, H.J., et al., *Metabolic syndrome in nondiabetic individuals associated with maladaptive carotid remodeling: the Hoorn Study.* Am J Hypertens, 2011. **24**(4): p. 429-36.
190. Glagov, S., et al., *Compensatory enlargement of human atherosclerotic coronary arteries.* N Engl J Med, 1987. **316**(22): p. 1371-5.
191. Bots, M.L., et al., *Common Carotid Intima-Media Thickness and Risk of Stroke and Myocardial Infarction: The Rotterdam Study.* Circulation, 1997. **96**(5): p. 1432-1437.
192. Lorenz, M.W., et al., *Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis.* Circulation, 2007. **115**(4): p. 459-67.

193. Ferreira, I., et al., *Clustering of metabolic syndrome traits is associated with maladaptive carotid remodeling and stiffening: a 6-year longitudinal study.* Hypertension, 2012. **60**(2): p. 542-9.
194. Carallo, C., et al., *Wall shear stress is lower in the carotid artery responsible for a unilateral ischemic stroke.* Atherosclerosis, 2006. **185**(1): p. 108-13.
195. Njoroge, J.N., et al., *High Urinary Sodium Is Associated With Increased Carotid Intima–Media Thickness in Normotensive Overweight and Obese Adults.* American Journal of Hypertension, 2011. **24**(1): p. 70-76.
196. Santaniemi, M., et al., *Metabolic syndrome in the prediction of cardiovascular events: The potential additive role of hsCRP and adiponectin.* European Journal of Preventive Cardiology, 2013.
197. Matsuzawa, Y., et al., *Adiponectin and Metabolic Syndrome.* Arteriosclerosis, Thrombosis, and Vascular Biology, 2004. **24**(1): p. 29-33.
198. Koivistoinen, T., et al., *Systemic hemodynamics in young adults with the metabolic syndrome: the Cardiovascular Risk in Young Finns Study.* Ann Med, 2010. **42**(8): p. 612-21.
199. Kumada, M., et al., *Association of Hypoadiponectinemia With Coronary Artery Disease in Men.* Arteriosclerosis, Thrombosis, and Vascular Biology, 2003. **23**(1): p. 85-89.
200. Chen, M.-P., et al., *Hypoadiponectinemia Is Associated With Ischemic Cerebrovascular Disease.* Arteriosclerosis, Thrombosis, and Vascular Biology, 2005. **25**(4): p. 821-826.
201. Matthews, K.A., et al., *Are Changes in Cardiovascular Disease Risk Factors in Midlife Women Due to Chronological Aging or to the Menopausal Transition?* Journal of the American College of Cardiology, 2009. **54**(25): p. 2366-2373.
202. El Khoudary, S.R., et al., *Progression rates of carotid intima-media thickness and adventitial diameter during the menopausal transition.* Menopause, 2013. **20**(1): p. 8-14.
203. Ford, E.S., W.H. Giles, and W.H. Dietz, *Prevalence of the metabolic syndrome among us adults: Findings from the third national health and nutrition examination survey.* Jama, 2002. **287**(3): p. 356-359.
204. Park, J.H., H.M. Kwon, and J.K. Roh, *Metabolic syndrome is more associated with intracranial atherosclerosis than extracranial atherosclerosis.* European Journal of Neurology, 2007. **14**(4): p. 379-386.
205. Boden-Albala, B., et al., *Metabolic Syndrome and Ischemic Stroke Risk: Northern Manhattan Study.* Stroke, 2008. **39**(1): p. 30-35.
206. O'Leary, D.H., et al., *Carotid-Artery Intima and Media Thickness as a Risk Factor for Myocardial Infarction and Stroke in Older Adults.* New England Journal of Medicine, 1999. **340**(1): p. 14-22.
207. Bennett, P.C., et al., *Ethnic differences in common carotid intima–media thickness, and the relationship to cardiovascular risk factors and peripheral arterial disease: the Ethnic-Echocardiographic Heart of England Screening Study.* QJM, 2011. **104**(3): p. 245-254.
208. Kuller, L., et al., *Differences in Prevalence of and Risk Factors for Subclinical Vascular Disease Among Black and White Participants in the Cardiovascular Health Study.* Arteriosclerosis, Thrombosis, and Vascular Biology, 1998. **18**(2): p. 283-293.
209. D'Agostino, R.B., et al., *Ethnic Differences in Carotid Wall Thickness: The Insulin Resistance Atherosclerosis Study.* Stroke, 1996. **27**(10): p. 1744-1749.

210. Mottillo, S., et al., *The Metabolic Syndrome and Cardiovascular Risk: A Systematic Review and Meta-Analysis.* Journal of the American College of Cardiology, 2010. **56**(14): p. 1113-1132.
211. Beijers, H.J.B.H., et al., *Metabolic Syndrome in Nondiabetic Individuals Associated With Maladaptive Carotid Remodeling: The Hoorn Study.* Am J Hypertens, 2011. **24**(4): p. 429-436.
212. Ferreira, I., et al., *Clustering of Metabolic Syndrome Traits Is Associated With Maladaptive Carotid Remodeling and Stiffening / Novelty and Significance.* Hypertension, 2012. **60**(2): p. 542-549.
213. Glagov, S., et al., *Compensatory Enlargement of Human Atherosclerotic Coronary Arteries.* New England Journal of Medicine, 1987. **316**(22): p. 1371-1375.
214. Korshunov, V.A., S.M. Schwartz, and B.C. Berk, *Vascular Remodeling.* Arteriosclerosis, thrombosis, and vascular biology, 2007. **27**(8): p. 1722-1728.
215. Ward, M.R., et al., *Arterial Remodeling.* Circulation, 2000. **102**(10): p. 1186-1191.
216. Kubis, N., et al., *Adaptive common carotid arteries remodeling after unilateral internal carotid artery occlusion in adult patients.* Cardiovascular Research, 2001. **50**(3): p. 597-602.
217. Scuteri, A., et al., *The central arterial burden of the metabolic syndrome is similar in men and women: the SardiNIA Study.* European heart journal, 2010. **31**(5): p. 602-613.
218. Iannuzzi, A., et al., *Carotid Artery Remodeling in Middle-Aged Women With the Metabolic Syndrome (from the "Progetto ATENA" Study).* The American journal of cardiology, 2005. **96**(8): p. 1162-1165.
219. Koskinen, J., et al., *Arterial Structure and Function After Recovery From the Metabolic Syndrome.* Circulation, 2010. **121**(3): p. 392-400.
220. Mattsson, N., et al., *Arterial structure and function in young adults with the metabolic syndrome: the Cardiovascular Risk in Young Finns Study.* European heart journal, 2008. **29**(6): p. 784-791.
221. Empana, J.-P., et al., *The Metabolic Syndrome and the Carotid Artery Structure in Noninstitutionalized Elderly Subjects.* Stroke, 2007. **38**(3): p. 893-899.
222. Friedewald, W.T., R.I. Levy, and D.S. Fredrickson, *Estimation of the Concentration of Low-Density Lipoprotein Cholesterol in Plasma, Without Use of the Preparative Ultracentrifuge.* Clinical Chemistry, 1972. **18**(6): p. 499-502.
223. *Intensive Diabetes Therapy and Carotid Intima–Media Thickness in Type 1 Diabetes Mellitus.* New England Journal of Medicine, 2003. **348**(23): p. 2294-2303.
224. Meyer, A.A., et al., *Improvement of Early Vascular Changes and Cardiovascular Risk Factors in Obese Children After a Six-Month Exercise Program.* Journal of the American College of Cardiology, 2006. **48**(9): p. 1865-1870.
225. Nissen, S.E., et al., *Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: The asteroid trial.* JAMA, 2006. **295**(13): p. 1556-1565.
226. Dickhout, J.G., S. Basseri, and R.C. Austin, *Macrophage Function and Its Impact on Atherosclerotic Lesion Composition, Progression, and Stability: The Good, the Bad, and the Ugly.* Arteriosclerosis, thrombosis, and vascular biology, 2008. **28**(8): p. 1413-1415.
227. Dalager, S., et al., *Artery-Related Differences in Atherosclerosis Expression: Implications for Atherogenesis and Dynamics in Intima-Media Thickness.* Stroke, 2007. **38**(10): p. 2698-2705.

228. Assmann, G. and A.M. Gotto, *HDL Cholesterol and Protective Factors in Atherosclerosis.* Circulation, 2004. **109**(23 suppl 1): p. III-8-III-14.
229. Boutouyrie, P., et al., *Association Between Local Pulse Pressure, Mean Blood Pressure, and Large-Artery Remodeling.* Circulation, 1999. **100**(13): p. 1387-1393.
230. Rossouw, J.E., *Hormones, genetic factors, and gender differences in cardiovascular disease.* Cardiovascular Research, 2002. **53**(3): p. 550-557.