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Relationships among Cynical Hostility, Metabolic Syndrome, and Cardiac Structure and Function in Multi-Ethnic Post-Myocardial Infarction Patients: A Structural Modeling Approach

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Paul Stephen Wachowiak

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BACKGROUND: Risk factors associated with Metabolic Syndrome (MetS) have been implicated in cardiovascular disease (CVD) development and outcomes in both healthy and diseased populations. Few studies have investigated the relationships between psychological variables, MetS factors, and indices of cardiac structure and function among healthy individuals in a single conceptual model. No studies to date have analyzed these relationships in a single model among patients with extant CVD. METHODS: The present study examined associations between cynical hostility (CynHo), MetS factors, and cardiac structure and function in 186 multi-ethnic (81.7% Hispanic) post-myocardial infarction (MI) patients (69.4% men) with a mean age of 53.3 (SD=8.8) years. Structural equation modeling (SEM) was used to specify and test a model of MetS that had both good statistical fit and was based on theory, empirical evidence, and logical grounds. Primary MetS variables included waist circumference (WC), the homeostatic model of insulin resistance (HOMA-IR), glucose area under the curve (G-AUC), triglycerides (TRIG), high-density lipoprotein cholesterol (HDL-C), and diastolic blood pressures (DBP). Secondary

MetS variables included plasminogen activator inhibitor-1 (PAI-1), a measure of fibrinolysis, and a latent inflammation variable comprised of C-reactive protein and interleukin-6. Cardiac function variables were fractional shortening (FS), a measure of cardiac contractility, E/A ratio, a measure of cardiac compliance, and rate-pressure product (RPP), a measure of myocardial oxygen demand. Cardiac structure variables were left ventricular mass index (LVMI), left ventricular posterior wall thickness at diastole (LVPWTd), and interventricular septal thickness at diastole (IVSTd) which together constituted the latent variable cardiac mass (CM). Cynical hostility (CynHo) was measured using a 13-item cynicism subscale of the Cook-Medley hostility scale. RESULTS: The final structural model had good model fit (χ^2 (102)=100.65, p=0.52, CFI=1.00, RMSEA=0.00, and SRMR=0.04). In this model, direct paths were supported between WC and CM and all MetS factors except TRIG and G-AUC. WC was indirectly associated with DBP via CM. In addition, WC demonstrated indirect relationships with the cardiac function measures. The model supported positive direct paths between HOMA-IR and G-AUC, TRIG, and PAI-1, but not inflammation or HDL-C. With respect to cardiac function, HOMA-IR demonstrated a direct positive association with RPP and direct inverse associations with FS and E/A ratio. No direct paths were supported between other MetS variables except one between TRIG and HDL-C. CynHo had a direct positive relationship with HOMA-IR but none with WC. CONCLUSIONS: The relationships observed suggest that, similar to findings in healthy individuals, central adiposity and insulin resistance play a primary role in cardiac structural

and functional impairment in post-MI patients. Unlike findings in healthy individuals, however, mediating relationships between other MetS factors and cardiac structural and functional impairment were not supported. Possible reasons underlying these findings are discussed. With respect to CynHo, our findings suggest that CynHo could promote the progression of metabolic dysfunction and cardiac disease via factors that influence the efficiency of glucose metabolism. Potential factors are discussed. Taken together, interventions for post-MI patients should take into account both direct and indirect effects of CynHo, central obesity, and IR on the progression of CVD in this population to reduce adverse outcomes and improve quality of life.

Dedications

To everyone who has been a friend, both near and far. To my siblings Stephen, Brenda, and Kristopher. Finally, to my grandmother Betty and my great grandparents, Anna and George, who believed in me from the beginning.

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Chapter 1: Introduction

1.1 Cardiovascular Disease & Tertiary Prevention

Cardiovascular disease (CVD) arguably constitutes one of the greatest health crises our nation has ever faced. According to American Heart Association estimates from 2004, almost 80 million Americans suffer from one or more forms of CVD, representing an increase in incidence of greater than 20% since 1999 (Rosamond, Flegal, Friday, Furie, Go, et al., 2007). Nearly 2,400 Americans die of CVD each day, an average of approximately 1 death every 36 seconds (Rosamond et al., 2007). Further, CVD continues to be the leading cause of mortality in the United States (US), accounting for 36% of all deaths in 2004 and listed as a primary or contributing mortality factor for approximately 1.4 million individuals (Rosamond et al., 2007). In fact, CVD claims more lives each year than cancer, accidents, lower respiratory diseases, and diabetes mellitus combined (Minino, Heron, & Smith, 2006).

In its simplest definition, CVD is a general class of diseases that involves the heart and/or the blood vessels and includes such conditions as coronary artery disease (CAD), arrhythmia, hypertension (HTN), angina, heart failure, heart valve disease, and congenital heart disease (www.americanheart.org). While CVD technically refers to any disease that affects the cardiovascular system, it is most often used to refer to those related to atherosclerosis. Atherosclerosis is a disease process characterized by vascular inflammation, endothelial dysfunction, and the buildup of plaque (e.g., lipids, calcium, and cellular debris) within the intima (i.e., subendothelial layer) of the blood vessel

resulting in vascular remodeling, abnormalities of blood flow, and diminished oxygen supply to target organs (Libby, 1998; Ross, 1999).

Coronary heart disease (CHD), also referred to as CAD or ischemic heart disease, is the end result of the plaque accumulation and subsequent narrowing of the lumen of the coronary arteries (Zipes, Libby, Bonow, & Braunwald, 2005). As the myocardium's supply of oxygen and nutrients becomes increasingly restricted due to ischemia, angina may be experienced, particularly during exertion, and arrhythmic functioning of the myocardium is possible (Zipes et al., 2005). After decades of progression, some of the plaques may rupture resulting in a myocardial infarction (MI). MI typically occurs following acute plaque rupture with the ensuing thrombosis filling the lumen of the coronary artery to the point of occlusion resulting in damage and death to the myocardial tissue (Zipes et al., 2005). More than 80% of the nearly 1.2 million MIs that occurred in the US in 2006 were the result of coronary atherosclerosis (Burke & Virmani, 2007). CHD, which includes MI, angina, and arrhythmia, is the most common form of CVD and the single largest cause of mortality for both men and women in the US (Rosamond et al., 2007).

Effective treatment methods for individuals with established CHD is an area of medicine that has seen increasing attention in recent years (Bartels, Davidson, & Gong, 2007; Bose, von Birgelen, & Erbel, 2007). Among individuals who have experienced MI, treatment falls under the domain of tertiary prevention. Tertiary prevention refers to activities aimed at restoring highest function, minimizing the negative effects of disease, and preventing disease-related

complications (U.S. Preventive Services Task Force, 1996). Activities serving these purposes are typically surgical, pharmacological or behavioral in nature, or a combination of these. Ultimately, tertiary prevention methods in post-MI patients are critical to prevent future cardiac incidents and mortality.

In order to facilitate the development of effective treatment strategies for post-MI patients, it is important that health care providers first possess an understanding of the primary causes of CHD. Biobehavioral factors that have traditionally been implicated include obesity, diabetes, HTN, poor diet, physical inactivity, smoking, and dyslipidemia (www.americanheart.org). Psychological factors have also been identified as potentially important risk factors (Holmes, Krantz, Rogers, Gottdiener, & Contrada, 2006). No single factor, however, has been able to reliably predict CHD development historically (Schneiderman & Skyler, 1996). Therefore, in addition to understanding the primary independent causes of CHD, it is vital for practitioners to have an understanding of the complex relationships among relevant psychological, behavioral, and biological factors as they interact to produce, as well as affect the progression of, frank disease. Such an understanding would ideally incorporate knowledge of the temporal nature of the key pathophysiological processes. This understanding would allow modifiable factors early in the pathogenesis of CHD to be targeted to reverse the disease process. To date, however, important gaps remain in our understanding of CHD pathogenesis. Identification of the nature of the relationships between risk factors central to CHD pathogenesis and progression

would undoubtedly prove to be a vital step in enhancing treatment quality and improving outcomes in this population.

This dissertation will examine the impact of relationships between psychological, behavioral, and biological factors on CVD severity in a post-MI cohort. More specifically, the current study proposes a model of pathogenic processes of a metabolic origin that affect changes in the cardiovascular system. The primary goal of the study is to identify the critical factors to be targeted to enable the reversal of disease processes in this population.

1.2 Metabolic Syndrome

An increasing recognition of the similarities among risk factors for type 2 diabetes mellitus (DM2) and CVD has led to the development of a diagnostic classification known as the metabolic syndrome (MetS). The MetS refers to a constellation of interrelated risk factors of metabolic origin that appears to directly promote the development of atherosclerotic CVD, DM2, and kidney disease (Grundy, Cleeman, Daniels, Donato, Eckel, et al., 2005). Diagnosis of the MetS is considered important due to studies suggesting that the aggregation of risk factors confers greater risk for CHD development than does each factor independently (Alexander, Landsman, Teutsch, & Haffner, 2003; Kaplan, 1996; Reilly & Rader, 2003; Scuteri, Najjar, Morrell, & Lakatta, 2005). Despite debate over this contention (Iribarren, Go, Husson, Sidney, Fair, et al., 2006), diagnosis of the syndrome is considered a very useful clinical tool to identify individuals at high risk for developing CVD or DM2.

The most commonly recognized components of the MetS include insulin resistance (i.e., hyperglycemia, hyperinsulinemia), obesity, dyslipidemia, and hypertension. Abdominal obesity and insulin resistance (IR), however, are

thought to be the primary physiological forces underlying the development of CVD via the MetS (Eckel, Grundy, & Zimmet, 2005; Reaven, 1988). Some consider abdominal adiposity to be the initiating factor of the MetS (Alberti, Zimmet, & Shaw, 2005). Confirmatory factor analyses indicate that MetS is a collection of related factors that likely shares a common physiological cause (Pladevall, Singal, Williams, Brotons, Guyer, et. al., 2006; Shen, Goldberg, Llabre, & Schneiderman, 2006; Shen, Todaro, Niaura, McCaffery, Zhang, et al., 2003). Shen and colleagues (2006) reported convincing evidence for a single factor structure represented by four components: IR, obesity, dyslipidemia, and, to a lesser extent, blood pressure. Further, findings from this study indicate that the proposed structure is generalizable across sex and ethnicity. Other factors proposed to be associated with MetS include inflammatory variables (e.g., C-reactive protein, interleukin-6), fibrinolytic variables (e.g., plasminogen activator inhibitor-1; PAI-1), microalbuminuria, angiotensin II, leptin, and adiponectin (Reilly & Rader, 2003).

There are currently six separate definitions of the MetS created by various organizations including the World Health Organization (WHO; 1999), the European Group for the Study of Insulin Resistance (EGIR; Balkau & Charles, 1999), the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP-III; 2001), the American Association of Clinical Endocrinologists (AACE; Bloomgarden, 2003), the International Diabetes Foundation (IDF; Alberti, Zimmet, & Shaw, 2006), and the American Heart Association / National Heart, Lung and Blood Institute (AHA / NHLBI; Grundy, Cleeman, Daniels, Donato,

Eckel, et al., 2005). The WHO and EGIR criteria require a laborious and costly measurement of IR and therefore tend to be used only in the arena of research (Ritchie & Connell, 2007). The ATP-III diagnostic criteria were designed to be used in outpatient settings with an emphasis on minimizing cost and burden to physicians and patients. For this reason as well as its demonstrated prognostic sensitivity, ATP-III criteria have been widely used in both clinical and research domains. To meet updated ATP-III criteria, individuals must demonstrate at least three of the following risk factors: abdominal obesity (waist circumference >102 cm for men and >88 cm for women), high triglycerides (≥150 mg/dL), low levels of HDL cholesterol (<40 mg/dL for men and <50 mg/dL for women), high blood pressure (systolic ≥130mmHg and/or diastolic ≥85 mmHg), and high fasting glucose (≥100 mg/dL). It has been reported, however, that the use of one definition over another makes little difference in prognostic implications (Hanley, Karter, Williams, Festa, D'Agostino Jr., et al., 2005)

The MetS has become a major public health challenge throughout the world. Despite differing definitions of the syndrome, it is estimated that about 25% of adults are affected worldwide (Eckel, Grundy, & Zimmet, 2005). In the US, the rates of MetS are even higher and have risen considerably over a short period of time. A recent study found that the unadjusted prevalence of MetS in the US ranged from approximately 35% to 39% of all US adults depending on whether NCEP or IDF criteria were applied (Ford, 2005). Eleven years prior, the prevalence among US adults was 21.8% using NCEP criteria (Ford, Giles, & Dietz, 2002). Not surprisingly, such increases in the occurrence of MetS parallel

the rising incidence of CVD and DM2. As mentioned earlier, the presence of the MetS in individuals has been found to be an independent risk factor for the development of DM2 (Hanson, Imperatore, Bennett, & Knowler, 2002; Lorenzo, Williams, Hunt, & Haffner, 2007; Meigs, Rutter, Sullivan, Fox, D'Agostino Jr., et al., 2007) and CVD (Bonora, Kiechl, Willeit, Oberhollenzer, Egger, et. al., 2003; Golden, Folsom, Coresh, Sharrett, Szklo, et al., 2002) in addition to being associated with a variety of adverse outcomes (Bonora, Kiechl, Willeit, Oberhollenzer, Egger, et al., 2007; Hanley, Williams, Stern, & Haffner, 2002; Jeppesen, Hansen, Rasmussen, Ibsen, Torp-Pedersen, et al., 2007; Lorenzo et al., 2007; Malik, Wong, Franklin, Kamath, L'Italien, et al., 2004; Rutter, Meigs, Sullivan, D'Agostino Sr., & Wilson, 2005; Saely, Aczel, Marte, Langer, Hoefle, et al., 2005; Scuteri et al., 2005). People with MetS are twice as likely to die from, and three times as likely to experience MI or stroke compared with people without the syndrome (www.idf.org/home/index.cfm?node=1429). Further, MetS in post-MI patients has been associated with increased infarct size and in-hospital complications (Clavijo, Pinto, Kuchulakanti, Torguson, Chu, et. al., 2006) as well as an increased risk of cardiac events in a 2 year period following the MI (Nakatani, Sakata, Sato, Mizuno, Shimizu, et al., 2007). Diabetic individuals experiencing MI may be at even greater risk of adverse outcomes (Haffner, Lehto, Ronnemaa, Pyorala, & Laakso, 1998).

To date, the causes of and mechanisms behind the MetS and how it leads to CVD are not fully understood. Most studies investigating MetS factors in relation to CVD development and prognosis are cross-sectional. Most studies

also tend to focus on how selected factors influence the development of CVD in initially healthy individuals as opposed to relationships in populations with manifest disease. More importantly, few studies have examined the interaction of several MetS components and their effect on cardiovascular functioning in a single model. As these relationships begin to be addressed, our understanding of MetS and its effect on the development and progression of CVD will grow as will our ability to prevent and treat the various manifestations of the disease.

Similarities among risk factors for DM2 and CVD have led to the development of the metabolic syndrome. The metabolic syndrome represents a constellation of risk factors thought to confer greater CVD risk than that associated with the independent effect of each of its factors. The primary components the metabolic syndrome include insulin resistance, obesity, dyslipidemia, and hypertension. Future studies should examine the causes of and mechanisms behind metabolic syndrome and how it leads to both CVD development as well as poor prognoses in individuals with manifest disease.

1.2.1 Insulin resistance.

Given the suggested primacy of the role of IR in the development of MetS (Reaven, 1988), an understanding of the role of insulin in healthy physiological functioning is important. Insulin, an anabolic polypeptide hormone produced by the β-cells of the pancreas, plays a role in a number of critical metabolic processes (Kumar & O'Rahilly, 2005; Reaven, 1999). Its primary function is to regulate the metabolism of carbohydrates and maintain glucose homeostasis (Muniyappa, Montagnani, Kon Koh, & Quon, 2007). Specifically, insulin promotes the uptake and storage of glucose in skeletal muscle and adipose tissue by such processes as increasing glycogen synthesis (Levine, Goldstein, Klein, & Huddlestun, 1949) and activating the transporter GLUT4 (Cohen, 2006).

Insulin also affects fat and protein metabolism, stimulating lipogenesis, diminishing lipolysis, and increasing amino acid transport into cells (Ferrannini & Mari, 1998). Without insulin, extreme hyperglycemia, hyperlipidemia, and protein wasting would ensue, resulting in keto-acidosis and, ultimately, death (Ferrannini & Mari, 1998).

In addition to its classic metabolic effects, insulin has a clear impact on the cardiovascular system (Muniyappa et al., 2007; Scherrer & Sartori, 1997). In the vasculature, for example, normal insulin signaling stimulates production of nitric oxide (NO) from the endothelium, increasing arterial muscle tone and forcing the arterial wall to relax, which increases systemic blood flow and glucose absorption (Scherrer & Sartori, 1997; Zeng & Quon, 1996). In the heart, studies have found that normal insulin signaling has positive effects on myocardial compliance and contractility (Abel, 2004; Brownsey, Boone, & Allard, 1997), increases myocardial blood flow and oxygen consumption (Baron, 1994; Sundell & Knuuti, 2003), protects the myocardium from reperfusion injury and ischemia, and prevents apoptosis of myocardial cells (Das, 2003). Finally, normal insulin signaling has been found to possess an anti-inflammatory effect (Dandona, Aljada, Mohanty, Ghanim, Hamouda, et al., 2001; Das, 2001; Stentz, Umpierrez, Cuervo, & Kitabchi, 2004; Takebayashi, Aso, & Inukai, 2004), an anti-oxidant effect, an antithrombotic effect (decreased tissue factor), a profibrinlytic effect (decreased PAI-1), and a platelet inhibitory effect (Chaudhuri, Janicke, Wilson, Tripathy, Garg, et al., 2004). For these reasons, appropriate insulin metabolism has been

hypothesized to be cardio-protective in both humans (Chaudhuri et al., 2004) and animals (Shamir, Shehadeh, Rosenblat, Eshach-Adiv, Coleman, et al., 2003).

Dysregulation of insulin metabolism, or IR, on the other hand, has been found to produce numerous serious adverse physiological effects. As previously mentioned, it is thought to be a primary mechanism underlying MetS, and is implicated in the development of DM2 and CVD (McFarlane, Banerji, & Sowers, 2001; Rao, 2001; Reaven, 1988). In an IR state, normal amounts of insulin are inadequate to allow glucose to enter fat, muscle and liver cells leading to local and/or systemic hyperglycemia. To compensate for this, the beta (β) cells of the pancreas stimulate an increase in insulin secretion sufficient to trigger glucose absorption, a condition referred to hyperinsulinemia (Kumar & O'Rahilly, 2005; Reaven, 1999). Over time, the inability of the pancreatic β-cells to produce sufficient insulin in the hyperglycemic state characterizes the transition from IR to DM2 (Kumar & O'Rahilly, 2005). In addition to hyperglycemia and hyperinsulinemia, the direct metabolic effects of IR include increased lypolysis resulting in hydrolysis of stored triglycerides and elevated free fatty acids in the blood, increased protein catabolism, and decreased protein synthesis (Dandona, Aljada, Chaudhuri, Mohanty, Garg, 2005). Further, studies have found that hyperinsulinemia can lead to IR, potentially exacerbating the underlying resistance (Iozzo, Pratipanawatr, Pijl, Vogt, Kumar, et al., 2001).

Measurement of IR is often gauged by the degree of sensitivity that insulin possesses at the cellular level in tissues and organs of the body. Such measurement has been accomplished through a variety of methods historically.

One technique employed to determine IR levels is the euglycemic-hyperinsulinemic clamp (DeFronzo, Tobin, & Andres, 1979). This technique, which measures the amount of glucose necessary to compensate for an increased insulin level, is considered to be the best available standard for the measurement of insulin sensitivity (Ferrannini & Mari, 1998). Although the method features exemplary precision, the drawbacks of administering the procedure include high costs and greater time demands (Ferrannini & Mari, 1998). A simpler method involves estimating the degree of hyperinsulinemia present via measurement of circulating plasma insulin levels as IR and hyperinsulinemia tend to be highly correlated (Laakso, 1993; McAuley, Williams, Mann, Walker, Lewis-Barned, et al., 2001). Similarly, fasting glucose has commonly been used to estimate insulin sensitivity as hyperglycemia is directly related to IR. While some have questioned the sensitivity of these surrogate markers (Ferrannini & Iozzo, 2006), a large majority of studies conducted to date have employed them (Pankow, Jacobs Jr., Steinberger, Moran, & Sinaiko, 2004; Rubins, Robins, Collins, Nelson, Elam, et al., 2002; Sung, Kim, & Reaven, 2007).

Efforts to obtain insulin sensitivity proxies that are simple to administer in clinical settings and cost effective, while possessing good sensitivity, have resulted in investigators employing the oral glucose tolerance test (OGTT; Albareda, Rodriguez-Espinosa, Murugo, de Leiva, & Corcoy, 2000; Hanley, Williams, Gonzalez, D'Agostino, Jr., Wagenknecht, et al., 2003). The OGTT is initiated by the administration of a 75-gram oral glucose load to determine how quickly it is cleared from the blood, typically over a period of 2 hours. Blood

glucose and insulin levels are measured 5 times over the 2 hour period, once every 30 minutes, via intravenous blood draw. The values obtained from this test are used to determine the presence and degree of patients' systemic IR as well as their DM2 status. If fasting glucose levels are greater than 100 mg/dL and less than 125mg/dL, the patient is considered to have impaired fasting glycemia (IFG; American Diabetes Association, 2005; WHO, 2007). If two-hour glucose levels are 140 to 199 mg/dL, the patient is considered to have impaired glucose tolerance (IGT; American Diabetes Association, 2005; WHO, 2007). Values above these limits confer a diagnosis of DM2 on the patient (American Diabetes Association, 2005; WHO, 2007). Although both IFG and IGT are associated with an increased risk of cardiovascular pathology and mortality (Barr, Zimmet, Welborn, Jolley, Magliano, et al., 2007), IFG is thought to be a lesser risk than IGT; having both confers the greatest risk (Unwin, Shaw, Zimmet, & Alberti, 2002). A recent study reported that IFG often progresses to DM2 in less than three years (Nichols, Hillier, & Brown, 2007).

A more sensitive measure of IR than fasting glucose or insulin values alone is the homeostasis model assessment of insulin resistance (HOMA-IR; Matthews, Hosker, Rudenski, Naylor, Treacher, et al., 1985). The HOMA-IR utilizes a mathematical formula that incorporates fasting levels of both glucose and insulin to quantify IR and beta-cell function. HOMA-IR has been found to possess a high degree of correlation with the euglycemic clamp method of IR assessment in healthy (Bonora, Kiechl, Willeit, Oberhollenzer, Egger, et al., 1998), hypertensive (Lansang, Williams, & Carroll, 2001), and diabetic (Howard,

Bergman, Wagenknecht, Haffner, Savage, et al., 1998) patients. In addition, HOMA-IR has been associated with metabolic and cardiovascular markers and outcomes in a number of studies (Haffner, Miettinen, & Stern, 1997; Jeppesen et al., 2007).

As mentioned earlier, IR is independently associated with the development of a number of diseases, but most of the attention has focused on its relationship with DM2 and, more recently, with CVD (Rader, 2007). Regarding DM2, IR has long been considered to be the best known predictor of its onset (McNulty, Ettinger, Gilchrist, Kozak, Chambers, 2001). It has been clearly implicated in the onset of symptomatology in the approximately 20 million U.S. adults who have diabetes, 6 million of whom remain undiagnosed, and the additional 16 million individuals who have IGT (Centers for Disease Control and Prevention, 2005). Worldwide, DM2 is estimated to affect over 210 million people in the adult population alone (International Diabetes Federation, 2007). The role of IR in the pathogenesis of CVD, however, has been more controversial. Recent studies investigating the relationship between IR and CVD have found that CVD risk begins to increase considerably earlier than the onset of DM2 or even IFG (Rader, 2007).

Within the past decade, IR has been studied in a number of cohorts and its relationship to CVD is beginning to become better understood. The majority of studies conducted to date regarding this relationship have focused on healthy populations. In individuals initially free of DM2 and CVD, prospective studies have reported that IR predicts incident CVD (Bonora et al., 2007; Hanley et al.,

2002; Jeppesen, et al., 2007; Meigs, Wilson, Fox, Vasan, Nathan, et al., 2006; Rutter et al., 2005). In a sample 919 men and women aged 40-79 years without CVD at baseline, Bonora and colleagues (2007) reported that over 15 years of follow-up, insulin-resistant individuals had greater than twice the risk of incident CVD compared to non-resistant individuals after adjustment for several risk factors. Studies have also found IR to be independently associated with atherogenesis among individuals without known CVD or DM2 (Cardellini, Marini, Frontoni, Hribal, Andreozzi, et al., 2007; Howard, O'Leary, Zaccaro, Haffner, Rewers, et al., 1996).

Outside of studies among healthy individuals, a number of studies have examined the relationship between DM2 and CVD (Anderson, Wilson, Odell, & Kannel, 1991; Bonora, Formentini, Calcaterra, Lombardi, Marini, et al., 2002; Nathan, Meigs, & Singer, 1997; Rader, 2007). Studies have found that individuals with DM2 have a risk for MI equal to that of non-diabetic individuals who have had a previous infarction (Haffner et al., 1998) and the infarcts tend to be larger (Abraham, 2003; Abbud, Shindler, Wilson, & Kostis, 1995). Cardiovascular mortality appears to be affected by DM2 status as well. One study reported that individuals with DM2 have a 3-7 times increased risk of cardiovascular death than non-diabetics (Haffner et al., 1998). Another study found DM2 status to be the most important predictor of recurrent MI/fatal CHD over 6-9 years in a cohort of 1635 patients (aged 45-70 years) surviving at least 28 days after a first MI (Leander, Wiman, Hallqvist, Andersson, Ahlbom, et al., 2007). Recognition of the connection between DM2 and CVD has led to the

recent creation of a joint task force composed of cardiologists and diabetologists with the aim of improving diagnosis and care within these overlapping populations (Ryden, Standl, Bartnik, Van den Berghe, Betteridge, et al., 2007).

Studies reporting outcomes associated with IR in individuals with known CHD are few in number (Lazzeri, Sori, Chiostri, Gensini, & Valente, 2009; Robins, Rubins, Faas, Schaefer, Elam, et al., 2003; Rubins et al., 2002; Saely et al., 2005). In one such study, Robins and colleagues (2003) found that individuals with IR had significantly higher risk of a cardiovascular event at 5-year follow-up, regardless of initial DM2 status, compared to those without IR. In another study, HOMA-IR was found to be an independent predictor of in-hospital mortality in non-diabetic post-MI patients (Lazzeri et al., 2009).

The physiological mechanisms underlying the relationship between IR and CVD continue to be explored (Ferrannini & Iozzo, 2006). It is possible that IR (and corresponding hyperinsulinemia) is atherogenic in its own right (Howard, O'Leary, Zaccaro, Haffner, Rewers, et al., 1996; Reaven, 1988). It is also possible that IR promotes atherosclerosis by its effect on other cardiovascular risk factors (Golden et al., 2002; Hedblad, Nilsson, Janzon, & Berglund, 2000; Howard et al., 1996; Meigs, Larson, D'Agostino Jr., Levy, Clouse, et al., 2002). An atherogenic effect of insulin may occur through one or more mechanisms. A direct effect of insulin on the atherosclerotic process could include its promotion of increased lipid synthesis within artery tissue as well as proliferation of smooth muscle cells (Howard et al., 1996). Studies in animal cohorts with prior endothelial injury have found that long-term administration of insulin results in

lipid-containing lesions and arterial wall thickening (Ridray, 1995; Stout, 1990). Factors suggested to mediate the IR-atherosclerosis process include procoagulability with increased expression of PAI-1, increased expression of vascular cell adhesion molecule-1, reduced adiponectin concentration, and instability of atherosclerotic plaques resulting from increased expression of matrix metalloproteinases by macrophages (Boyle, 2007). Although it is not known if a reduction in IR will result in lower CVD mortality, recent interventions have reported that pioglitazone (an insulin sensitizing agent) administration decreased carotid wall intimal-media thickness in individuals with DM2 (Koshiyama, Shimono, Kuwamura, Minamikawa, Nakamura, 2001). In addition, pioglitazone has been found to increase high-density lipoprotein concentrations, decrease free fatty acid levels, and increase plasma adiponectin levels (Boyle, 2007).

In addition to its relationship with atherosclerotic processes, IR is highly interrelated with the other risk factors that comprise the MetS (DeFronzo & Ferrannini, 1991; Reaven, 2005; 1988; Shen et al., 2003). It has been well established that the combination of IR and compensatory hyperinsulinemia increases the probability that an individual will be hypertensive and dyslipidemic, conditions that substantially increase the risk of CVD (Reaven, 2005). Increasingly, pathophysiological models with greater specificity and complexity have been proposed detailing the mechanisms by which IR influences MetS-related factors and cardiovascular function (Dandona et al., 2005; Mather, Anderson, & Verma, 2001; Rader, 2007).

Insulin resistance, considered by many to be the primary organizing feature of the metabolic syndrome, denotes a physiological state

characterized by disordered carbohydrate and lipid metabolism resulting in hyperglycemia, hyperinsulinemia, and DM2. Insulin resistance is a broad construct and, as such, can be measured via several methods with varying degrees of precision. Insulin resistance is related to CVD development and events both directly and indirectly via its effect on other metabolic syndrome factors.

1.2.2 Obesity.

The prevalence of obesity in the US has begun to reach alarming proportions, increasing steadily since it was first measured about 45 years ago. In the time period from 1960-1962, the prevalence of obesity was 13.4% (Flegal, Carroll, Ogden, & Johnson, 2002). From 1976-1980 to 1988-1994, the prevalence increased from 15.0% to 23.3%. The most recent data (2003-2004) indicates that 66.3% of American adults aged 20 years and greater are overweight, 32.2% of which are obese (Ogden, Carroll, Curtin, McDowell, Tabak, et al., 2006). Extreme obesity (BMI ≥ 40) has also increased and is currently estimated to affect 1 in 20 adults (Ogden et al., 2006). Because obesity is responsible for more health care expenditures than any other medical condition (Hensrud & Klein, 2006), it has the effect of financially saddling great numbers of families and straining the resources of the entire health care system.

Obesity has been implicated in a number of disease states including CVD, DM2, sleep apnea, dyslipidemia, HTN, and numerous cancers, as well as mortality (Hensrud & Klein, 2006). Its association with CVD, however, may be most responsible for its pervasive effects. Although the association between obesity and the development and atherosclerosis is controversial, studies have demonstrated a relationship (De Michele, Panico, Iannuzzi, Celentano, Ciardullo, et al., 2002; Lakka, Lakka, Salonen, Kaplan, & Salonen, 2001). Studies

demonstrating the impact of obesity on CVD outcomes, however, particularly mortality, are less contestable (Chen, Yang, Zhou, Smith, Offer, et al., 2006; Jousilahti, Tuomilehto, Vartiainen, Pekkanen, & Puska, 1996; Kang, Shaw, Hayes, Hachamovitch, Abidov, et al., 2006; Kim, Meade, & Haines, 2006; Seidell, Verschuren, van Leer, & Kromhout, 1996; Yan, Daviglus, Liu, Stamler, Wang, et al., 2006). Results from a large recent prospective study involving 17,643 middle-aged men and women initially free of CHD and DM2 followed for a mean of 32 years indicated that the risk for CHD death for obese participants (i.e., a BMI of 25.0 – 29.9) with high blood pressure or high cholesterol levels was greater than twice that of participants with normal weights and equivalent risk, after adjustment for traditional cardiovascular risk factors (Yan et al., 2006).

Recently, however, studies applying advances in the measurement of adipose tissue have found that the distribution of fat may have a profound impact on the strength of obesity-CVD relationship. While studies such as the one carried out by Yan and colleagues (2006) involve an overall or global measure of obesity (i.e., BMI), studies are increasingly investigating the effects of visceral obesity on CVD. Visceral obesity – sometimes referred to as central adiposity, abdominal obesity, omental adiposity, upper body obesity, or truncal obesity – is defined by a high degree of fatty tissue underneath the abdominal muscle wall (Ritchie & Connell, 2007). Long-term prospective studies demonstrate that measures of visceral obesity are stronger predictors of both coronary events (Lakka, Lakka, Tuomilehto, & Salonen, 2002; Rexrode, Buring, & Manson, 2001) and mortality (Price, Uauy, Breeze, Bulpitt, & Fletcher, 2006; Prineas, Folsom, &

Kaye, 1993; Visscher, Seidell, Molarius, van der Kuip, Hofman, et al., 2001) than are measures of overall obesity. Further, studies have reported that the association between central obesity measures and CVD are independent of overall body weight measures (Hauner, 1995) in both obese and non-obese subjects (Carey, 1998).

The two most commonly used measures of central obesity are waist-hip ratio (WHR) and waist circumference (WC). While WHR has been used in several CVD studies historically, investigators have increasingly used WC as the primary index of central adiposity as studies have identified it as a better predictor of visceral adipose tissue (Pouliot, Despres, Lemieux, Moorjani, Bouchard, et al., 1994; Raikkonen, Matthews, & Kuller, 1999; Samaras & Campbell, 1997). In fact, the shared variance between WC and visceral fat has been reported to be as much as 75% (Ferland, Despres, Tremblay, Pinault, Nadeau, et al., 1989; Pouliot et al., 1994). Importantly, studies have found that WC was a better predictor of CVD-related mortality than WHR (Visscher et al., 2001) although not all studies are in agreement (Welborn, Dhaliwal, & Bennett, 2003). A recent study, however, found that WC was directly associated with all-cause mortality after adjusting for BMI (Bigaard, Frederiksen, Tjonneland, Thomsen, Overvad, et al., 2005).

Although the exact mechanisms behind obesity's effect on cardiovascular outcomes remain unclear, its interaction with other factors of the MetS appears to explain a significant portion of the association. A number of epidemiological studies have demonstrated a relationship between central obesity and

components of the MetS (Despres, Allard, Tremblay, Talbot, & Bouchard, 1985; Despres, Moorjani, Tremblay, Ferland, Lupien, et al., 1989; Folsom, Burke, Ballew, Jacobs Jr., Haskell, et al., 1989; Gillum, 1987; Rexrode, Carey, Hennekens, Walters, Colditz, et al., 1998; Thompson, Ryu, Craven, Kahl, & Crouse, 1991). Perhaps explaining its effect on cardiovascular outcomes, visceral fat was found to be more harmful to healthy metabolic functioning than fat located elsewhere on the body (Arner, 1998; Bergman, Kim, Hsu, Catalano, Chiu, et. al., 2007; Hauner, 1995; Kissebah, 1997) and hence of greater importance in MetS pathogenesis (Bosy-Westphal, Geisler, Onur, Korth, Selberg, et al., 2006; Shen, Punyanitya, Chen, Gallagher, Albu, et al., 2006). Although this idea has been challenged (Jensen, 2006; 1997), the stronger association of IR with visceral fat appears to suggest a convincing link between visceral fat and MetS (Meek, Nair, & Jensen, 1999; Mittelman, Van Citters, Kirkman, & Bergman, 2002). Similar to its role in CVD outcome studies, WC appears to be the preferred proxy for visceral fat as several studies have found it to be the strongest predictor of MetS factors (Onat, Avci, Barlan, Uyarel, Uzunlar, et al., 2004; Pouliot, Despres, Lemieux, Moorjani, Bouchard, et al., 1994; Wei, Gaskill, Haffner, & Stern, 1997). As a result, WC has been included as a diagnostic criterion in the majority of MetS formulations (Ritchie & Connell, 2007).

As mentioned, the effect of central obesity on CVD most likely involves a synergistic interplay with other MetS factors. Its association with particular MetS components, however, may have greater impact on CVD pathogenesis (Dandona et al., 2005). The robust relationships identified between central

adiposity and IR, inflammation, and dyslipidemia have received the most attention (Despres et al., 1985; Forouhi, Sattar, & McKeigue, 2001; Foster, Weinsier, Birch, Norris, Bernstein, Wang, et al., 1987; Hotamisligil, Shargill, & Spiegelman, 1993; Pouliot, Despres, Nadeau, et al., 1992; Samaras & Campbell, 1997; Santos, Lopes, Guimaraes, & Barros, 2005). Hypotheses as to how central obesity influences these factors in CVD pathogenesis have been proposed.

Recent studies have suggested a causal relationship between visceral obesity and IR (Bergman, Kim, Hsu, Catalano, Chiu, et al., 2007; Dandona et al., 2005; Ritchie & Connell, 2007). One of the primary hypotheses put forth in this context highlights the direct role of free fatty acids (FFAs; Arner, 1998; Boden, 1997; Boden, Chen, Ruiz, White, & Rosetti, 1994; Carey, 1998; Lam, van de Werve, Giacca, 2003; Randle, Garland, Hales, & Newsholme, 1963). Previously thought of as solely a passive energy repository, adipose tissue has recently been recognized as an endocrine organ that produces a number of metabolically active substances, one of which is FFA (Fischer-Posovszky, Wabitsch, & Hochberg, 2007; Kershaw & Flier, 2004). FFAs are generally produced via lypolysis, or the breakdown of fat stored in fat cells. As visceral fat cells have been reported to have higher rates of basal lypolysis (Hellmer, Marcus, Sonnenfeld, & Arner, 1992; Kissebah, Vydelingum, Murray, Evans, Hartz, et al., 1982), they are thought to generate more FFAs in the liver as well as in systemic circulation (Bjorntorp, 1990; Kissebah & Peiris, 1989). Almost 50 years ago, Randle and colleagues (1963) found that increased FFA concentrations impaired

glucose metabolism. Later, Arner and colleagues (1998) described a process whereby visceral fat-produced FFAs are released into the liver via the portal vein resulting in increased lipid synthesis, particularly of small very low-density lipoprotein (VLDL) particles, and hepatic hyperglycemia (Boden, 1997; Brunzell & Hokanson, 1999; Carey, 1998; Matsuzawa, Shimomura, Nakamura, Keno, Kotani, et al., 1995). The response of the pancreas to manage the hyperglycemic state manifests in hyperinsulinemia which, over time, contributes to hepatic IR, decreased high-density lipoprotein (HDL) concentrations, and increasing concentrations of non-metabolized FFAs (Carey, 1998; Mooradian, Haas, & Wong, 2006; Svedberg, Bjorntorp, Smith, & Lonnroth, 1990; Wajchenberg, 2000). FFAs are then thought to accumulate in the blood and body tissue leading to the development of peripheral IR (Belfort, Mandarino, Kashyap, Wirfel, Pratipanawatr, et al., 2005; Carey, 1998). The purported role of FFAs in the genesis of IR is highlighted by a study of DM2 patients reporting that up to half of the variance in IR was explained by FFAs (Boden & Chen, 1995).

The recent proposition, however, that obesity is a proinflammatory state has prompted investigators' interest in the interplay among adipose tissue, inflammation, and insulin action (Dandona, Aljada, & Bandyopadhyay, 2004; Dyck, Heigenhauser, & Bruce, 2006; Festa, D'Agostino Jr., Howard, Mykkanen, Tracy, et al., 2000; Hotamisligil, 1999; Hotamisligil, Shargill, & Spiegelman, 1993; Shoelson, Herrero, & Naaz, 2007; Xu, Barnes, Yang, Tan, Yang, et al., 2003). Studies in this domain have led to the hypothesis that obesity-induced inflammatory cytokines, or adipokines, begin to induce IR *before* FFAs become

involved in the process (Dandona et al., 2005). This hypothesis was fueled by the seminal study by Hotamisligil and colleagues (1993) that found that tumor necrosis factor α (TNF-α) was expressed by adipose tissue, was overexpressed in obesity, and was a mediator of IR. Further, these investigators found that neutralizing the effects of this cytokine resulted in a restoration of insulin sensitivity. Subsequently, studies have reported that increased plasma concentrations of TNF-α, interleukin-6 (IL-6), C-reactive protein (CRP), and a number of other inflammatory markers are elevated in obesity and secreted by adipose tissue (Funahashi, Nakamura, Shimomura, Maeda, Kuriyama, et al., 1999; Kern, Ranganathan, Li, Wood, & Ranganathan, 2001; Pradhan, Manson, Rifai, Buring, & Ridker, 2001; Vozarova, Weyer, Hanson, Tataranni, Bogardus, et al., 2001). Although various mechanisms have been proposed as to how inflammatory factors cause IR, recent hypotheses suggest their interference with insulin signal transduction via the actions of specific proteins (Rui, Yuan, Frantz, Shoelson, & White, 2002; Senn, Klover, Nowak, Zimmers, Koniaris, et al., 2003). IR, in turn, is thought to further promote the production of inflammatory factors as well as the increased production of FFAs, resulting in greater IR (Dandona et al., 2005).

In addition to the production of inflammatory markers by adipose tissue, dietary habits may to be involved in the production of inflammation. Studies have found that increased macronutrient intake induces an inflammatory response (Dandona, Mohanty, Ghanim, Aljada, Browne, et al., 2001) and generates oxidative stress, which also activates inflammatory processes (Wang, Leonard,

Castranova, Vallyathan, & Shi, 1999). It has been suggested that meals consisting of large portions of processed carbohydrates and low fiber, a diet common to many individuals, result in the inability of insulin to suppress the inflammation generated by the meal. Interestingly, it has been found that in comparison to an isocaloric fast food meal, consumption of meal rich in fruit and fiber did not cause inflammation or oxidative stress (Dandona et al., 2005; Mohanty, Daoud, Ghanim, Ravishankar, Szudzik, et al., 2004).

Studies have also demonstrated associations between central adiposity and other MetS factors including HTN (Francischetti & Genelhu, 2007) and impaired fibrinolysis in MetS patients (Guerre-Millo, 2004; Trost, Pratley, & Sobel, 2006). The presence of particular obesity-related adipokines appears to be a strong mediator of these associations. Leptin, a protein involved in the regulation of appetite, appears to be the primary link between obesity, increased SNS activity and HTN (Mathew, Patel, Reams, Freeman, Spear, et al., 2007). Angiotensinogen, a peptide in the blood that causes vasoconstriction, has also been implicated in the genesis of HTN (Giacchetti, Faloia, Sardu, Camilloni, Mariniello, et al., 2000; Guerre-Millo, 2004). Aside from specific mechanisms, however, a large body of evidence has suggested that excessive weight gain is the most common cause of HTN (Francischetti & Genelhu, 2007). PAI-1, the primary marker of impaired fibrinolysis, has also been found to be increased in obese individuals from a variety of populations (Alessi, Poggi, & Juhan-Vague, 2007). The relationship between obesity and PAI-1 has been found to be particularly strong among those with increased central adiposity (Morange,

Alessi, Verdier, Casanova, Magalon, et al., 1999; Pannacciulli, De Mitrio, Marino, Giorgino, & De Pergola, 2002; Sakkinen, Wahl, Cushman, Lewis, & Tracy, 2000) and IR (Festa, D'Agostino Jr., Mykkanen, Tracy, Zaccaro, et al., 1999; Juhan-Vague, Alessi, & Morange, 2000).

Lifestyle interventions, which generally involve dietary improvements, caloric restriction, and increased exercise to promote weight loss, have been found to have a profound effect on a number of factors associated with the MetS (Sarti & Gallagher, 2006). Interventions promoting weight loss have resulted in an improvement in cardiovascular risk factors in patients with IGT and DM2 (Ratner, Goldberg, Haffner, Marcovina, Orchard, et al., 2005; Pi-Sunyer, Blackburn, Brancati, Bray, Bright, et al., 2007) as well as in individuals with CHD (Daubenmier, Weidner, Sumner, Mendell, Merritt-Worden, et al., 2007). In patients with CHD, a recent study investigated the effect of 3-month changes in health behaviors on 3-month changes in coronary risk factors (Daubenmier et al., 2007). Reductions in dietary fat intake predicted decreases in weight, total cholesterol, LDL cholesterol, and interacted with increased exercise resulting in lower perceived stress. Increased stress management skills were related to reductions in weight, hemoglobin A1c (in patients with DM2), total cholesterol/HDL cholesterol ratio (in men), triglycerides, and hostility. In middle-aged individuals with DM2, decreased caloric intake and increased physical activity resulted in greater weight loss, reductions in CVD medications, and improvements in systolic and diastolic pressure, triglycerides, and HDL cholesterol at 1-year follow-up compared with those only receiving education and

support (Pi-Sunyer et al., 2007). Weight loss as part of a lifestyle intervention has also significantly reduced individuals' incidence of developing the MetS (Orchard, Temprosa, Goldberg, Haffner, Ratner, et al., 2005) and DM2 (Knowler, Barrett-Connor, Fowler, Hamman, Lachin, et al., 2002; Kosaka, Noda, & Kuzuya, 2004; Pan, Li, Hu, Wang, Yang, et al., 1997; Tuomilehto, Lindstrom, Eriksson, Valle, Hamalainen, et al., 2001). Further, weight loss has been associated with lower cardiac event and mortality rates (Eriksson & Lindgarde, 1998; Singh, Rastogi, Rastogi, Niaz, & Beegom, 1996) and a regression of atherosclerosis in CHD patients (Ornish, Scherwitz, Billings, Brown, Gould, et al., 1998). Individuals with CAD who engaged in a fat modified and fruit and vegetable enriched diet and participated in moderate physical activity over a period of 3 years demonstrated a greater decline in cardiac event rates and total mortality compared to individuals just following a low-fat diet (Singh et al., 1996). In addition, individuals in the diet-exercise condition demonstrated significant improvements in central obesity, fasting and post-prandial blood glucose, plasma insulin levels, blood pressure, triglycerides, and HDL cholesterol compared with those in the comparison group.

Obesity, particularly central obesity, plays a significant role in metabolic syndrome pathogenesis. Although debated, waist circumference is considered the primary index of central obesity as it has been identified as the best predictor of metabolically-active visceral adipose tissue. Central obesity contributes to insulin resistance and dyslipidemia via the production of several adipokines including free fatty acids. Further, central obesity is associated with hypertension, impaired fibrinolysis, and vascular dysfunction. Lifestyle interventions promoting weight loss have been reported to profoundly improve CVD risk factors and outcomes in patients with MetS, CHD and DM2.

1.2.3 Dyslipidemia.

Dyslipidemia refers to a disruption in the amount of lipids in the blood typically characterized by elevated levels of small, dense low density lipoprotein (LDL) particles, increased triglycerides (TRIG), and reduced high density lipoprotein (HDL) cholesterol levels (Bamba & Rader, 2007; Nesto, 2005). The constellation of these lipid abnormalities, particularly elevated TRIG and low HDL-C, has been termed "atherogenic dyslipidemia" and been found to be a robust risk factor for CHD (Bamba & Rader, 2007; Braunstein, Cheng, Cohn, Aggarwal, Nass, et al., 2001; Rubins, Robins, Collins, Iranmanesh, Wilt, et al., 1995). In addition to their collective role in CHD, studies have demonstrated that each of the particles is an independent risk factor (Bainton, Miller, Bolton, Yarnell, Sweetnam, et al., 1992; Gardner, Fortmann, & Krauss, 1996; Pischon, Mohlig, Hoffmann, Spranger, & Weikert, 2007; Sarwar, Danesh, Eiriksdottir, Sigurdsson, Wareham, et al., 2007; Stampfer, Krauss, Ma, Blanche, Holl, et al., 1996). A recent meta-analysis of prospective population-based studies indicated that individuals with elevated triglycerides had a 72% greater chance of developing CHD than those with lower values (Sarwar et al., 2007). Several prospective studies have reported that low HDL cholesterol is independently associated with the development of CVD in initially healthy individuals (Despres, Lemieux, Dagenais, Cantin, & Lamarche, 2000; Goldbourt, Yaari, & Medalie, 1997; Gordon, Castelli, Hjortland, Kannel, & Dawber, 1977) as well as with the adverse prognoses of those with manifest disease (Foody, Ferdinand, Pearce, Lytle, Cosgrove, et al., 2000; Niessner, Hofmann, Kypta, Steinwender,

Kerschner, et al., 2007; Tervahauta, Pekkanen, & Nissinen, 1995; Wolfram, Brewer, Xue, Satler, Pichard, et al., 2006). For patients with established CHD, HDL cholesterol may be the most critical lipid marker regarding prognosis as current drug therapy tends to be most effective for improving LDL cholesterol and triglyceride levels (Tenenbaum, Fisman, Motro, & Adler, 2006). One-year follow-up results in MI patients treated with stent implantation indicated that individuals with lower HDL cholesterol concentrations had an increased incidence of major cardiac events and mortality, regardless of baseline LDL cholesterol levels and statin therapy (Wolfram et al., 2006). Other studies have suggested that HDL cholesterol may be one of the strongest predictors of CVD, particularly in individuals with the MetS (McNeill, Katz, Girman, Rosamond, Wagenknecht, et al., 2006).

While a genetic predisposition may contribute to certain types of dyslipidemia (Garg & Simha, 2007), MetS factors play a primary role in the development and progression of dyslipidemia. As previously discussed, central adiposity is associated with a dyslipidemic profile, in particular with increased plasma TRIG levels and low levels of HDL cholesterol (Despres, 2007). Individuals with IR also tend to demonstrate this profile with studies indicating strong relationships between IR and increased total and VLDL cholesterol, lower HDL cholesterol, and hypertriglyceridemia independent of insulin levels (Haffner, D'Agostino, Mykkanen, Tracy, Howard, et al., 1999; Laakso, Sarlund, & Mykkanen, 1990). A recent study of nondiabetic individuals reported that both IR and obesity were positively associated with TRIG and negatively related to HDL

cholesterol (Ferrannini, Balkau, Coppack, Dekker, Mari, et al., 2007). One explanation that has been proposed to account for these shared associations is that visceral obesity underlies both IR and dyslipidemia (Rader, 2007). Some studies, however, have found IR to be associated with dyslipidemia independent of obesity and level of aerobic fitness (Laws & Reaven, 1992). Additional support for a relationship between IR and dyslipidemia comes from prospective (Salonen, Lakka, Lakka, Valkonen, Everson, et al., 1998) and cross-sectional studies (Orchard, Becker, & Bates, 1983; Stout, 1990; Zavaroni, Dall'Aglio, Alpi, Bruschi, Bonora, et al., 1985) linking high plasma insulin levels to hypertriglyceridemia and low HDL cholesterol. Results from the prospective study indicated that in 975 middle-aged men without DM2, hyperinsulinemia was associated with a greater than 2-fold increase in the incidence of dyslipidemia at 4-year follow-up, independent of body weight (Salonen et al., 1998). Despite studies examining the association between IR and dyslipidemia in apparently healthy populations, however, no studies were located specifically investigating the relationship in a cohort with established CVD.

One of the major mechanisms thought to fuel dyslipidemia in the insulin-resistant state is the increased flow of FFAs from adipose tissue to the liver due to increased lypolysis (Rader, 2007). In the liver, FFAs promote increased TRIG synthesis which often leads to the increased production of very low density lipoprotein (VLDL) cholesterol. The accumulation of such lipid metabolites in the liver appears to promote hepatic IR which, in turn, increases production of apo-CIII, a protein that blocks the uptake of remnant lipoprotein particles (Rader,

2007). Generally, healthy insulin sensitivity inhibits the hepatic secretion of VLDL-triglycerides into circulation. IR, however, causes a loss of this inhibition and, as a result, leads to increased plasma concentrations of these atherogenic particles (Bamba & Rader, 2007). IR-driven hyperinsulinemia has been associated with the increased production of VLDL cholesterol which ultimately results in high serum TRIG levels and low serum HDL levels (Howard, 1999; Nesto, 2005; Olefsky, Farquhar, & Reaven, 1974; Olefsky, Reaven, & Farquhar, 1974; Tobey, Greenfield, Kraemer, & Reaven, 1981). Overall, elevated levels of circulating VLDL-triglycerides and decreased concentrations of large HDL particles in insulin-resistant states tend to result in deposition of cholesterol into the intimal layer of blood vessels (Bhattacharyya & Libby, 1997). Over time, endothelial dysfunction contributes to increasing concentrations of cholesterol in the intima which becomes trapped by the activity of macrophages, resulting initially in the development of atherogenic fatty streaks followed by mature atherosclerotic lesions (Bhattacharyya & Libby, 1997).

Other factors associated with the MetS, beyond obesity and IR, demonstrate strong associations with dyslipidemia (Olefsky et al., 1974; Timar, Sestier, & Levy, 2000). Prospective studies in healthy individuals have reported a relationship between dyslipidemia and HTN (Halperin, Sesso, Ma, Buring, Stampfer, et al., 2006; Sesso, Buring, Chown, Ridker, & Gaziano, 2005; Wildman, Sutton-Tyrrell, Newman, Bostom, Brockwell, et al., 2004). In a recent study of 3,110 men initially free of HTN, CVD, and cancer from the Physicians' Health Study followed over a mean of 14.1 years, men in the highest quintiles of

total cholesterol and non-HDL cholesterol had a 23% and 39% increased risks of developing HTN, respectively, compared with participants in the lowest quintile (Halperin et al., 2006). Furthermore, men in the highest quintile of HDL cholesterol had a 32% decreased risk of developing HTN compared with those in the lowest quintile. These associations were independent of obesity and DM2. Few studies were found for patients with established heart disease. One cross-sectional study found that high TRG levels were associated with uncontrolled DBP in women with HTN (Bog-Hansen, Lindblad, Gullberg, Melander, & Rastam, 2003).

Inflammatory markers have also been associated with dyslipidemia. Studies have reported that cytokines induce tissue and plasma events that lead to changes in lipoproteins (Chait, Han, Oram, & Heinecke, 2005; Khovidhunkit, Memon, Feingold, & Grunfeld, 2000). For example, apolipoprotein A-I, the major apolipoprotein of HDL, has been reported to decrease during inflammation (Chait et al., 2005). Animal studies have found that an induced acute phase response (e.g., elevated levels of CRP and serum amyloid A) resulted in increased VLDL secretion and reduced plasma HDL (Cabana, Siegel, & Sabesin, 1989; Tietge, Maugeais, Lund-Katz, Grass, deBeer, et al., 2002). Studies within humans have found that inflammatory cytokines lead to increases in TRIG and decreases in HDL cholesterol (Chait et al., 2005). A recent large study of community-dwelling older adults found that elevated IL-6 levels were associated with low HDL independent of smoking, BMI, WC, HTN, DM2, physical activity, alcohol intake, oral hypoglycemics, CRP, IL-18, and TNF-alpha levels (Zuliani, Volpato, Ble,

Bandinelli, Corsi, et al., 2007). Another study reported that CRP was correlated with high TRIG and low HDL cholesterol levels in non-diabetic individuals (Yudkin, Stehouwer, Emeis, & Coppack, 1999). Recent reviews, however, have pointed out that associations between lipids and circulating inflammatory markers in epidemiological studies tend to be weak (Lowe, 2005; Ridker, 2003). Despite findings in healthy individuals and epidemiological studies, no studies were identified reporting an association between lipids and inflammatory markers in patients with manifest CHD.

Reductions in cholesterol levels have been found to lead to a number of improvements in the cardiovascular health profile of individuals with varying degrees of IR, including those with DM2 (Schwartz, 2006). The initial approach to this end generally involves lifestyle changes, specifically increased physical activity and improved diet to achieve weight loss and smoking cessation (Solano & Goldberg, 2006). Statin therapy, recommended for most individuals with DM2 and CVD, is the first-line pharmacological treatment for dyslipidemia (Grundy, Benjamin, Burke, Chait, Eckel, et al., 1999). In addition to improving the values associated with each lipid (Bakker-Arkema, Davidson, Goldstein, Davignon, Isaacsohn, et al., 1996; Crouse, Frohlich, Ose, Mercuri, & Tobert, 1999; Mabuchi, Haba, Tatami, Miyamoto, Sakai, et al., 1981), statins have been found to have a wide range of effects including the enhancement of endothelial NO synthesis (Kaesemeyer, Caldwell, Huang, & Caldwell, 1999), antiproliferative effects on smooth muscle cells (Negre-Aminou, van Vliet, van Erck, van Thiel, van Leeuwen, et al., 1997), and reductions of platelet aggregation (Mayer, Eller,

Brauer, Solleder, Schafer, et al., 1992), PAI-1 (Isaacsohn, Setaro, Nicholas, Davey, Diotalevi, et al., 1994), and CRP (Mishra & Basson, 2007; Ridker, 2003; Ridker, Rifai, Pfeffer, Sacks, & Braunwald, 1999). Statin use has also been found to result in decreased risk of coronary events (Packard, 1998). A study investigating diabetic and glucose intolerant MI patients reported that statin therapy was effective at reducing a number of such events including CHD death and recurrent MI (Goldberg, Mellies, Sacks, Moye, Howard, et al., 1998). Depending on the efficacy of statin therapy, the particular patient profile, and/or the goals of treatment, other medications that have been found effective at regulating dyslipidemia include ezetimibe, nicotinic acid, resins, and fibrates. Recent studies have found that fenofibrate, in addition to being a successful therapy for improving plasma lipid profiles, significantly decreased markers of low-grade inflammation associated with dyslipidemia and HTN (Coban, Ozdogan, Yazicioglu, & Sari, 2005; Wu, Ou, Chou, Hsiao, Lin, et al., 2007).

Dyslipidemia is a risk factor for atherosclerosis. High density lipoprotein cholesterol is a particularly important indicator following myocardial infarction as prospective studies have reported that individuals with low concentrations have an increased incidence of major cardiac events and mortality, regardless of statin therapy and other cholesterol levels. Dyslipidemia's association with insulin resistance, obesity, inflammation, and hypertension make it a major contributor to vascular dysfunction.

1.2.4 Hypertension.

Hypertension (HTN) is a medical condition in which arterial blood pressure is chronically elevated. It is typically characterized by a systolic pressure consistently higher than 140 mmHg or a diastolic pressure consistently above 90 mmHg (Smith & Kampine, 1990). (In the NCEP ATP-III definition, HTN is defined

as systolic pressures ≥ 130 mmHg and diastolic pressures ≥ 85). Persistent HTN is a risk factor for a number of cardiovascular outcomes including stroke, MI, heart failure and arterial aneurysm in addition to being a leading cause of chronic renal failure (Hall, 1999). In the US, HTN is thought to afflict approximately 72 million people age 20 and older (American Heart Association's 2007 Heart Disease and Stroke Statistical Update). It has been estimated that from 1994 to 2004, the mortality rate associated with HTN increased 15.5 percent causing the death of over 54,000 individuals in the US in 2004 (American Heart Association's 2007 Heart Disease and Stroke Statistical Update). HTN can be classified as either essential (primary) or secondary. Essential HTN indicates that no specific medical cause can be identified to explain the elevated blood pressure, whereas secondary HTN indicates that the high blood pressure is a result of another known condition (e.g., kidney disease). At present, 90-95% of all HTN cases are identified as essential HTN (American Heart Association's 2007 Heart Disease and Stroke Statistical Update).

Strong associations between HTN and CVD have been identified in numerous prospective studies over the past 40 years. In initially healthy populations, HTN has been implicated in the development of atherosclerosis (Conen, Ridker, Buring, & Glynn, 2007; Fan, 2006; Irace, Cortese, Fiaschi, Carallo, Sesti, et al., 2005) and outcomes such as stroke, MI, and increased mortality (Antikainen, Jousilahti, & Tuomilehto, 1998; Domanski, Mitchell, Pfeffer, Neaton, Norman, et al., 2002; Miura, Dyer, Greenland, Daviglus, Hill, et al., 2001; O'Donnell, Ridker, Glynn, Berger, Ajani, et al., 1997; Strandberg, Salomaa,

Vanhanen, Pitkala, & Miettinen, 2002; van den Hoogen, Feskens, Nagelkerke, Menotti, Nissinen, et al., 2000; van Trijp, Grobbee, Peeters, van Der Schouw, & Bots, 2005; Vasan, Larson, Leip, Evans, O'Donnell, et al., 2001; Weitzman & Goldbourt, 2006). Regarding its contribution to the development of atherosclerosis, HTN has been found to increase the risk two to three times (Bedi, Varshney, & Babbar, 2000). Further, it has been suggested that HTN exacerbates the atherosclerotic process and contributes to the destabilization of atherosclerotic plaque in those with evident disease (Escobar, 2002).

Outcome studies among individuals with manifest CHD are fewer in number (Flack, Neaton, Grimm, Shih, Cutler, et al., 1995; Wong, Cupples, Ostfeld, Levy, & Kannel, 1989). In a large cohort of men aged 35 to 57 years with prior MI from the Multiple Risk Factor Intervention Trial, the association of SBP and DBP with CHD and all-cause mortality varied over a 16-year follow-up period. During early follow-up, relationships were evident in older men (age 45 to 57 years) only. After 2 years, the relationship became positive and graded. By 15 years, cumulative CHD mortality percentages for men with screening SBP < 120, 120 to 139, 140 to 159, and ≥160 mmHg were 19.7%, 21.3%, 27.5%, and 32.0%, respectively. DBP mortality relationships, while still positive and graded, were slightly less robust. When SBP and DBP were jointly considered, both CHD and all-cause mortality rates were approximately 40% higher for participants with SBP ≥ 140 mmHg versus < 140 mmHg regardless of DBP level after 2 years (Flack, Neaton, Grimm, Shih, Cutler, et al., 1995). A meta-analysis summarizing some of the findings in the area concluded that the mortality rate in

patients with CHD is 2.3 times greater when HTN is present (Stamler, Stamler, & Neaton, 1993).

To date, a number of hypotheses have been suggested as to the causes and mechanisms underlying elevations in blood pressure. Factors that have been implicated in the development of HTN include aging, genetics, obesity, lack of exercise, high dietary intake of sodium and alcohol, and psychosocial stress (Bjorntorp, Holm, Rosmond, & Folkow, 2000; Marteau, Zaiou, Siest, & Visvikis-Siest, 2005; Mathew, Patel, Reams, Freeman, Spear, et al., 2007; O'Rourke & Hashimoto, 2007; Penner, Campbell, Chockalingam, Zarnke, & Van Vliet, 2007). Overactivity of the sympathetic nervous system (SNS), identified in conjunction with many of these factors, is thought to be the primary mediator of the increased pressure (Grassi, 2006; Julius & Nesbitt, 1996). Ultimately, SNS overactivity, triggered by factors such as baroreceptor impairment and IR, is thought to underlie HTN's role in the development and/or progression of MetS and CVD (Aso, Wakabayashi, Nakano, Yamamoto, Takebayashi, et al., 2006; Grassi, 2006; Mancia, Bousquet, Elghozi, Esler, Grassi, et al., 2007). Under normal circumstances, it is the function of the SNS is to manage energy expenditure and prepare the body for physical activity by inducing increases in heart rate, vasoconstriction, and cardiac contractility via the release of adrenergic catecholamines. Chronic engagement of the system, however, exerts a number of adverse effects on the cardiovascular system including the genesis of arterial remodeling, endothelial dysfunction, left ventricular hypertrophy, and vascular hypertrophy (Grassi, 2006). Studies have found that left ventricular hypertrophy

has been positively associated with plasma norepinephrine levels in normotensive men, as well as those with borderline HTN and mild to moderate HTN (Corea, Bentivoglio, Verdecchia, & Motolese, 1984; Ferrara, Mancini, de Simone, Pisanti, Capone, et al., 1989). Further, left ventricular hypertrophy increases myocardial oxygen demand and promotes a decrease of coronary reserve, both of which contribute to myocardial ischemia (Escobar, 2002). Thus, structural and functional changes induced by SNS overactivity can promote increased vascular resistance and HTN in peripheral arteries and arterioles, particularly in the presence of decreased vessel elasticity.

Although its relationship with other MetS factors has been found to be the least robust in factor analysis studies (Shen et al., 2006; 2003), HTN is thought to be a vital component of the MetS. A primary reason for its importance in the MetS may likely be its association with IR. A number of studies have reported associations between HTN and IR (Bonora, Bonadonna, Del Prato, Gulli, Solini, et al., 1993; Diabetes Prevention Program Research Group, 2002; Ferrannini, Buzzigoli, Bonadonna, Giorico, Oleggini, et al., 1987; Ferrannini, Natali, Capaldo, Lehtovirta, Jacob, et al., 1997; Garcia-Puig, Ruilope, Luque, Fernandez, Ortega, et al., 2006; Pollare, Lithell, & Berne, 1990; Rubies-Prat, Ordonez-Llanos, Martin, Blanco-Vaca, Molina, et al., 2001; Saad, Rewers, Selby, Howard, Jinagouda, et al., 2004). One recent study in patients with essential HTN found that abnormal glucose metabolism was present in over two-thirds of the sample. The prevalence of isolated IR, IFG, IGT, undiagnosed DM2, and known DM2 was 9.3%, 11.2%, 22.5%, 11.5%, and 13.9% of the patients respectively (Garcia-Puig

et al., 2006). Studies that have measured IR directly (i.e., via the euglycemic insulin clamp) in nondiabetic populations with untreated essential HTN have found insulin sensitivity to be negatively associated with blood pressure (Ferrannini et al., 1987; Pollare et al., 1990). A study from the European Group for the Study of Insulin Resistance reported a positive association between fasting insulin levels and DBP indicating that blood pressure elevations may also be related to hyperinsulinemia (Ferrannini et al., 1997). In a large multicenter study of participants with IGT, SBP was significantly, albeit weakly, associated with fasting insulin and HOMA-IR among participants not on antihypertensive medications after adjusting for age, sex, and BMI (Diabetes Prevention Program Research Group, 2002). Associations between HTN and IR have led some investigators to conceive of HTN as an insulin resistant state (Bonora et al., 1993; Ferrannini et al., 1987; Garcia-Puig et al., 2006). Despite studies that have reported a positive relationship, however, a direct association between IR / hyperinsulinemia and blood pressure has remained controversial. One study, while finding that glucose levels were significantly higher in nondiabetic untreated hypertensive men compared to healthy controls, found no difference in insulin levels between the groups (Brands, Hall, & Keen, 1998; Rubies-Prat et al., 2001).

Although prospective data is scarce, some evidence suggests that IR precedes the onset of established HTN (Landsberg, 1996; Osei, 1999). Support for this contention comes from studies in both healthy individuals and in the offspring of hypertensives (Allemann & Weidmann, 1995; Landsberg, 1996). Support also comes from studies reporting a reduction in blood pressure via

interventions that improve insulin sensitivity in both animal (Majithiya & Balaraman, 2006) and human populations (DeFronzo & Ferrannini, 1991; Ogihara, Rakugi, Ikegami, Mikami, & Masuo, 1995). Mechanisms that have been suggested linking IR / hyperinsulinemia with blood pressure elevations include SNS overactivity, renal sodium retention, and impairment of endothelial function caused by decreased nitric oxide production and elevated arterial stiffness (Esler, Rumantir, Wiesner, Kaye, Hastings, et al., 2001; Landsberg, 1996; Osei, 1999; Sarafidis & Bakris, 2007). Evidence supporting these factors as mediators in the pathway from IR to HTN includes: 1) the positive association between blood pressure and joint elevations in norepinephrine and post-prandial insulin levels (Ward, Sparrow, Landsberg, Young, Vokonas, et al., 1996), 2) studies demonstrating that insulin decreases urinary sodium excretion by increasing distal sodium reabsorption (Kageyama, Yamamoto, Isogai, & Fujita, 1994), and 3) the finding that hyperglycemia, hyperinsulinemia, and hypertriglyceridemia promote increased arterial stiffness (Osei, 1999). Others have argued, however, that sympathetic activity is primary and results in both HTN and IR (Julius & Majahalme, 2000).

While a link between IR and HTN seems apparent, considerable evidence has suggested that obesity is the primary cause of arterial HTN (Francischetti & Genelhu, 2007; Gelber, Gaziano, Manson, Buring, & Sesso, 2007). Obesity has been proposed to lead to HTN through a number of potential mechanisms. One hypothesis suggests that obesity (via overeating) promotes an increase in SNS activity (O'Dea, Esler, Leonard, Stockigt, & Nestel, 1982), mediated by insulin, in

an attempt to stabilize body weight by stimulating thermogenesis (Landsberg, 2001). One of the consequences of SNS activation (a global increase of norepinephrine) in this context is thought to be an elevation in blood pressure. While obese individuals may be resistant to the effects of insulin on glucose uptake, it has been suggested that they may still be sensitive to the stimulating effects of insulin on the SNS (Landsberg, 2001). There is also increasing evidence that activation of the SNS in obesity may be stimulated by factors beyond insulin. Leptin, a protein expressed in and secreted by adipocytes, is strongly associated with increased SNS activity, sodium retention, and HTN (Bravo, Morse, Borne, Aguilar, & Reisin, 2006; Mathew, Patel, Reams, Freeman, Spear, et al., 2007). Angiotensinogen, another protein expressed in and secreted by adipose tissue, invokes the activation of the renin-angiotensin-aldosterone system which has also been causally implicated in HTN (Giacchetti, Faloia, Sardu, Camilloni, Mariniello, et al., 2000). Finally, high circulating levels of FFAs, increased vascular production of endothelin-1, and decreased concentrations of adiponectin have been reported as potential mechanisms for obesity-related HTN (Francischetti & Genelhu, 2007).

Other MetS factors have also been found to be related to HTN. As previously discussed, dyslipidemic profiles have been both cross-sectionally associated with or implicated in the development of HTN (e.g., Halperin et al., 2006). As will be discussed in greater depth in the following section, inflammatory processes also play a role in HTN. A number of studies have found that inflammatory markers such as CRP are implicated in blood pressure

elevations (Bautista, Lopez-Jaramillo, Vera, Casas, Otero, et al., 2001; Festa et al., 2000; Imatoh, Miyazaki, & Une, 2007; Sung, Suh, Kim, Kang, Kim, et al., 2003). Finally, several studies have reported a relationship between HTN and fibrinolytic factors (Armas-Hernandez, Hernandez-Hernandez, Armas-Padilla, Sosa-Canache, Cammarata, et al., 2007; Auwerx, Bouillon, Collen, & Geboers, 1988; Eliasson, Jansson, Nilsson, Asplund, 1997; Landin, Tengborn, & Smith, 1990; Svendsen et al., 1996; Wall, Jern, Bergbrant, & Jern, 1995). A recent study found that plasminogen, tissue-type plasminogen activator, and PAI-1 concentrations were significantly elevated in middle-aged patients with essential HTN compared to normotensive individuals suggesting a state of hyper-coagulability. It was proposed that this tendency might partly explain the greater occurrence of thrombotic complications in individuals with HTN.

Hypertension and sympathetic nervous system activity are important factors associated with the metabolic syndrome via their connection with insulin resistance, obesity, dyslipidemia, inflammation, coagulation factors, and cardiac structural and functional changes. While a direct relationship between insulin resistance and hypertension remains unclear, obesity is more clearly implicated in the development of hypertension through a direct path as well as an indirect path involving insulin resistance and sympathetic nervous system activity.

1.3 Ancillary Metabolic Syndrome Factors

The preceding sections introduced information pertinent to the primary components of the MetS (IR, obesity, dyslipidemia, and HTN) including their contribution to CVD, their interrelationships, and their associations with other factors associated with the MetS. The next sections will examine ancillary MetS factors such as inflammation and impaired fibrinolytic activity that occur concurrently with the primary factors and are thought to significantly contribute to

CVD pathogenesis and outcomes. A review of their associations with CVD and other MetS factors, including a discussion of possible explanatory mechanisms, will also be provided in the subsequent sections.

1.3.1 Inflammation.

Abundant evidence has accumulated over the past fifteen years linking inflammatory processes with atherosclerosis (Auer, Berent, Lassnig, & Eber, 2002; Dandona & Aljada, 2002; Hansson, 2005; Lee, Allison, Song, & Barrett-Connor, 2007; Makita, Nakamura, & Hiramori, 2005; Ross, 1999). According to a leading theorist, atherosclerotic lesions represent a series of highly specific responses of the innate immune system to vascular injury (Ross, 1999). Such injury typically begins with damage to the endothelium leading to plaque formation caused by the action of monocytes and macrophages on lipid particles trapped within the arterial wall. Inflammation is the end result of this process as the injury prompts the production of a number of inflammatory markers including pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) as well as acute-phase proteins such as C-reactive protein (CRP; Lowe, 2005). In addition to plaque formation, however, inflammation plays a role in IR, vasoconstriction, plaque rupture and thrombosis, decreased heart rate variability, and impaired coronary blood flow, all of which increase susceptibility to cardiovascular events including MI (Barutcu, Sezgin, Sezgin, Gullu, Esen, et. al., 2007; Duncan & Schmidt, 2001; Koenig & Rosenson, 2002; Li, Qin, Li, Zeng, Gao, et al., 2007; Libby, Ridker, & Maseri, 2002; Madsen, Christensen, Toft, & Schmidt, 2007). Indeed, the unique physiological effects of inflammation in

diverse areas such as metabolism and endothelial functioning have led some investigators to speculate as to whether it might be the “common soil” of CHD and DM2 (Duncan & Schmidt, 2001).

CRP, an acute-phase protein produced by the liver during acute inflammation, has been the most widely examined of the inflammatory markers (Rifai & Ridker, 2002). Studies within initially healthy populations have found CRP to be a strong independent predictor of cardiovascular events including stroke, MI, and peripheral vascular disease (Danesh, Wheeler, Hirschfield, Eda, Eiriksdottir, et al., 2004; Danesh, Whincup, Walker, Lennon, Thomson, et al., 2000; Pai, Pischon, Ma, Manson, Hankinson, et al., 2004; Park, Detrano, Xiang, Fu, Ibrahim, et al., 2002; Pischon, Mohlig, Hoffmann, Spranger, Weikert, et al., 2007; Ridker, Stampfer, & Rifai, 2001; Ridker, Buring, Shih, Matias, & Hennekens, 1998). Among healthy women, high levels of CRP were found to predict earlier occurrence of MI and a greater likelihood fatal infarction (Bansal & Ridker, 2007). In populations with manifest disease, CRP levels are also strongly related to cardiovascular events (Cao, Arnold, Manolio, Polak, Psaty, et al., 2007; Retterstol, Eikvar, Bohn, Bakken, Erikssen, & Berg, 2002; Ridker, Rifai, Pfeffer, Sacks, Moye, et al., 1998; Speidl, Graf, Hornykewycz, Nikfardjam, Niessner, et al., 2002; Zairis, Adamopoulou, Manousakis, Lyras, Bibis, et al., 2006; Zebrack, Anderson, Maycock, Horne, Bair, et al., 2002). In post-MI patients followed for over 10 years, the relative risk for cardiac mortality doubled with increasing CRP levels after adjusting for serum cholesterol level, fibrinogen, smoking, and HTN. Patients in the lowest quartile had a 6-times greater risk of

cardic mortality compared to patients in the highest quartile. In another study, patients with stable CAD developed prior to age 50 who had CRP concentrations in the highest tertile had a 3.8-fold risk for death, MI, or need for coronary revascularization compared with the patients in the first tertile at follow-up (mean of 54 months). Additionally, CRP levels in the third tertile independently predicted risk after adjustment for cardiovascular risk factors including lipids (Speidl et al., 2002).

Mechanisticly, it remains unclear whether CRP plays a direct role in atherogenesis or simply acts as a surrogate marker for other inflammatory mediators (Rifai & Ridker, 2002). In vitro studies, however, have found that in humans, CRP activates the complement system (Biro, Rovo, Papp, Cervenak, Varga, et al., 2007), increases monocyte production of tissue factor (Cermak, Key, Bach, 1993), and induces adhesion molecule expression in endothelial cells (Pasceri, Willerson, & Yeh, 2000). Further, recent studies have reported that CRP mediates the uptake of LDL by macrophages, suggesting a direct atherogenenic connection (Fu & Borensztajn, 2000; Zwaka, Hombach, & Torzewski, 2001).

IL-6 is a pro-inflammatory cytokine considered to be one of the most important mediators of the acute phase response (Lowe, 2005; Van Snick, 1990). It is secreted by numerous cells of the body including both immune (e.g., T cells, macrophages) and non-immune cells (e.g., arterial smooth muscle cells) and typically in a protective response to injury (Papanicolaou, Wilder, Manolagas, & Chrousos, 1998). Although IL-6 is implicated in a wide range of discrete

physiological processes, it is thought to play a critical role in the genesis of CVD via its strong influence on metabolic, endothelial, and fibrinolytic dysfunction (Yudkin, Kumari, Humphries, & Mohamed-Ali, 2000). In the area of lipid metabolism, for example, IL-6 has been found to decrease lipoprotein lipase activity and stimulate lipolysis (Yudkin et al., 2000). In the areas of endothelial and fibrinolytic function, IL-6 has been found to increase the production of adhesion molecules, fibrinogen, and platelets, all of which are associated with a procoagulant state (Yudkin et al., 2000). Finally, it should be noted that IL-6 plays a primary role in the hepatic synthesis of CRP (Bataille & Klein, 1992; Heinrich, Castell, & Andus, 1990) and, as a result, is generally highly correlated with the acute-phase protein (Ridker, Rifai, Stampfer, & Hennekens, 2000).

As with CRP, studies linking IL-6 with CVD development and outcomes are numerous (Lee et al., 2007; Luc, Bard, Juhan-Vague, Ferrieres, Evans, et al., 2003; Ridker et al., 2000; Tzoulaki, Murray, Lee, Rumley, Lowe, et al., 2007; Tzoulaki, Murray, Lee, Rumley, Lowe, et al., 2005). Within a large sample of apparently healthy men, those in the highest quartile of IL-6 had greater than twice the risk of MI 6 years later than those in the lowest quartile. Further, each quartile increase in IL-6 conferred a 38% increase in risk despite adjustment for other cardiovascular risk factors including CRP (Ridker et al., 2000). Compared to studies in healthy populations, far fewer exist that investigate the role of IL-6 in patients with evident cardiac disease (Fisman, Benderly, Esper, Behar, Boyko, et al., 2006; Pradhan, Manson, Rossouw, Siscovick, Mouton, et al., 2002). One study of individuals with angina or previous MI followed for a mean of 6.3 years

indicated that elevated IL-6 levels were strongly associated with future reinfarction and/or mortality (Fisman et al., 2006).

Perhaps not surprisingly, both CRP and IL-6 demonstrate associations with specific factors of the MetS (Bautista, Vera, Arenas, & Gamarra, 2005; Chen, Wildman, Hamm, Muntner, Reynolds, et al., 2004; Davey Smith, Lawlor, Harbord, Timpson, Rumley, et al., 2005; Deepa, Velmurugan, Arvind, Sivaram, Sientay, et al., 2006; Dyck et al., 2006; Festa et al., 2000; Forouhi, Sattar, & McKeigue, 2001; Gonzalez, Guerrero, Soto, Diaz, Martinez-Olmos, et al., 2006; Hak, Stehouwer, Bots, Ploderman, Schalkwijk, et al., 1999; Muller, Martin, Koenig, Hanifi-Moghaddam, Rathmann, et al., 2002; Ndumele, Pradhan, & Ridker, 2006; Pannacciulli, Cantatore, Minenna, Bellacicco, Giorgino, et al., 2001; Ridker, 2001; Shoelson et al., 2007; Yudkin, Stehouwer, Emeis, & Coppack, 1999; Yudkin et al., 2000). With respect to IR, several studies have reported a strong association with inflammatory markers (Chen et al., 2004; Gonzalez et al., 2006; Muller et al., 2002). Prospective studies reporting a connection between CRP and DM2 development, however, provide clearer evidence that inflammation contributes to IR (Hu, Meigs, Li, Rifai, & Manson, 2004; Laaksonen, Niskanen, Nyyssonen, Punnonen, Tuomainen, et al., 2004; Pradhan et al., 2001). As previously discussed, recent investigations linking inflammatory markers to IR have found the strongest relationships to be driven by the presence of obesity, particularly central obesity (Dandona & Aljada, 2002; Dandona et al., 2005; Festa et al., 2000; Pannacciulli et al., 2001; Yudkin et al., 1999). Although several studies have confirmed that inflammatory markers are

elevated predominantly in obese, insulin resistant individuals and decrease with weight loss (Esposito, Ciotola, Giugliano, 2006; Haffner, Temprosa, Crandall, Fowler, Goldberg, et al., 2005; McLaughlin, Abbasi, Lamendola, Liang, Reaven, et al., 2002), a few studies have reported the relation between CRP or IL-6 and IR to be independent of measures of central and global obesity (Deepa et al., 2006; Festa et al., 2000; McLaughlin et al, 2002; Chen et al., 2004). Studies have also found inflammation to be independently associated with obesity after adjusting for several cardiovascular risk factors including IR (Aronson, Bartha, Zinder, Kerner, Markiewicz, et al., 2004; Pannacciulli et al., 2001). Consistent findings of this sort have prompted investigators to declare central obesity to be the major factor associated with elevated inflammation (CRP) in individuals with MetS (Aronson et al., 2004; Florez, Castillo-Florez, Mendez, Casanova-Romero, et al., 2006; Forouhi et al., 2001; Santos, Lopes, Guimaraes, & Barros, 2005) and DM2 (Kahn, Zinman, Haffner, O'Neill, Kravitz, et al., 2006).

As mentioned earlier, inflammation has also been found to be associated with both dyslipidemia and HTN. Regarding the link between inflammatory markers and HTN, experimental data from cross-sectional studies indicate that CRP levels, in particular, are independently related to elevations in blood pressure (Bautista et al., 2001; Festa et al., 2000; Imatoh et al., 2007; Sung et al., 2003). One study investigating the association of inflammatory markers with elevated blood pressure in healthy individuals, participants in the top two quartiles of IL-6 were more than twice as likely to be hypertensive (systolic BP >or=140 and/or diastolic BP >or=90 mmHg) than those in the first quartile after

adjustment for age, sex, BMI, family history of high blood pressure, and other inflammatory markers (Bautista, Vera, Arenas, & Gamarra, 2005). The CRP-HTN association, however, was not statistically significant. With respect to patients with CVD, few studies were located reporting associations between inflammatory markers and blood pressure. One recent study of hypertensive patients, however, reported that CRP levels were significantly higher in hypertensive than normotensive participants such that those in the highest tertile had a two-fold higher risk than those in the lowest tertile (Imatoh, Miyazaki, & Une, 2007). No studies were found in other CVD cohorts including post-MI patients.

Hypotheses have been suggested as to potential mechanisms underlying the relationship between inflammation and HTN. One current hypothesis is based on studies demonstrating that both CRP and IL-6 are associated with endothelial dysfunction, vascular resistance, and/or arterial stiffness (Kim, Kang, Kim, Seo, Park, et al., 2007; Kullo, Seward, Bailey, Bielak, Grossardt, et al., 2005; Nakhai-Pour, Grobbee, Bots, Muller, & van der Schouw, 2007; Naya, Tsukamoto, Morita, Katoh, Furumoto, et al., 2007), known risk factors for HTN. A recent study found that CRP was independently related to increase of aortic artery stiffness over and above traditional risk factors and atherosclerosis (Nakhai-Pour et al., 2007). Additionally, CRP was found to be associated with arterial stiffness of other arteries in treated hypertensive patients, independent of cardiovascular risk factors (Kim et al., 2007).

Few studies have indicated an association between inflammation and atherothrombotic variables. In one recent study, however, participants who received infusions of recombinant human CRP demonstrated an activation of coagulation processes in addition to increased systemic inflammation (Bisoendial, Kastelein, Levels, Zwaginga, van den Bogaard, et al., 2005). Other studies have reported that patients with atrial fibrillation, a disorder associated with a prothrombotic or hypercoagulable state, demonstrated concomitant elevations in inflammatory markers (CRP and IL-6), tissue factor, and blood viscosity, findings not seen in comparison to healthy controls (Conway, Buggins, Hughes, & Lip, 2004). Finally, study results have indicated that tumor necrosis factor alpha is a key component in the obesity-linked elevation of PAI-1 (Samad, Uysal, Wiesbrock, Pandey, Hotamisligil, et al., 1999). Based on the associations reported between various inflammatory markers and formal and informal MetS factors, investigators have suggested that chronic subclinical inflammation is a significant feature of the MetS (Festa et al., 2000; Frolich, Imhof, Berg, Hutchinson, Pepys, et al., 2000; Hak et al., 2001; Pannacciulli et al., 2001). In fact, it has been proposed that CVD, MetS, and DM2 are all diseases of the innate immune system as each has in common the inflammatory response and endothelial dysfunction (Pickup & Crook, 1998).

Although not a formal factor in metabolic syndrome criteria, the association of inflammation with other metabolic syndrome components and its relationship to CVD development and outcomes suggests a strong rationale for its consideration. Inflammation plays a role in several CVD processes including plaque formation, insulin resistance, vasoconstriction, plaque rupture and thrombosis, and impaired coronary blood flow, all of which increase susceptibility to events such as myocardial infarction.

1.3.2 Impairment of fibrinolysis.

The fibrinolytic system plays a key role in intravascular homeostasis and influences vessel wall remodeling (Alessi & Juhan-Vague, 2006; Nicholl, Roztocil, & Davies, 2006). Its primary function is as an endogenous defense mechanism for the prevention of thrombosis resulting from cardiovascular injury such as atherosclerosis and MI (Vaughan, 2005). Through the process of fibrinolysis, potentially harmful fibrin clots, the products of coagulation, are sufficiently broken down to be passed out of systemic circulation. Normal fibrinolysis requires that inactive plasminogen be converted to plasmin, fibrin's primary degradation enzyme, by tissue plasminogen activator (t-PA) and urokinase. High circulating levels of plasminogen activator inhibitor type 1 (PAI-1), however, impair the process by inhibiting t-PA, ultimately resulting in excessive intravascular fibrin levels (Cesarman-Maus & Hajjar, 2005). While impaired fibrinolytic activity has consistently been found to be associated with an increased risk for MI (Vaughan, 2005), more recent research has begun to focus on its involvement in the initiation and progression of atherosclerosis (Jovin & Muller-Berghaus, 2004; Raghunath, Tomaszewski, Brady, Caron, Okada, et al., 1995).

Extensive experimental and epidemiological evidence has accumulated linking PAI-1 to ischemic CVD (Kohler & Grant, 2000; Vaughan, 2005). Increased levels of PAI-1 and decreased plasma fibrinolytic activity have been reported in survivors of MI (Estelles, Tormo, Aznar, Espana, & Tormo, 1985) and in patients with coronary artery stenosis (Aznar, Estelles, Tormo, Sapena,

Tormo, et al., 1988; Francis, Kawanishi, Baruch, Mahrer, Rahimtoola, et al., 1988; Olofsson, Dahlen, & Nilsson, 1989). PAI-1 levels have also been implicated in MI recurrence (Hamsten, deFaire, Walldius, Dahlen, Szamosi, et al., 1987; Wiman, Andersson, Hallqvist, Reuterwall, Ahlbom, et al., 2000). Further, and perhaps more importantly, elevated plasma levels of PAI-1 were found to be associated with the subsequent development of a first MI in a population of middle-aged men and women independent of traditional risk factors (Thogersen, Jansson, Boman, Nilsson, Weinehall, et al., 1998). Outside of its role in thrombosis, however, a number of investigators have reported increased concentrations of PAI-1 in atherosclerotic plaques (Lupu, Bergonzelli, Heim, Cousin, Genton, 1993; Raghunath, Tomaszewski, Brady, Caron, Okada, et al., 1995; Schneiderman, Sawdey, Keeton, Bordin, et al., 1992). Studies of atherosclerotic coronary arteries indicate that PAI-1 is consistently elevated in relation to lesion severity and that the concomitant elevation of PAI-1 and its messenger ribonucleic acid suggests that the PAI-1 increase is regulated by local synthesis (Padro, Steins, Li, Mesters, Hammel, et al., 1997; Steins, Padro, Li, Mesters, Ostermann, et al., 1999). Not all studies, however, found a relationship between PAI-1 and lesion severity (Oseroff, Krishnamurti, Hassett, Tang, & Alving, 1989).

Research conducted over the past 20 years has established that PAI-1 is linked to the MetS (Alessi & Juhan-Vague, 2006). MetS factors have been found to explain a major portion of plasma PAI-1 level variability. A prospective study investigating more than 10,000 middle-aged men found that MetS factors

(including BMI, WHR, TRIG and HDL levels, physical activity and DM2) explained 23% of the variance in PAI-1 (Scarabin, Aillaud, Amouyel, Evans, Luc, et al., 1998). Another study reported even greater variance explained, with the relationship being stronger in men than in women (45% versus 26%; Henry, Tregouet, Alessi, Aillaud, Visvikis, et al., 1998). Regarding its association with specific MetS factors, a large body of research exists. Positive correlations have been reported between PAI-1 and fasting plasma insulin in nondiabetics with a range of body weights (Meigs, Mittleman, Nathan, Tofler, Singer, et al., 2000; Vague, Juhan-Vague, Aillaud, Badier, Viard, et al., 1986), in non-diabetic obese women (Juhan-Vague, Vague, Alessi, Badier, Valadier, et al., 1987; Vague, Juhan-Vague, Chabert, Alessi, & Atlan, 1989), in individuals with glucose intolerance (Meigs et al., 2000), in patients with DM2 (Juhan-Vague, Roul, Alessi, Ardissone, Heim, & Vague, 1989), and in patients with angina pectoris (Juhan-Vague, Alessi, Joly, Thirion, Vague, et al., 1989; Juhan-Vague, Thompson, & Jespersen, 1993). Past research has also linked PAI-1 to abdominal obesity (Kozek, Katra, Malecki, & Sieradzki, 2004; Landin, Stigendal, Eriksson, Krotkiewski, Risberg, Tengborn, & Smith, 1990; Svendsen, Hassager, Christiansen, Nielsen, & Winther, 1996), HTN (Armas-Hernandez et al., 2007; Auwerx et al., 1988; Eliasson et al., 1997; Landin et al., 1990; Svendsen et al., 1996; Wall et al., 1995), hypertriglyceridemia (Gray, Panahloo, Mohamed-Ali, Patterson, & Yudkin, 1997; Hamsten, Wiman, de Faire, & Blomback, 1985; Ihnken, Speiser, Ruf, Thiel, Schlepper, et al., 1993; Juhan-Vague et al., 1987), fasting blood glucose (Heldgaard, Sidelmann, Hindsberger, Olivarius Nde,

Henriksen, et al., 2006; Svendsen et al., 1996), and the development of DM2 (Eliasson, Jansson, Lindahl, & Stegmayr, 2003; Festa, D'Agostino Jr., Tracy, & Haffner, 2002; Reaven, 1988). The close connection between PAI-1 and MetS factors is further supported by the finding that plasma concentrations of PAI-1 become increasingly higher as a function of MetS severity (Juhan-Vague, Alessi, Mavri & Morange, 2003). Due to this close association, some investigators have proposed that PAI-1 should be considered an official component of the MetS (Juhan-Vague, Alessi, & Vague, 1991; Mertens, Verrijken, Michiels, Van der Planken, Ruige, et al., 2006).

While elevations in PAI-1 are associated with all of the factors comprising the MetS, its connection with IR and obesity may explain a large portion of its relationship with the other factors. In a study of obese patients with and without DM2, PAI-1 correlated positively with IR (measured via hyperinsulinemic euglycemic clamp) after adjusting for BMI, fasting insulin, WHR, TRIG, and systolic and diastolic blood pressures (Potter van Loon, Kluft, Radder, Blankenstein, & Meinders, 1993). A number of studies have also found that the correlations between BMI, WHR, triglycerides and PAI-1 disappeared after adjustment for insulin (Juhan-Vague, Alessi, et al., 1989; Vague et al., 1986; Vague et al., 1989; Juhan-Vague, Roul, et al., 1989). Additionally, intervention studies have reported that if IR is improved, plasma PAI-1 concentrations decrease (Kruszynska, Yu, Olefsky, & Sobel, 2000; Trost, Pratley, & Sobel, 2006). One such study of DM2 patients reported that treatment with troglitazone

increased fibrinolytic activity by lowering plasma insulin levels and enhancing insulin sensitivity in peripheral tissue (Kruszynska et al., 2000).

In addition to its relation to IR and/or hyperinsulinemia, PAI-1 levels are consistently elevated in obese individuals, particularly those with abdominal obesity. Intervention studies have found that moderately overweight and obese individuals losing weight through caloric restriction resulted in decreased plasma PAI-1 levels (Folsom, Qamhieh, Wing, Jeffery, Stinson, et al., 1993; Rissanen, Vahtera, Krusius, Uusitupa, & Rissanen, 2001). Rissanen and colleagues' (2001) study of obese women found that the decline in PAI-1 over a one-year follow-up period was dependent upon the magnitude of weight loss. Recent studies linking PAI-1 production to adipose tissue provide further evidence of a robust relationship between PAI-1 and obesity (Juhan-Vague et al., 2000; Sakkinen, Wahl, Cushmen, Lewis, & Tracy, 2000).

While IR and obesity are related to increases in PAI-1, current data does not support IR as a direct mechanism (Juhan-Vague, Alessi, & Vague, 2000). It may be that abdominal obesity in insulin resistant states is responsible for the elevated plasma PAI-1 levels. Recently, production of PAI-1 by adipose tissue has been proposed to be responsible for the increased PAI-1 levels observed in IR (Juhan-Vague, Alessi, & Morange, 2000). Another possibility is that the increased synthesis of TNF-α by adipose tissue in IR leads to increased PAI-1, as it has been found that TNF-α up-regulates endothelial cell production of PAI-1 (van Deventer, Buller, ten Cate, Aarden, Hack, et al., 1990). Other possible mediators of obesity and fibrinolytic factors include IL-6, leptin, and hormonal

abnormalities (De Pergola & Pannacciulli, 2002). These findings suggest that IR and associated hyperinsulinemia contribute to impaired fibrinolysis via their influence on adipocytes and vascular cells, thus contributing to atherosclerotic progression.

Fibrinolytic variables play a critical role in atherothrombosis. Elevated PAI-1 has been associated with the components of the metabolic syndrome including obesity, dyslipidemia, hypertension, and inflammation, and is independently linked with insulin resistance. A potential mechanism underlying its association with these variables involves stimulation of PAI-1 production directly or indirectly by adipose tissue.

1.4 Cynical Hostility

Research over the past 50 years has increasingly focused on the role of psychosocial factors in the development and progression of CHD. A major reason underlying the increased focus on psychosocial factors in CHD is that traditional risk factors are only able to explain about 50% of the variance in CHD incidence (Kubzansky & Kawachi, 2000). The psychosocial factors that have been researched most extensively in relation to CHD include psychological stress and stressors (Black, 2006; Bunker, Colquhoun, Esler, Hickie, Hunt, et al., 2003; Goldstein, 1995; Tennant, 2000), negative emotions such as anger, depression, and anxiety (Kubzansky & Kawachi, 2000; Sirois & Burg, 2003), and personality attributes such as hostility. The relationship between hostility and CHD has been investigated by many groups over the years with prospective studies in both healthy and diseased populations reporting associations (Smith, Glazer, Ruiz, & Gallo, 2004).

In individuals initially free of CHD, prospective studies have found hostility to be related to atherosclerosis, cardiac events, and mortality (Barefoot, Larsen,

von der Lieth, & Schroll, 1995; Boyle, Michalek, & Suarez, 2006; Niaura, Todaro, Stroud, Spiro, Ward, et al., 2002; Todaro, Con, Niaura, Spiro, Ward, et al., 2005). A meta-analysis of over 45 studies conducted by Miller and colleagues concluded that hostility to be an independent predictor of CHD (Miller, Smith, Turner, Guijarro, & Hallet, 1996). Prospective studies in patients with manifest CHD, however, are fewer in number (Chaput, Adams, Simon, Blumenthal, Vittinghoff, et al., 2002; Matthews, Gump, Harris, Haney, & Barefoot, 2004). Among men in the MRFIT sample experiencing a non-fatal CV event early in the study, high hostility levels were associated with a five-fold increased risk of CV death at later follow-up (Matthews et al., 2004). A recent meta-analysis on studies of CHD patients reported the association identified between hostility and poor prognosis persisted after contolling for disease status and treatment (Chida & Steptoe, 2009). Several studies, however, did not find associations between hostility and CHD outcomes (e.g., Kaufmann, Fitzgibbons, Sussman, Reed, Einfalt, et al., 1999).

Some investigators have hypothesized that particular aspects of hostility may confer an even greater health risk to individuals (Barefoot, Dodge, Peterson, Dahlstrom, & Williams Jr., 1989.) In a large prospective study of initially healthy individuals, Barefoot and colleagues (1989) identified 3 subscales from the 50-item MMPI-based (Hathaway & McKinley, 1943) Cook-Medley scale (CMHo; Cook & Medley, 1954) that were related to survival as well as portions of the measure that were not. One subscale that demonstrated a particularly robust association with mortality was cynicism. The experience and expression of

cynicism has been referred to as a long-standing attitudinal disposition characterized by a general distrust of the integrity or professed motives of others (Kubzansky & Kawachi, 2000). Notably, cynical hostility is thought to reflect attitudes (i.e., cognitions) rather than overt expressions of anger and aggression (Barefoot et al., 1989). Prospective studies in both healthy (Almada, Zonderman, Shekelle, Dyer, Daviglus, et al., 1991; Barefoot, et al., 1989; Everson, Kauhanen, Kaplan, Goldberg, Julkunen, et al., 1997) and CHD cohorts (Boyle, Williams, Mark, Brummett, Siegler, et al., 2004) have reported associations between cynical hostility and adverse outcomes. In one study of 936 middle-aged CHD patients followed for almost 15 years, cynical hostility was found to be a predictor of CHD and total mortality (Boyle et al., 2004). Despite the attempt to identify particularly caustic elements of hostility, some researchers have suggested that the type of hostility assessed by the entire CMHo scale can be described as cynical hostility (Smith & Frohm, 1985).

Mechanisms that have been proposed to explain the relationship between hostility and CHD include: 1) exaggerated CV and neuroendocrine responses to stressors (Christensen & Smith, 1993; Lepore, 1995; Smith et al., 2004); 2) psychosocial characteristics (e.g., increased interpersonal conflict; less social support) that make them more vulnerable (Smith, 1992); 3) poor health behaviors (Everson, et al., 1997); or 4) contributions by other biological factors such as polymorphisms in serotonergic systems that have been related to both hostility and CVD (Smith et al., 2004; Smith & Gallo, 2001).

Exaggerated biological responsivity and a greater proclivity for negative health behaviors in cynically hostile individuals have been found to affect several indices of the MetS. One recent study reported that the MetS mediated the relationship between cynical hostility and CVD (Nelson, Palmer & Pedersen, 2004). Stronger support comes from a large prospective study where hostility was positively associated with WHR, BMI, fasting insulin, serum TRIG, and total daily caloric intake and inversely related to HDL cholesterol (Niaura, Banks, Ward, Stoney, Spiro, et al., 2000). Path analysis suggested that the effects of hostility on insulin, TRIG, and HDL cholesterol were mediated by its effects on BMI and WHR, which, in turn, had an effect on lipids and blood pressure through insulin. In another sample of individuals from the same cohort not taking diabetic medications, men with high levels of both cynical hostility and norepinephrine were found to have increased HOMA-IR and circulating plasma insulin levels after adjustment for several covariates including WHR and HTN (Zhang, Niaura, Dyer, Shen, Todaro, et al., 2006). A cross-sectional study of middle-aged men found that hostility was associated with hyperinsulinemia, hyperglycemia, dyslipidemia, HTN, increased abdominal obesity, and increased PAI-1 after adjusting for BMI, age, education, smoking, alcohol consumption, and physical activity (Räikkönen, Keltikangas-Järvinen, Adlercreutz, & Hautanen, 1996). A recent meta-analysis found that Cook-Medley hostility scores were significantly related to BMI, WHR, and IR leading the authors to conclude that these factors may be particularly important mediators of the relationship between hostility and CHD (Bunde & Suls, 2006). Despite the apparent relationships between hostility,

IR, and central adiposity, some studies have failed to find support for these associations (Philip & Facchini, 1995). With respect to other MetS factors, studies have reported associations between hostility and inflammatory markers (Graham, Robles, Kiecolt-Glaser, Malarkey, Bissell, et. al., 2006; Ranjit, Diez-Roux, Shea, Cushman, Seeman, et al., 2007; Zhou, Kusnecov, Shurin, DePaoli, & Rabin, 1993), cholesterol levels (Chikani, Reding, Gunderson, & McCarty, 2004; Stoney, Bausserman, Niaura, Marcus, & Flynn, 1999; Waldstein, Manuck, Bachen, Muldoon, & Bricker, 1990), and coagulation variables (von Kanel, Mills, Fainman, & Dimsdale, 2001).

A mechanism linking psychological factors to metabolic dysfunction has been described by Bjorntorp (2001; 1996). Studies within humans have documented that the fight or flight response (i.e., anger and hostility) results in an increase in SNS activation and cortisol secretion (Bjorntorp, 1991; Suarez, Kuhn, Schanberg, Williams Jr., & Zimmermann, 1998). Further, it has been proposed that consistent fight or flight responses lead to a central redistribution of body fat (Bjorntorp, 2001). In addition to promoting the production of visceral fat, however, it has been suggested that elevated cortisol levels might alter insulin sensitivity, thus promoting hyperinsulinemia (Vitaliano, et al., 1996). Further, it has been reported that cortisol and insulin promote lipid accumulation, particularly in visceral fat depots as seen in Cushing's syndrome (Bjorntorp, 1996).

Studies have reported associations between cynical hostility, CVD development and progression, and factors of the metabolic syndrome. In particular, cynical hostility is thought to lead to metabolic dysfunction and CVD via chronic engagement of the sympathetic nervous system and the

hypothalamic-pituitary-adrenal axis. Cynical hostility has been reported to be associated with obesity and insulin resistance, but findings are inconsistent.

1.5 Cardiovascular Structure and Function

Factors associated with the MetS lead to CVD development and adverse outcomes via their direct and indirect impacts on the structure and function of the heart and vasculature. The next sections will examine the empirical evidence supporting the relationship between MetS factors and measures of CV structure and function.

1.5.1 Cardiac structure.

CVD is associated with a number of cardiac structural changes. Alterations in cardiac structure have been found to be related directly and indirectly to factors of the MetS, particularly obesity, IR, and HTN (Ferrara, Cardoni, Mancini, & Zanchetti, 2007). All of these factors have been implicated in one of the principle changes to cardiac structure, namely the development of left ventricular hypertrophy (LVH). LVH refers to a thickening of the myocardium of the left ventricle of the heart and, in the context of CVD, is associated with the progression of atherosclerosis, stroke incidence, and increased CV and all-cause mortality (Bikkina, Levy, Evans, Larson, Benjamin, et al., 1994; Koren, Devereux, Casale, Savage, & Laragh, 1991; Levy, Garrison, Savage, Kannel, & Castelli, 1990). LVH typically develops in response to chronic pressure or volume overload in the heart (Selvetella & Lembo, 2005), and increases with age, blood pressure, and obesity (Levy, Anderson, Savage, Kannel, Christiansen, et al., 1988).

Several studies in patients initially free of CHD have reported independent associations between obesity and various indicators of LVH (Di Bello, Santini, Di Cori, Pucci, Palagi, et al., 2006; Heckbert, Post, Pearson, Arnett, Gomes, et al., 2006; Lauer, Anderson, & Levy, 1992; Levy, et al., 1988; Peterson, Waggoner, Schechtman, Meyer, Gropler, et al., 2004; Powell, Redfield, Bybee, Freeman, & Rihal, 2006). In a study by Peterson and colleagues (2004), obesity in young otherwise-healthy women was associated with concentric LV remodeling; obese women had higher end-diastolic septal and posterior wall thickness, LV mass, and relative wall thickness than non-obese women (Peterson et al., 2004). Other studies have reported that obesity was associated with LV hypertrophy (Levy et al., 1988), LV wall thickness, and LV mass independent of blood pressure (Lauer et al., 1992). Studies investigating obesity and LVH in patients with manifest CVD are less common. In individuals meeting criteria for MetS, LV mass and prevalence of LVH were elevated in those with higher WC (Ferrara et al., 2007). In pre-diabetic as well as DM2 patients with CVD, BMI and fat mass were associated with LV mass, particularly in women. In DM2 patients without CVD, fat mass was only slightly correlated with left ventricular mass (Kuch, von Scheidt, Peter, Döring, Piehlmeier, et al., 2007). Importantly, weight loss has been shown to decrease LV mass (Syed, Rosati, Torosoff, El-Hajjar, Feustel, et al., 2009) in obese patients as well as LV mass and blood pressure in overweight hypertensive patients (MacMahon, Wilcken, & Macdonald, 1986).

Evidence for a link between IR and indices of LV mass is mixed. Relationships have been reported, however, in non-diabetic hypertensive

individuals (Hara-Nakamura, Kohara, Sumimoto, & Hiwada, 1994; Tomiyama, Doba, Kushiro, Yamashita, Kanmatsuse, et al., 1997), diabetic hypertensive individuals (Palmieri, Bella, Arnett, Liu, & Oberman, 2001) and non-diabetic, obese normotensive individuals (Iacobellis, Ribaudo, Zappaterreno, Vecci, Tiberti, et al., 2003; Sasson, Rasooly, Bhesania, & Rasooly, 1993). Of note, few studies have found associations independent of body size. An exception is a study of non-diabetic American Indian men and women that found that fasting insulin was independently associated with increased LV mass in men and relative wall thickness and septal thickness in women after adjustments for BMI, age, height, and systolic blood pressure (Ilercil, Devereux, Roman, Paranicas, O'Grady, et al., 2002). Another comes from a population-based study of relatively healthy hypertensive adults reporting an association between DM2 status and higher LV mass, greater concentric LV geometry, and lower myocardial function, independent of age, sex, body size, and arterial BP (Palmieri et al., 2001). Several studies have reported the absence of a relationship between IR and LV mass after adjusting for body size (Ebinc, Ebinc, Ozkurt, Dogru, & Yilmaz, 2006; Ferrara, Vaccaro, Cardoni, Panarelli, Laurenzi, et al., 2003; Vaccaro, Cardoni, Cuomo, Panarelli, Laurenzi, et al., 2003).

In comparison, studies investigating blood pressure and LV hypertrophy have been much more extensive, but most have only reported cross-sectional associations (Gardin, Brunner, Schreiner, Xie, Reid, et al., 2002; Gardin, Wagenknecht, Anton-Culver, Flack, Gidding, et al., 1995; Hammond, Devereux, Alderman, & Laragh, 1988; Lauer et al., 1992; Levy et al., 1988; Lorber, Gidding,

Daviglus, Colangelo, Liu, et al., 2003; Silva, Flexa, & Zanella, 2007). A major prospective study of healthy non-obese participants in the Framingham Heart Study found that the prevalence of LV hypertrophy was strongly associated with 30-year average SBP (odds ratios for every 20-mm Hg increase in blood pressure: 3.20 in men and 3.27 in women) and slightly less robust for DBP (Lauer, Anderson, & Levy, 1991). Some researchers have also reported that LV hypertrophy is implicated in the development of HTN (Post, Larson, & Levy, 1994).

Although considerably fewer studies exist, other MetS factors that have been associated with LV hypertrophy include dyslipidemia (Anan, Yonemochi, Masaki, Takahashi, Fukunaga, et al., 2007; Sundstrom, Lind, Vessby, Andren, Aro, et al., 2001), inflammatory markers (Malavazos, Corsi, Ermetici, Coman, Sardanelli, et al., 2007), and fibrinolytic factors (Diamantopoulos, Andreadis, Vassilopoulos, Theodorides, Giannakopoulos, et al., 2003). Sundstrom and colleagues (2001) reported that in late middle-aged adults, a 1-SD increase in fasting LDL/HDL cholesterol, serum triglycerides, or FFA concentrations increased the odds of having LV hypertrophy by 27% to 41% over 20 years. A recent study of normotensive obese women found that absolute and indexed LV mass, end-diastolic septum thickness, end-diastolic posterior wall thickness were associated with IL-6 and CRP levels (Malavazos et al., 2007). Finally, in a study of middle-aged newly-diagnosed hypertensive men and women, LV mass indices were higher in individuals with elevated PAI-1 levels compared to those with lower concentrations (Diamantopoulos et al., 2003).

Alterations in cardiac structure have been found to be related directly and indirectly to factors of the metabolic syndrome, particularly obesity, IR, and HTN. Each of these factors has been implicated in the development left ventricular hypertrophy which has been associated with the progression of atherosclerosis and increased mortality.

1.5.2 Cardiac function.

Closely related to cardiovascular structural changes in CVD are cardiac functional changes (Grossman, Oren, & Messerli, 1994). Cardiac function is an important indicator of the overall health of the CV system regardless of the stage of CVD. For individuals with advanced disease such as those who have experienced MI, cardiac function may become even more critical as damage to heart tissue impedes the delivery of blood to organs of the body and may contribute to cardiomyopathy. Cardiac function is measured via several indices including cardiac compliance – an index of LV diastolic function (e.g., inflow velocities such as E/A ratio), cardiac contractility – an index of LV systolic function (e.g., fractional shortening, ejection fraction), and myocardial oxygen demand (e.g., rate-pressure product; Smith & Kampine, 1990).

Cardiac compliance describes the ease at which a chamber of the heart (or the lumen of a blood vessel) expands when it is filled with a volume of blood (Sutton, 1999). Compliance is determined by the physical properties of the cardiac muscle and associated tissues which impact ventricular contraction and relaxation. It is generally defined as the change in volume divided by the change in pressure. Filling of the left ventricle (i.e., end-diastolic volume) depends upon the venous return and the compliance of the ventricle during diastole. Individuals with LV hypertrophy demonstrate a reduction in ventricular compliance and

therefore less ventricular filling (decreased end-diastolic volume), a greater end-diastolic pressure, and a decrease in stroke volume. Depending on the changes in stroke volume and end-diastolic volume, ejection fraction values may or may not decrease. A commonly used measure of compliance dysfunction is the E/A ratio which reflects early (E) and late, or atrial (A) filling velocities recorded in centimeters per second (Sutton, 1999). In general, when diastolic dysfunction is present, a greater portion of end-diastolic volume is the result of late filling rather than early filling yielding a reduced E/A ratio. A normal E/A ratio for healthy individuals between the ages of 41 and 60 years is 1.28 ± 0.25 (Sutton, 1999).

Cardiac contractility refers to the degree to which cardiac muscle fibers are able to shorten, independent of preload and afterload, and is a major determinant of output during systole (Sutton, 1999). A commonly used index of contractility is fractional shortening (FS) which measures and ratios the change in the diameter of the left ventricle between the contracted and relaxed states. FS is similar to LV ejection fraction which measures and ratios blood volumes. The normal range for FS in healthy individuals is 0.18-0.42, or 18-42% (Sutton, 1999). Values above 30% are considered normal, with 26 to 30% representing mild decreases in function (Keene & Oeffinger, 2000). A decrease in the shortening fraction usually precedes a detectable decrease in ejection fraction (Sutton, 1999).

Myocardial oxygen demand (consumption) is a functional index that assesses the amount of oxygen used by the heart. Oxygen demand has been linked with gender, age, BMI, and physical activity level (Hui, Jackson, & Weir,

2000). Individuals with healthier cardiac function demonstrate a reduced oxygen demand, an assertion supported by studies of the effects of exercise training on this index (Lovell, Cuneo, & Gass, 2009). Rate pressure product (RPP) is often used as a proxy for myocardial oxygen demand and is calculated by multiplying an individual's heart rate and systolic blood pressure. Comparing RPP values provides an index of the degree to which an individual's heart is burdened. The RPP for an individual with a resting heart rate of 73 beats per minute and a systolic blood pressure of 120 mmHg is 8,760 mmHg·BPM.

Insulin resistance, central adiposity, and various other components of the MetS have been found to be risk factors for cardiac dysfunction (Banerjee & Peterson, 2007). With respect to myocardial oxygen demand, studies have reported that DM2 status is associated with an elevated heart rate and RPP (Foo, Sekhri, Knight, Deaner, Cooper, et al., 2004). With respect to diastolic dysfunction, results from a large cross-sectional population-based study revealed that patients with MetS demonstrated significantly greater impairment in cardiac compliance as indicated by a reduced E/A ratio (Ferrara, Cardoni, Mancini, & Zanchetti, 2007). Another population-based study of middle-aged urban Portuguese individuals indicated a graded association between increasing number of concurrent components of the MetS and a decreased E/A ratio after adjusting for age, sex, SBP and Framingham risk score (Azevedo et al., 2007). One cross-sectional study reported that patients with MetS demonstrated diastolic dysfunction independent of LV hypertrophy or systolic dysfunction (Masugata, Senda, Goda, Yoshihara, Yoshikawa, et al., 2006).

Few studies were found reporting associations in patients with manifest CVD. One recent study in post-MI patients without known DM2 reported significantly lower tissue Doppler derived E/A ratio in patients with disturbed glucose metabolism compared with patients with normal glucose tolerance (Henareh, Lind, Brodin, & Agewall, 2007). Another study found that glucose intolerance was related to abnormal LV filling in normotensive subjects 2 months after MI, independent of LV ejection fraction (Salmasi, Frost, & Dancy, 2005). Regarding prognosis following MI, diastolic dysfunction seems to be an important outcome marker as abnormal diastolic properties are related to progressive LV dilatation, development of heart failure, and cardiac death (Poulsen, 2001).

Associations between IR and cardiac contractility have been reported in a limited number of studies (Deng, Huang, Lu, & Hung, 2007; Goldstein, Hurwitz, Llabre, Schneiderman, Gutt, et al., 2001). In one study, culturally diverse healthy men and women (aged 25-44 years) with reduced cardiac contractility demonstrated higher fasting and postload insulin and glucose levels and lower insulin sensitivity in addition to greater BMI (Goldstein et al., 2001). A study of hypertensive patients without DM2, however, reported no association between HOMA-IR and contractility measured via fractional shortening (Evrengul, Dursunoglu, Kaftan, Kilicaslan, Tanriverdi, et al., 2005). With respect to patients with manifest disease, one study reported that individuals with DM2 demonstrated both a lower ejection fraction and stroke volume (Heckbert et al., 2006). It has been suggested that defects in both diastolic and systolic function contribute to the high prevalence of CVD in this population (Schaffer, 1991).

Central obesity is also closely linked to cardiac functional disturbances. Several cross-sectional studies have reported associations between obesity and systolic and diastolic functioning (Alwi, Harun, Sukmono, Suwondo, Oemardi, et al., 2006; Crisostomo, Araujo, Camara, Carvalho, Silva, et al., 1999; Di Bello, Santini, Di Cori, Pucci, Palagi, et al., 2006; Pascual, Pascual, Soria, Vicente, Hernandez, et al., 2003; Peterson, Waggoner, Schechtman, Meyer, Gropler, et al., 2004; Powell, Redfield, Bybee, Freeman, & Rihal, 2006). Significant research indicates that systolic function (assessed by ejection fraction or load independent measures such as fractional shortening) is usually normal in obesity (de Simone, Devereux, Mureddu, Roman, Ganau, et al., 1996; Vasan, 2003). One study in individuals without evident CVD, however, reported that ejection fraction, fractional shortening, and mean velocity of circumferential shortening were elevated, but only in slight and moderate obesity (Pascual, Pascual, Soria, Vicente, Hernandez, et al., 2003). Diastolic function, on the other hand, is more commonly affected by obesity. In a large population-based investigation, BMI was associated with several indices of impaired diastolic filling (Fischer, Baessler, Hense, Hengstenberg, Muscholl, et al., 2003). In another study, E/A ratio was increased and pulmonary diastolic velocity was decreased in obese compared to non-obese women (Alwi et al., 2006). Obesity has been proposed to impair LV filling due to changes in loading conditions primarily associated with increased LV mass, which is generally considered the have the greatest impact on ventricle compliance or “stiffness” (Alpert, 2001; Störk, Möckel, Danne, Völler, Eichstädt, et al., 1995).

In addition to studies of global obesity, central obesity has been linked to cardiac dysfunction (Gong, Tan, Fang, Song, Li, et al., 2009; Licata, Scaglione, & Dominguez, 1999). In a recent study from the Framingham cohort, visceral adipose tissue, BMI, and WC were directly correlated with diastolic dysfunction in women but not men (Fox, Gona, Hoffmann, Porter, Salton, et al., 2009). Another study of patients with MetS reported that WHR independently predicted both LV systolic and diastolic dysfunction (Gong et al., 2009). No studies were found linking obesity to cardiac dysfunction in patients with manifest CHD.

Studies reporting associations between cardiac dysfunction and other MetS factors are limited. With respect to HTN, one study found that FS and E/A ratio were significantly lower in non-diabetic hypertensive patients compared to healthy controls (Evrengul et al., 2005). Another study in obese patients with newly diagnosed HTN reported significantly elevated A wave, lower E/A ratio, and longer E deceleration time compared to obese normotensive patients, but no difference in LV mass (Persic, Ruzic, Miletic, Balen, Jovanovic, et al., 2007). The investigators proposed that HTN may significantly contribute to LV diastolic impairment in obese patients before the development of structural aberrations. In a study of normotensive obese women, indices of diastolic function (including deceleration time and isovolumetric relaxation time) and visceral adipose tissue were correlated with IL-6 and CRP levels, suggesting that inflammation may mediate visceral obesity and cardiac dysfunction (Malavazos, Corsi, Ermetici, Coman, Sardanelli, et al., 2007). No studies were identified describing

relationships between these MetS factors and cardiac dysfunction in CHD patients.

Beyond the cardiac changes that occur preceding a MI, several structural and functional changes occur following a MI. Following MI, both systolic and diastolic functioning are modified as the MI produces a loss of contractile tissue and changes in ventricular geometry (Moller, Egstrup, Kober, Poulsen, Nyvad, et al., 2003). This structural remodeling often results in the stiffening and enlargement of the left ventricle over time, the degree to which is dependent on the location and severity of the MI. Left ventricular enlargement and functional impairment following MI are associated with the development of adverse cardiac events (St John Sutton, Pfeffer, Plappert, Rouleau, Moyé, et al., 1994; White, Norris, Brown, Brandt, Whitlock, & Wild, 1987). In one longitudinal study, CV death and/or LV dilation occurred in >50% of patients by 2 years (St John Sutton, Pfeffer, Moye, Plappert, Rouleau, et al., 1997). In this study, LV end-diastolic and/or end-systolic sizes increased progressively from baseline to 2 years in more than 70% of the patients. Predictors of CV death and/or dilatation included age, prior MI, lower ejection fraction, angina, heart failure, LV size, and infarct size. Importantly, use of the ACE inhibitor Captopril attenuated diastolic LV dilation, having an effect primarily during the first year of follow-up. Studies have identified a number of functional impairments associated with MI including decreased ejection fraction and fractional shortening (St John Sutton et al., 1994; White, Norris, Brown, Brandt, Whitlock, & Wild, 1987) and abnormal early diastolic LV filling (Bonow, Bacharach, Green, Kent, Rosing, et al., 1981;

Giannuzzi, Imparato, Temporelli, de Vito, Silva et al., 1994) characterized by a slower LV relaxation pattern (Fujii, Yazaki, Sawada, Aizawa, Watanabe, et al., 1985) and a short deceleration time of early filling.

Cardiac function is measured via several indices including LV compliance, LV contractility, and myocardial oxygen demand. Obesity, insulin resistance, hypertension, and inflammation have all been found to be associated with cardiac dysfunction in previous studies.

1.6 Rationale

The escalating prevalence of CHD, despite advances in pharmacological treatment for diseases such as HTN and DM2, underscores the importance of considering multiple risk factors in its development and progression. The MetS is a constellation of interrelated risk factors of metabolic origin thought to confer greater CHD risk as a cluster than when considering each factor separately. While the pathophysiological mechanisms underlying the development of MetS and CV dysfunction remain unclear, knowledge regarding several relationships has increased in recent years. Central obesity and IR are major factors underlying the MetS; prospective studies have found increased visceral fat to be the primary cause of IR. Psychological factors such as hostility have also been associated with MetS development via obesity, increased SNS activity, and poor health behaviors. Evidence supports links between hyperinsulinemia, obesity, HTN, and SNS overactivity which are thought to collectively promote and exacerbate an insulin resistant state. Increased IR, particularly in obesity, is thought to fuel HTN, which has been found to contribute to the destabilization of atherosclerotic plaque and increase mortality risk in those with extant disease. Inflammation is thought to be an essential feature of atherosclerosis and, due to

its robust association with MetS factors, is increasingly considered a critical factor in MetS pathogenesis. Similar to the role of inflammation, dyslipidemia and fibrinolytic activity are also prominent MetS components in that they mediate the underlying pathogenic processes culminating in cardiac and vascular dysfunction and changes in cardiac structure.

To date, most studies have focused on bivariate relationships between selected MetS factors or the influence of these factors on CVD outcomes in initially healthy individuals. Few studies, however, have examined associations among MetS factors and indices of CV dysfunction in a population with manifest disease (i.e., MI patients) in a **single conceptual model**. The development of a structural model incorporating several of the empirically supported bivariate relationships would extend the current understanding of MetS pathophysiology in this population. In addition, because the major components of the MetS are modifiable, an understanding of the syndrome in this cohort would assist in the design of interventions for tertiary prevention. The identification and targeting of factors occurring early in the progression of MetS would be instrumental not only to decrease the risk of future cardiac incidents in this population, but perhaps also provide an empirical foundation from which to initiate a reversal of the disease process. The present study proposes to extend prior investigations of the MetS by modeling the association between MetS factors in a sample of men and women who experienced MI approximately 8 weeks prior to data collection. Further, in addition to utilizing a more comprehensive representation of MetS

components than previous studies, this study will examine relationships between cynical hostility, MetS factors, and indices of CV structure and function.

1.7 Hypotheses

The primary objective in the present study was to specify and test a structural model of the MetS and its association with indices of CV structure and function in a cohort of post-MI patients. The variables selected for the model included risk factors identified in the NCEP ATP-III definition of MetS as well as CV variables tested in a similar recent analysis of healthy individuals which is presented in Figure 1 (Klaus, Hurwitz, Llabre, Skyler, Goldberg, et al., 2009). Similar to the findings from the Klaus et al. (2009) study, MetS factors were expected to demonstrate statistically significant interrelationships and be associated with cardiac structure and function in the present study. In addition, cynical hostility was expected to be related to critical MetS factors including central adiposity and IR which promote the development and progression of CVD.

Chapter 2: Methods

2.1 Participants

Participants for the present analyses consisted of 186 patients hospitalized with MI between November 2001 and February 2006. Participants were a selected subset of individuals enrolled in a 6-month prospective study (GREAT HEART) investigating the effectiveness of a 12-week Cognitive Behavioral Therapy (CBT) intervention compared to standard care. The intervention covered topics including: education about heart disease, stress reduction, coping, problem-solving, diet and exercise, and anger management. The aim of the intervention was to reduce both psychological and physiological risk factors associated with CHD.

2.2 Procedure

2.2.1 Screening.

Prospective patients for the Great Heart study included 1,335 individuals from the critical care (CCU) and cardiac units of Jackson Memorial Hospital (JMH) meeting study inclusion criteria who were initially identified through a review of their medical charts. Of these individuals, 242 met both inclusion and exclusion criteria and were invited to participate in the study.

Inclusion criteria for this study were: (a) an elevation of the marker proteins (cardiac enzymes) Creatine Kinase Isoenzyme MB (CKMB) and Troponin-T that were at least twice the upper limit value of standardized reference bands outlined by the American Heart Association (2003) for healthy individuals (CKMB: 0 – 6.7 ng/mL; Troponin-T: 0 – 0.03 ng/mL); (b) if CKMB and

troponin-T levels were not greater than two times the upper limit of normal, a rising and falling pattern was considered diagnostic if this diagnosis was made by the cardiologist in the participating hospital; (c) medically eligible patients were further required to manifest either (1) symptoms compatible with MI, and (2) characteristic evolutionary electrocardiogram (ECG) changes.

Exclusion criteria for this study were: (a) experienced a life-threatening non-cardiac condition with a 1-year prognosis of mortality likely; (b) were too ill with severe cardiac complications (e.g. remains on ventilator); (c) had physical/logistical barriers that would interfere with full participation (e.g. limited mobility); (d) possessed a language barrier that might interfere with the comprehension of forms, and/or participating in CBT; (e) presented with a major psychiatric comorbidity (e.g., dementia, schizophrenia, alcoholism); (f) were involved in another research protocol; (g) refused to participate; (h) experienced an MI subsequent to a procedure (e.g. PTCA, CABG); (i) were unable to complete the screening and/or baseline instruments; (j) were inaccessible for intervention and/or follow-up visits (e.g. lives too distant); (k) died before randomization; (l) were taking antidepressant medication for less than 14 days at time of recruitment; (m) were receiving psychotherapy at time of recruitment.

2.2.2 Pre-baseline assessment.

During pre-baseline assessment, patients were asked to review and sign an Informed Consent Form approved by the University of Miami Institutional Review Board (UMIRB). As part of the pre-baseline assessment interview, complete study details were provided. A research nurse, experienced in working

with MI patients, conducted interviews to assess patients' depression symptoms and severity. Participants provided demographic information including age, sex, marital status, living situation, primary language, race/ethnicity, income, employment status, and years of formal education. Relevant medical history and background were also obtained by patient interview and chart review, including treatment of index MI, family history of heart disease, patient history of depression, current antidepressant medication use, indices of heart disease severity, and medical comorbidities. Assessments took place during the initial hospital stay. If the patient had already been discharged from the hospital, interested patients were invited to come in for the pre-baseline assessment at the University of Miami Behavioral Medicine Research Center (BMRC) located in the Miami Veterans Administration Hospital.

2.2.3 Baseline assessment.

Of the 242 patients who completed pre-baseline assessment, 32 refused to participate and 24 were excluded due to medical reasons (e.g., necessity for ventilator) resulting in a final sample of 186 patients. During the baseline visit, which was required to take place at least 1 month post-MI and within 28 days of the pre-baseline assessment, patients signed an additional Informed Consent Form approved by the UMIRB. Baseline assessment for all participants began in the early-morning hours (approximately 8:30 AM), and for most participants, extended into the early afternoon (approximately 1:30 PM). During the visit, patients were given a comprehensive physiological examination which included a brief standard physical exam, a blood draw, an oral glucose tolerance test

(OGTT), and echocardiography. Additionally, patients completed a psychosocial assessment battery which included several measures assessing areas such as quality of life, social support, physical activity, ethnic identity, coping, hostility, anxiety, and depression. Examinations and assessments were conducted by a research team consisting of medical doctors, nurses, and doctoral level research psychologists.

2.2.4 Peripheral Venous Blood Draw.

Blood samples were obtained after a 12-hour fast to determine the quantitative values of a number of physiological variables. For the present study, this included an assessment of plasma inflammatory markers (CRP, IL-6), fibrinolytic variables (PAI-1), lipids (HDL and TRIG), and metabolic efficiency variables (insulin and glucose). Upon arrival, participants' fidelity to the specified blood draw requirements was assessed (i.e., 12-hour fast, no caffeine, no medications, no smoking). Following this procedure and a brief review of the planned protocol for the day, an indwelling venous catheter (22-gauge) was inserted into the dominant arm of each patient for blood collection. Blood was drawn approximately every 3 minutes after catheter insertion for a period of 15 minutes. At the 15-minute point and subsequently every 30 minutes up to 120 minutes, one 5cc vile of blood was drawn as part of the OGTT protocol (explained below). The time of collection occurred between 9:00 and 11:00 AM for the majority of participants.

All blood draws were performed by a trained phlebotomist. Blood samples were transported to the appropriate laboratories (BMRC and the UM Diabetes

Research Institute) for storage and/or processing within 1 hour of collection. Blood was collected in eleven sterile tubes: two contained sodium citrate; six contained potassium and the anticoagulant ethylene diamine tetra acetate (EDTA); three did not contain any additives. Plasma was removed from samples in the EDTA tubes and stored at -80°C until use. Samples collected in the tubes without an additive were allowed to clot at 25°C for 30 minutes, at which time serum was separated and stored at -80°C until use.

2.2.5 Blood assays.

Values for biological samples were obtained via the following methods. Plasma insulin concentrations were measured using an insulin-specific kit from Linco/Millipore, (St. Charles, Missouri). Plasma glucose levels were quantified by an enzymatic glucose oxidase method using a Beckman Glucose Analyzer-2 (Beckman Instruments). PAI-1 values were determined by quantitative spectrolyse/fibrin enzyme-linked immunosorbent assay (Tine Elise, Biopool).

High sensitivity C-reactive protein (hsCRP) assays were performed on the Behring nephelometer using the manufacturer's reagents, quality controls, and methods (Dade Behring, Inc.; Deerfield, Illinois). All tests utilized a serum standard which was diluted to provide a reference range, in order to avoid matrix effects in this matrix-sensitive methodology. Diluted serum was incubated with polystyrene particles coated with monoclonal antibodies to CRP to produce agglutination and light-scattering in proportion to the concentration of antigen. The serum standard has a reference value in the range of 21.7 mg/L, which was diluted to give a range of 0.08 to 6 mg/L. Intra-assay and interassay coefficients

of variation (CVs) are <4.4% and <5.7% respectively (Passing & Bablok, 1983). The median normal concentration of CRP is 1.6 mg/L, with 90% of apparently healthy individuals having a value less than 3mg/L and 99% less than 12mg/L (Ridker, 2001). Unless measured in the days immediately following MI, higher values are abnormal and indicate the presence of organic disease or acute infection; values > 10 mg/L are thought to represent inflammation not related to CVD (Pearson, Mensah, Alexander, Anderson, Cannon, et al., 2003; Pepys, 1996).

IL-6 was measured in diluted EDTA plasma using the sandwich enzyme (ELISA) immunoassay employing a double antibody technique, manufactured by R&D Systems (Quantikine HS®; Minneapolis, MN). Incubation of antigen with plate-immobilized monoclonal anti-IL-6 antibodies causes binding of antigen and provides epitopes for the binding of a second, enzyme-linked polyclonal anti-IL-6 antibody. This provides a colorimetric assessment of antigen concentration after the addition of amplifier enzymes that generate NAD, required to detect the low readings in the plasma. The reference curve reads from 0-10 pg/ mL with sensitivity typically less than 0.039 pg/mL, and a serum range of 0.37-10.1 pg/mL. Normal values in a healthy population are 0.45-9.96 pg/mL. Intra-assay and interassay CVs are <7.5% and <7.9% respectively (Sakamoto, Arakawa, Mita, Ishiko, Ikei, et al., 1994; Self, 1985).

2.2.6 Oral glucose tolerance test.

The OGTT was administered to assess fasting and post-prandial levels of glucose and insulin as well as to determine patients' efficiency at metabolizing a

standardized quantity of glucose over a 2-hour period. Only fasting values of glucose and insulin were measured in patients who reported a history of DM2 at study entry. Oral glucose (75 grams) was administered in a solution of flavored water at a concentration of 25-35 g/dL which was consumed within one minute. Two blood samples were obtained before glucose was ingested to assess fasting concentrations (at –15 and 0 minutes). Blood samples were then collected at 30, 60, 90, and 120 minutes following glucose consumption to determine glucose and insulin metabolism over time. The sum of the changes in glucose from baseline to 30, 60, 90, and 120 minutes was used as an index of overall glucose tolerance (G-AUC) for patients not reporting a history of DM2 (N=119). Insulin sensitivity (resistance) was assessed with plasma glucose and insulin values from the OGTT using the Homeostatic model insulin assessment approach (HOMA-IR). Designation of DM2 status was assigned to participants based on glucose fasting values or patient self-report.

2.2.7 Echocardiography.

Two-dimensional and Doppler echocardiograms were recorded in the left lateral decubitus position using a cardiac phased-array ultrasound imaging system (Hewlett Packard SONOS 2500) interfaced with a Panasonic videocassette recorder and computer for signal processing and data storage. Images were recorded on videotape and measured digitally by an echocardiography technician using a Nova-Microsonic ImageVue workstation.

In accordance with the American Society of Echocardiography conventions, measurements were recorded individually for five cardiac cycles and were expressed as an average. The technician was blind to patient data.

Structural information collected in the present study included LV posterior wall thickness at diastole (LVPWTd), interventricular septal thickness at diastole (IVSTd), and LV mass (LVM). LV wall thickness measurements were derived from two dimensional images using leading edge to leading edge. End diastole was defined as the frame coinciding with the onset of the Q wave of the ECG. End systole was marked by the frame preceding early diastolic opening. LVM was calculated using the modified Simpson rule formula (Weyman, 1994). LV mass index (LVMI) was calculated for each participant by adjusting for body surface area. Normal LVMI values for males and females have been reported to be 76±13 grams/m^2 and 66±11 grams/m^2, respectively, in a previous study of healthy middle aged individuals (Helak & Reichek, 1981). Septal and posterior wall thicknesses were assessed at end diastole and end systole using the parasternal long axis view at the level of the cordal-mitral junction. The LV outflow tract dimension was measured at end diastole.

Continuous wave Doppler ultrasound was utilized for the assessment of cardiac functioning. At a sweep speed of 100 mm/sec, Doppler recordings were measured digitally along the outer border of the brightest portion of the velocity contour. Functional indices assessed in the present study included LV cardiac compliance, LV contractility, and myocardial oxygen demand. Contractility was represented by fractional shortening (FS) which, as previously mentioned,

measures and ratios the change in the diameter of the left ventricle between the contracted and relaxed states. Values for FS were computed using the following formula: LV end-diastolic diameter minus LV end-systolic diameter divided by LV end-diastolic diameter. The normal range for FS in healthy individuals has been reported to be 0.18-0.42, or 18-42% (Sutton, 1999). The ratio of early diastolic filling to atrial kick velocities (E/A ratio) was used as a measure of compliance. A normal E/A ratio for healthy individuals between the ages of 41 and 60 years has been reported to be 1.28 ± 0.25 (Sutton, 1999). Rate pressure product (RPP) was used as a measure of myocardial oxygen demand which, as previously mentioned, provides an index of the degree to which an individual's heart is burdened. RPP was calculated by multiplying an individual's resting heart rate and resting systolic blood pressure. The RPP for a middle-aged individual with a resting heart rate of 73 beats per minute and a systolic blood pressure of 120 mmHg is 8,760 mmHg·BPM.

2.2.8 Cynical Hostility.

The Cook-Medley Hostility Scale (CMHo; Cook & Medley, 1954) is a 50-item true-false scale derived from the Minnesota Multiphasic Personality Inventory (Hathaway & McKinley, 1943). Scores range from 0-50 with a higher score depicting an individual characterized by dislike and distrust of others (Cook & Medley, 1954). Typical items include: "I commonly wonder what hidden reason another person may have for doing something nice for me," and "I think a great many people exaggerate their misfortunes in order to gain the sympathy and help of others." In a study by Jorgensen and colleagues (2001) of middle-aged male

veterans undergoing coronary angiography, the median CMHo score was 19. The CMHo has been found to have adequate reliability (>0.80) and validity (Smith, 1992).

Applying factor analysis, subsequent researchers have defined subscales of the original scale including paranoid alienation, cynicism, hostile affect, aggressive responding, and social avoidance (Barefoot et al., 1989; Costa, Zonderman, McCrae, & Williams, 1986). Based on Barefoot and colleagues' (1989) study reporting a more robust association between the cynicism subscale and cardiac outcomes compared to the full-scale CMHo, the 13-item cynicism scale (CynHo) was tested in the present study's final model. Scores can range from 0-13 with higher scores denoting greater cynicism. A recent large community-based longitudinal study investigating the relationship between CynHo and atherosclerosis reported mean scores for this scale to be to be 3.6 (Everson-Rose, Lewis, Karavolos, Matthews, Sutton-Tyrrell, et al., 2006). In patients with manifest CHD, a prospective study of 232 individuals assessing the impact of CynHo on the progression of coronary atherosclerosis reported mean CynHo scores to be 7.8 (Angerer, Siebert, Kothny, Mühlbauer, Mudra, et al., 2000).

2.3 Statistics

2.3.1 Data screening.

Assumptions of normality were examined using SPSS 15.0 software. Skewness and kurtosis values were obtained and divided by their standard errors. Those with absolute values greater than 2 were considered deviant from

normality and were log transformed. Outliers were assessed via boxplots and were investigated to determine if they represented data error or problems with an assay. As values for all study variables were within acceptable ranges, none were omitted. Multicollinearity between variables was examined by performing multiple regression analyses and examining the tolerance and variance inflation factors. Regarding missing data, parameters were estimated using a full information maximum likelihood method (Allison, 2003). Studies have shown this method to be less biased than traditional methods and comparable to multiple imputation (Boomsma, 2000).

2.3.2 Structural equation modeling.

Structural equation modeling (SEM) was used to specify and test the models of MetS for the present study. SEM is an extension of the general linear model that allows for the analysis of a measurement model (factor analysis) and a structural model (path analysis) to create a statistically sound model. The measurement model consists of latent variables and their respective indicators. Indicators are measured variables while latent variables are unobserved constructs represented by two or more related indicators. The structural model consists of the proposed paths between exogenous and endogenous variables. It is important to note that such paths represent partial coefficients. Exogenous variables have no other causal variables and endogenous variables are the mediating and dependent variables. A model is tested using SEM goodness-of-fit tests to determine if the pattern of variances and covariances in the data is consistent with the structural model specified. Models with an average of three

or more indicators per latent variable are ideal as they tend to have fewer problems with underidentification and lack of model convergence upon testing the model (Kline, 1998).

2.3.3 Analysis plan.

As previously mentioned, the primary objective of the present study was to test a model of MetS and CV structure and function in a post-MI sample. Based on its congruence with current theory and good statistical fit, a model recently specified and tested by Klaus and colleagues (2009) was used as a guide in specifying the model in the present study. Additional theoretically supported pathways between MetS factors and indices of CV function were tested in the present study beyond those specified by Klaus and colleagues. As with the Klaus et al. (2009) model, the present model is only a "not-disconfirmed" model as other unexamined models may fit the data as well or better.

The Klaus et al. (2009) model is presented in Figure 1. In this model, the metabolic variables were specified as Central Adiposity (WC), Insulin Sensitivity (M), Inflammation (CRP; IL-6), Glucose Tolerance (G-AUC), Lipidemia (TRIG; HDL-C; total cholesterol/HDL-C ratio, TC/HDL-C), and Fibrinolysis (tissue plasmingen activator, tPA). Cardiovascular variables were specified as Cardiac Mass (LVMI, LVPWTd, IVSTd), Cardiac Compliance (E/A ratio), Cardiac Contractility (velocity of circumferential shortening--heart rate corrected, Vcf_c), Blood Pressure (DBP), and Myocardial Oxygen Demand (RPP; meridional end-systolic wall stress, mESS).

For comparative purposes, several variables included in the present study were the same as those tested in the Klaus et al. (2009) study. Not all of the variables were identical to those used in the Klaus et al. (2009) study however. In the Klaus et al. (2009) study, for example, IR was assessed using the euglycemic hyperisulinemia clamp method with insulin sensitivity (M) defined as the mean exogenous glucose disposal rate in mg/kg/minute. Due in large part to the presence of patients with DM2 in the present study, HOMA-IR, calculated from glucose and insulin values obtained following administration of an OGTT, was used as an index of IR. In addition, PAI-1 was used as the biomarker for impaired fibrinolysis and FS was used as an index of contractility in the present study. Due to analytic constraints (e.g., a lack of correlation among a factor's indicators or an inability to achieve model convergence) encountered in the creation of particular latent factors, the following variables were analyzed as separate indicators instead of latent constructs in the present study: 1) HDL-C and TRIG were analyzed separately instead of a Lipidemia latent variable, and 2) RPP was analyzed separately instead of a Myocardial Oxygen Demand latent variable. Because SBP was associated with a limited number of model variables compared to DBP, DBP was used as the sole index of Blood Pressure. In sum, the MetS variables tested in the present analyses included Central Adiposity (WC), Insulin Sensitivity (HOMA-IR), Inflammation (CRP; IL-6), Glucose Tolerance (G-AUC), Lipidemia (TRIG and HDL-C as separate indicators), Blood Pressure (SBP; DBP), and Fibrinolysis (PAI-1). Cardiac variables were specified

as Cardiac Mass (LVMI, LVPWTd, IVSTd), Cardiac Compliance (E/A ratio), Cardiac Contractility (FS), and Myocardial Oxygen Demand (RPP).

Given the relationships identified in the literature linking cynical hostility and CHD, a secondary objective of the present study was to assess the associations between CynHo and the MetS risk factors of IR and central adiposity. As such, pathways were specified and tested between CynHo, WC, and HOMA-IR. Age, sex, and race/ethnicity were entered as covariates for all factors in each SEM analysis. Additional covariates were specified for some of the variables based on theory including smoking history with Inflammation and CynHo. The most parsimonious models possessing both statistical and theoretical validity were interpreted. All statistical modeling was performed using M*plus* 3.01 software (Muthen & Muthen, 2006).

Chapter 3: Results

3.1 Data adjustments

The following variables were transformed using a natural log function to normalize their distribution: WC, HOMA-IR, G-AUC, PAI-1, CRP, IL-6, HDL-C, TRIG, DBP, E/A ratio, and RPP.

3.2 Sample characteristics

Demographic, personality, and behavioral characteristics of the sample are presented in Table 1. Study participants ranged in age from 27 to 72 years with a mean age of 53.31 (SD = 8.79) years. Participants were predominantly male (69.4%) and of Hispanic ethnicity (81.7%). Other ethnicities represented in the sample included non-Hispanic Blacks (14%), non-Hispanic Caucasians, and Pacific Islanders (4.3% collectively). Just over half of the participants were married (53.2%) and a slightly greater number (60.2%) were employed at least part-time prior to their MI. The average level of education was 11.88 (SD = 3.17) years and the average annual household income was $17,300 (SD = $14,800). The majority of participants (74.7%) were previous smokers, smoking for an average of 28.10 (SD = 13.80) years. As of baseline data collection, 21.5% were current smokers. Average full-scale CMHo and Cyn subscale scores were 23.43 (SD = 9.36) and 7.51 (SD = 3.38) respectively.

Table 2 presents descriptive statistics on the medical and index MI characteristics of the sample. For 78% of the participants, the index MI was their first MI experience. Approximately equal numbers of patients experienced Q wave (47.8%) versus non-Q wave (52.2%) infarctions, occurring primarily in the

inferior (62.4%) and anterior (45.1%) regions of the heart. Regarding the severity of the index MI, most patients (67.2%) had a Killip class score of 1 (i.e., less severe) on the 4-point scale. Patients' mean LV ejection fraction upon study entry was 50.17% (SD = 5.51). Applying NCEP ATP-III criteria, a substantial portion of study participants (79.0%) met the minimum requirements (i.e., 3 symptoms) for MetS diagnosis; several (49.5%) exhibited 4-5 symptoms. 37.6% of patients met the criteria for DM2 via values obtained on the OGTT; 28.6% of these individuals are insulin-treated. An additional 33.3% of the sample demonstrated impaired glucose tolerance. The majority of patients were taking antihypertensive, anticoagulation, and lipid-lowering medications (99.5%, 92.5%, and 87.6% respectively). Participants had an average BMI of 29.63 (SD = 5.01) kg/m^2.

Table 3 depicts descriptive statistics for the NCEP ATP-III defined MetS variables analyzed in this study. With respect to the central adiposity factor, patients' waist circumferences ranged from 71.12 to 135.26 centimeters (cm) with a mean of 98.47 (SD = 13.28) cm. Average fasting glucose and insulin levels were 110.05 (SD = 55.87) mg/dL and 13.06 (SD = 9.45) μU/mL respectively, resulting in a mean HOMA-IR value of 3.78 (SD = 3.56). The mean glucose AUC value, calculated only in patients without DM2, was 149.60 (SD = 44.69) mg/dL/120 minutes. With respect to lipidemia indices, participants' mean HDL-C and TRG concentrations were 40.01 (SD = 10.33) and 132.45 (SD = 78.83) mg/dL respectively. Patients' SBP ranged from 84.67 to 198.33 mmHg with an average of 124.01 (SD = 21.41) mmHg. DBP values ranged from 51.33

to 111.33 mmHg with a mean of 75.01 (SD = 11.74) mmHg. Statistics for 2 supplementary factors thought to contribute significantly to MetS processes, inflammation and impaired fibrinolysis, are also presented. The average PAI-1 value for patients in the sample was 39.13 (SD = 33.30) ng/mL. Participants' mean IL-6 and CRP values were 4.16 (SD = 3.92) pg/mL and 5.69 (SD = 9.19) mg/L respectively. Additional statistics are presented for CRP with values greater than 10 removed from the calculations based on recent research suggesting that such values likely indicate acute infection instead of CHD-related inflammation (Pearson, Mensah, Alexander, Anderson, Cannon, et al., 2003; Retterstol, Eikvar, Bohn, Bakken, Erikssen, et al., 2002). When these data were removed, the sample mean for CRP was 2.85 (SD = 2.57) mg/L.

Descriptive statistics for the cardiac structure and function variables analyzed in this study are presented in Table 4. With respect to cardiac structure indices, patients had a mean LVMI of 93.86 (SD = 11.97) $g/m^{2.7}$, a mean LVPWTd of 1.52 (SD = 1.52) cm, and a mean IVSTd of 1.19 (SD = 0.14) cm. Participants' E/A ratios, an index of cardiac compliance, ranged from 0.49 to 3.43 with an average of 1.18 (SD = 0.53). FS, an index of cardiac contractility, had a mean value of 19.70 (SD = 4.79) percent in this sample. Finally, patients' mean resting RPP value, an index of myocardial oxygen demand, was 87.65 (SD = 21.12) mmHg · beats/minute.

3.3 Bivariate associations

3.3.1 Intercorrelations among physiological variables.

Table 5 displays the Pearson correlations among MetS and CV variables analyzed in this study. WC demonstrated robust positive associations with a number of MetS indices including HOMA-IR, G-AUC, DBP, CRP, IL-6, and PAI-1. WC demonstrated a significant negative relationship with HDL-C and no association with TRIG. With respect to cardiac variables, WC was positively associated with LVMI, LVPWTd, and IVSTd, was marginally associated with RPP, and unrelated to FS and E/A ratio. HOMA-IR was also robustly associated with several MetS and cardiac structure and function variables. HOMA-IR was positively associated with WC, G-AUC, TRIG, DBP, CRP, PAI-1, RPP, LVPWTd, and IVSTd and negatively with E/A ratio. HOMA-IR was marginally positively associated with LVMI, marginally negatively associated with FS, and unrelated to HDL-C. G-AUC demonstrated strong positive correlations with WC, HOMA-IR, PAI-1, IVSTd, and RPP and negative correlations with FS and E/A ratio. G-AUC demonstrated a positive marginal association with HDL-C. Beyond its strong association with WC, HDL-C was inversely associated with TRIG, PAI-1, LVPWTd, IVSTd, E/A ratio, and CRP (marginally). Beyond its relationship with HOMA-IR, TRIG was negatively related to FS and E/A ratio. DBP demonstrated significant positive correlations with LVMI, LVPWTd, IVSTd, and RPP (in addition to WC and HOMA-IR). CRP was positively associated with IL-6 and PAI-1 (in addition to WC and HOMA-IR) and negatively with FS. IL-6 was also positively correlated with PAI-1 (in addition to WC and CRP) and negatively with FS. PAI-1

demonstrated a positive relation with RPP (in addition to relationships with WC, HOMA-IR, G-AUC, HDL-C, CRP, and IL-6). LVMI was positively associated with RPP and the 2 cardiac wall thickness dimensions (in addition to WC and DBP). FS correlated positively with E/A ratio (in addition to significant negative correlations with G-AUC, TRIG, CRP, and IL-6). E/A ratio, in summary, demonstrated negative associations with HOMA-IR, G-AUC, HDL-C, and TRIG. Similarly, RPP demonstrated positive associations with HOMA-IR, G-AUC, DBP, PAI-1, LVMI, and the 2 cardiac wall thicknesses.

3.3.2 Demographic, behavioral, and physiological variables.

Table 6 depicts statistically significant correlations between selected demographic, behavioral, MetS, and CV variables. The particular demographic and behavioral variables included in the table were selected based on associations reported in prior studies. Among the primary demographic variables, greater age at the collection of baseline data was associated with higher values of G-AUC, HDL-C, IL-6, and RPP. Younger age was related to a lower FS percentage and E/A ratio. With respect to sex, being male was associated with a greater WC, LVPWTd, IVSTd, and E/A ratio and a lower HDL-C value. Being of Hispanic ethnicity was related to a higher TRIG level and a lower HDL-C level. More years of education was marginally associated with a greater WC. Among selected behavioral variables, a history of smoking tobacco was related to higher TRIG concentrations and a greater WC (marginal). Smoking history was also associated with lower HDL-C concentrations. Current tobacco smoking was marginally correlated with increased CRP levels.

3.3.3 Hostility and selected variables.

Correlations between CMHo, CynHo, and selected demographic, behavioral, MetS, and cardiovascular variables are presented in Table 7. Higher scores on the CMHo index were associated with fewer years of education, a history of tobacco smoking, and a DM2 diagnosis (marginal). With respect to physiological variables, higher CMHo scores were related to greater HOMA-IR and higher TRIG and CRP (marginal) concentrations. Higher CynHo scores were associated with fewer years of education and a diagnosis of DM2. With respect to physiological variables, higher CynHo scores were related to greater HOMA-IR, higher TRIG concentrations (marginal), and a greater RPP.

3.4 Structural models

3.4.1 Klaus et al. (2009) model.

Figure 1 depicts the model presented by Klaus et al. (2009) representing associations between MetS and cardiac structure and function variables in a cohort of healthy (i.e., no manifest CHD, no DM2) individuals. Total accounted variance (R^2) in the factors specified in this model is also presented. All pathways presented are statistically significant. Fit indices for the structural model indicated good model fit (CFI=0.960; RMSEA=0.059; SRMR=0.035). With respect to the metabolic factors, the data supported pathways from Central Adiposity to Insulin Sensitivity, Inflammation, Lipidemia, and Fibrinolysis, and from Insulin Sensitivity to Inflammation, Lipidemia, and Glucose Tolerance. Sequential pathways were supported from Inflammation to Glucose Tolerance to Lipidemia to Fibrinolysis. Overall, the model explained 30% of the Insulin

Sensitivity variance, 60% of the Inflammation variance, and 32%, 44%, and 31%, of the variance in Fibrinolysis, Lipidemia, and Glucose Tolerance, respectively. For the cardiovascular factors, significant pathways were observed from Cardiac Mass to DBP, from Cardiac Compliance to Cardiac Contractility, DBP, and Myocardial Oxygen Demand, and from DBP, Cardiac Contractility, and Cardiac Compliance to Myocardial Oxygen Demand. Finally, with respect to pathways among metabolic and CV factors, the data supported paths from Central Adiposity to Cardiac Mass, from Insulin Sensitivity to Cardiac Contractility, from Fibrinolyis to Cardiac Compliance, from Glucose Tolerance to DBP, and from Inflammation to Myocardial Oxygen Demand. Overall, the model explained 49% of the variance in Cardiac Mass, 25% of the variance in Cardiac Compliance, and 17%, 30%, and 82% of the variance in Cardiac Contractility, DBP, and Myocardial Oxygen Demand, respectively.

3.4.2 MetS model in post-MI patients.

Figure 2 presents a model of the associations between CynHo, MetS factors, and CV structure and function in post-MI patients specified and tested in the present study. Significant path coefficients and total accounted variance (R^2) are presented. Fit indices for the structural model indicated a model with good fit (χ^2 (102)=100.65, p=0.52; CFI=1.00; RMSEA=0.00; and SRMR=0.04). Standardized estimates of the factor loadings for the 2 latent variables were: 1) Inflammation: CRP (0.80), IL-6 (0.67); and 2) Cardiac Mass: LVMI (0.41), LVPWTd (0.96), IVSTd (0.89).

With respect to the metabolic factors, the data supported pathways from Central Adiposity to HOMA-IR, Inflammation, HDL-C, and Fibrinolysis. Significant pathways were also identified between HOMA-IR and G-AUC, HOMA-IR and TRIG, and HOMA-IR and Fibrinolysis. The data did not support direct pathways between HOMA-IR and Inflammation and HOMA-IR and HDL-C nor did it support sequential pathways among other MetS factors except that from TRIG to HDL-C. Overall, the model explained 27% of the IR variance, 17% of the Inflammation variance, and 11%, 29%, 14%, and 41% of the variance in Fibrinolysis, HDL-C, TRIG, and Glucose Tolerance, respectively. For the cardiovascular factors, significant pathways were observed between Cardiac Mass and DBP and between DBP and Myocardial Oxygen Demand. Finally, with respect to associations among metabolic and CV factors, significant pathways were observed between Central Adiposity and Cardiac Mass, HOMA-IR and Cardiac Contractility, HOMA-IR and Cardiac Compliance, and HOMA-IR and Myocardial Oxygen Demand. Pathways were not supported from Fibrinolyis to Cardiac Compliance, from Glucose Tolerance to DBP, and from Inflammation to Myocardial Oxygen Demand. Overall, the model explained 33% of the variance in Cardiac Mass, 13% of the variance in Cardiac Compliance, and 6%, 8%, and 45% of the variance in Cardiac Contractility, DBP, and Myocardial Oxygen Demand, respectively. For ease of comparison, Table 8 provides a summary of the variances explained by the variables in both this and the Klaus et al. (2009) model. With respect to CynHo, a direct positive association between CynHo and HOMA-IR was observed.

3.5 Diabetic status

As previously mentioned, DM2 status was assigned to patients with fasting glucose values ≥ 126 and/or 2-hour glucose values ≥ 200 on the OGTT. Based on these criteria, 37.6% of patients in the cohort were identified as diabetic. In addition to associations with HOMA-IR, fasting and post-prandial glucose, fasting and post-prandial insulin, and G-AUC, DM2 status was related to older age, being female, an increased heart rate, greater Myocardial Oxygen Demand, and higher levels of CynHo. E/A ratio demonstrated a marginal association with DM2 status.

3.6 Control variables

Age, sex, and ethnicity were adjusted for in all structural analyses. In the final model (Figure 2), older age was associated with greater HDL-C, myocardial oxygen demand, and G-AUC and reduced cardiac compliance (i.e., a lower E/A ratio). Relative to men, being female was associated with lower cardiac mass, lower WC, higher HDL-C values, and greater IR. With respect to other ethnicities, being Hispanic was associated with lower HDL-C and greater TRIG values. As prior studies have suggested that smoking history and/or current smoking impacts inflammatory markers, pathways were specified from these variables to Inflammation in all the present analyses. No relationships were observed however. Finally, due to associations between tobacco smoking and cynical hostility identified in previous studies, a pathway was specified from smoking history to CynHo in all the present analyses. No associations were observed.

3.7 Analyses with CRP values > 10 removed

As previously mentioned, recent research suggests that CRP values greater than 10 likely reflect acute infection rather than CHD-related inflammation (Pearson, et al., 2003; Retterstol, et al., 2002). Removal of these values from the structural analyses (as well as patients' corresponding IL-6 values) did not significantly change model fit nor did it significantly alter the relationships reported between variables.

Chapter 4: Discussion

The primary aim of the present study was to test a structural model of associations among MetS factors and indices of cardiac structure and function in a cohort of post-MI patients. This model was specified based in part on a model recently specified and tested in Klaus et al.'s (2009) study of healthy individuals. To our knowledge, the present study is the first to analyze these relationships in a single model among patients with extant CVD. The Klaus et al. (2009) model was selected as a starting point for the present study for several reasons including: 1) the fact that it is the most comprehensive MetS model specified to date illustrating the inter-connectedness of MetS factors and their association with CV factors, 2) its use of SEM statistical techniques, and 3) its potential applications for informing interventions in post-MI patients. The relationships observed in the present study suggest that, similar to findings reported in studies of healthy individuals, central adiposity and insulin resistance play primary roles in CV structure and functioning in post-MI patients. Unlike findings in healthy patients, however, mediating relationships between other MetS factors and cardiac structural and functional impairment were not supported. Potential reasons underlying the pattern of relationships observed in the present analyses, as well as important implications of these findings, are discussed in what follows. In addition, similarities and differences in findings between the present study and Klaus and colleagues' (2009) study of healthy individuals, including potential reasons underlying the differences, will also be discussed.

The results of the present study support previous research indicating interrelationships among factors comprising the MetS (Klaus et al., 2009; Pladevall, et al., 2006; Shen, et al., 2006; Shen, et al., 2003). As suggested initially by Reaven and several other investigators since, IR and central adiposity appear to be the driving forces underlying MetS pathophysiology. In both the present study's cohort of post-MI patients and the Klaus et al. (2009) study of healthy individuals (i.e., individuals without HTN, DM2, or CVD), robust relationships were observed between both IR and central adiposity and other components of MetS. While the majority of the research conducted to date concerning these factors has involved healthy individuals, the present study's findings demonstrate that these relationships are not restricted to healthy populations. Supporting this assertion are findings in studies of individuals with DM2 (Bonora et al., 2002) and manifest CVD (Sasso, Carbonara, Nasti, Campana, Marfella, et al., 2004).

In the present study's final model (Figure 2), central adiposity was associated with greater IR and inflammation, decreased HDL-C, and impaired fibrinolysis. IR was associated with increased TRIG, greater glucose intolerance, and impaired fibrinolysis. These associations were consistent with findings from prior studies (e.g., DeFronzo & Ferrannini, 1991; Despres et al., 1989; Folsom et al., 1989; Reaven, 2005; 1988). In contrast to the Klaus et al. (2009) model, however, a direct pathway was not supported between IR and Inflammation. One reason that a direct effect between IR and Inflammation was not found in the present study could be that WC explains a greater proportion of variance in

Inflammation than IR in this cohort due to disease-related factors (i.e., medication use). With respect to interrelationships between other MetS factors specified in the final structural model, the only pathway observed between mediating MetS factors was that between TRIG and HDL-C. While a path between TRIG and HDL-C was expected, the lack of direct effects between other mediating MetS variables was not antipated given previous studies reporting direct relationships between inflammation and HTN (Imatoh et al., 2007), inflammation and dyslipidemia (Chait et al., 2005), and dyslipidemia and HTN (Bog-Hansen et al., 2003). These studies, however, featured cross-sectional designs and were conducted in healthy cohorts. Very few previous studies reported direct relationships among these variables in populations with manifest CHD. Despite the lack of direct associations, it is important to note that several of these factors demonstrated significant bivariate correlations with one another (e.g., G-AUC and PAI-1, HDL-C and PAI-1) or demonstrated nonsignificant associations in the expected direction. With few exceptions, the magnitudes of the relationships observed between MetS factors and the variance they explained in the model were much less robust in the present study compared to those reported in the Klaus et al. (2009) study.

There are several reasons that may account for the lack of direct effects between particular MetS factors, the reduced strength of associations, and/or the lesser percentage of variance explained in the present study compared to the Klaus et al. (2009) study. The most likely reason involves the extent and impact of disease on MetS factors. Whereas the sample in the Klaus et al. (2009) study

consisted of healthy individuals without diagnosed CV or metabolic conditions, the present study's sample was comprised entirely of patients with manifest CVD. Further, more than a third of the patients in the present study were positive for DM2 and 79% met criteria for MetS compared to 12% of the individuals in the Klaus et al. (2009) study. Not surprisingly, the values for the principle metabolic factors were much higher for individuals in the present study. For instance, mean values for WC, fasting glucose, G-AUC, TRIG, CRP, IL-6, and PAI-1 were 98.5 cm, 110.1 mg/dL, 149.6 mg/hr/dL, 132.5 mg/dL, 5.7 mg/L, 4.2 pg/mL, and 39.1 ng/mL, respectively. In the Klaus et al. (2009) study, values for these factors were 88.7 cm, 88.1 mg/dL, 119.9 mg/hr/dL, 108.7 mg/dL, 2.0 mg/L, 2.7 pg/mL, and 18.5 ng/mL, respectively. In addition, the magnitude of the dispersion of values for these factors was much greater in the present study. Although it cannot be concluded with certainty, greater variation in these values may also have affected the relationships observed between specific variables, particularly when potential reasons for the greater variation are considered.

A likely reason underlying the greater variation in values for MetS variables (and the corresponding decrease in the magnitude of associations) in the present study is the use of medications by patients in the post-MI cohort. Whereas individuals taking metabolic medications (e.g., lipid-lowering medications, antihypertensives) were excluded from participating in the Klaus et al. (2009) study, 99.5%, 92.5%, and 87.6% of patients in the present study were taking anti-hypertensives, anticoagulants, and lipid lowering medications, respectively. In addition, 35.5% of the diabetic patients in the present study were

being treated with insulin or oral medications to control hypoglycemia. As all of these medications are prescribed to regulate impaired functioning in a given domain, they function to bring the values of the target physiological variable closer to an established healthy norm. An example of such an effect can be seen with the use of lipid lowering medications. As most individuals with CHD demonstrate elevated LDL-C and TRIG and decreased HDL-C levels, they are generally prescribed one or more of these medications to improve health outcomes. Use of pravastatin, for example, was found to lower LDL-C values by 27% and was effective at reducing CHD death and recurrent MI in a clinical trial of diabetic and glucose intolerant MI patients (Goldberg, et al., 1998). In addition to effects on lipid levels, however, statins have also been found to enhance endothelial NO synthesis (Kaesemeyer, et al., 1999) and reduce PAI-1 (Isaacsohn, et al., 1994) and CRP (Mishra & Basson, 2007) concentrations. In addition to the wide range of effects that a given prescribed medication may have on indices of physiological functioning, patients' biological values may also be affected by a number of other factors including disease comorbidity and severity, medication type, length of time taking a medication, regularity of adherence to a medication, and differential effects of the medication based on individual differences in behavior and constitution. To better understand the impact of such factors on biological values, it would be ideal to measure and statistically control for each of them.

Differences in the range of ages and the proportion of men to women between the studies may also have impacted the associations observed. Prior

studies have reported that both age and sex have an effect on several metabolic variables (Razzouk & Muntner, 2009; Regitz-Zagrosek, Lehmkuhl, & Mahmoodzadeh, 2007). With respect to these variables, the Klaus et al. (2009) study enrolled a greater proportion of females (48.2% versus 30.6%) and younger participants (mean of 35.5 years versus 53.3 years) compared to the present study. Given that many of the factors cited above (e.g., medication adherence) were not adjusted for in the present analyses (with the exception of age and sex), it is likely that a greater portion of variance was left unexplained resulting in weaker or apparently non-existent associations. Despite this fact, however, associations were still observed between WC and HOMA-IR with the other MetS factors.

With respect to relationships among CV factors, findings from the present study indicated that greater cardiac mass was associated with higher DBP and greater myocardial oxygen demand. In addition to being supported by findings in the Klaus et al. (2009) study, these associations are supported by several prior studies in both healthy and diseased populations, including those with longitudinal designs, indicating that individuals with preclinical or manifest CVD often have greater cardiac mass with concomitant elevations in blood pressure and heart rate (Devereux, 1988; Haider, Larson, Franklin, Levy, Framingham Heart Study, 2003). Unlike findings reported in the Klaus et al. (2009) study, no direct paths between other measures of cardiac function, including compliance and contractility, compliance and DBP, and contractility and RPP, were observed

in the structural model of the present study. A marginal bivariate association was observed, however, between compliance and contractility.

Several factors could have contributed to the relative lack of direct associations observed among cardiac function variables in the current study. The most likely explanation involves differences in disease history and/or severity. Individuals who experience MI demonstrate varying degrees of functional impairment both at the time of MI and in the period of time following MI, depending on the severity of the infarction. As no studies to date in CHD populations have identified the extent of functional (or structural) impairment necessary to cause MI or generalizeable effects of MI-induced localized damage on cardiac functional parameters, values of these measures may not vary as a function of one another in this population. It is also conceivable that the medications taken by post-MI patients, particularly anti-hypertensives, may differentially affect systolic and diastolic performance. A recent study reported that administration of beta-blockers to patients resulted in statistically significant reductions in LV ejection fraction, stroke volume, and cardiac output, and an increase in end-systolic volume (Jensen, Jochims, Hunold, Forsting, Barkhausen, et al., 2009).

With respect to pathways between particular MetS factors and measures of CV structure and function, the data collected in the present study supported several of the pathways identified in Klaus et al. (2009). In the final model (Figure 2), a direct path was supported between greater central adiposity and greater cardiac mass. In addition, greater HOMA-IR was directly associated with

increased myocardial oxygen demand and reduced cardiac contractility and compliance. The association between IR and contractility paralleled the results reported in the Klaus et al. (2009) study and a limited number of others (Deng et al., 2007; Goldstein, et al., 2001). While there is limited support for this association in the literature, the present study corroborates findings in individuals with manifest disease. Prior research in patients with MetS (Masugata, et al., 2006) and DM2 (Masugata, Senda, Goda, Yoshihara, Yoshikawa, et al., 2008) has identified IR and obesity to be risk factors for LV diastolic dysfunction independent of LV hypertrophy or systolic dysfunction. This finding is also supported by recent studies of post-MI patients reporting an association between impaired glucose metabolism and diminished compliance (Henareh et al., 2007; Salmasi et al., 2005). Finally, prior research in diabetic patients with acute coronary syndromes supports the association identified between IR and increased RPP (Foo et al., 2004). To our knowledge, the present study is the first to identify the relationship in a sample comprised entirely of post-MI patients.

In contrast to findings from the Klaus et al. (2009) study, no direct pathways were observed between inflammation and myocardial oxygen demand and impaired fibrinolysis and reduced compliance in the present study. Although the lack of these direct associations in the present study does not corroborate the findings in Klaus et al. (2009), no other studies were identified in healthy or CHD populations reporting associations. It was somewhat unexpected that a direct pathway was not identified between LV mass and E/A ratio in both the present and the Klaus et al. (2009) study as prior researchers have suggested that LV

mass has a profound effect on LV compliance (Alpert, 2001; Stork et al., 1995). Since IR demonstrated a direct association with E/A ratio, it may be that a significant portion of the variance in compliance is explained by IR or its related biological effects. It could also be that LV mass affects indices of compliance other than E/A ratio. Despite the lack of a statistically significant path, however, the bivariate correlation was of a moderate magnitude and was in the correct direction. It was also unexpected that a direct association was not identified between central adiposity and E/A ratio. Although prior studies have indicated that measures of obesity are generally not related to indices of systolic function (i.e., LV ejection fraction and FS), several studies have reported a link between central obesity and diastolic dysfunction (Fox et al., 2009; Gong et al., 2009).

In addition to associations between physiological variables, findings from the present study support a direct relationship between CynHo and a component of the MetS, namely HOMA-IR. No associations were found between the full-scale CMHo scale and other MetS components despite prior studies reporting relationships with inflammation (Graham, et. al., 2006; Ranjit, et al., 2007; Zhou et al., 1993), cholesterol (Chikani et al., 2004; Stoney et al., 1999; Waldstein et al., 1990), and coagulation factors (von Kanelet al., 2001). As previously reported, the average full-scale CMHo and CynHo subscale scores were 23.43 (SD = 9.36) and 7.51 (SD = 3.38) respectively. While these values are higher than those reported in prior studies with apparently healthy samples (e.g., Barefoot et al., 1989), they are similar to those reported in patients with manifest CHD (Angerer et al., 2000). An association between CynHo and IR was

anticipated based on previous studies in population-based cohorts (Niaura, et al., 2000; Zhang, et al., 2006) and a study reporting that MetS mediated the relationship between cynical hostility and CVD (Nelson et al., 2004). Based on their path analysis, Niaura and colleagues (2000) reported that the association of hostility with several metabolic indices was mediated by its effects on BMI and WHR. The mediation proposed by these investigators, however, was not supported by the present study as CynHo was not associated with WC in the structural models or bivariate correlation. Zhang and colleagues (2006), in a subsequent study using data from the same population-based cohort, reported that men with high levels of both hostility and norepinephrine had increased HOMA-IR and circulating plasma insulin levels after adjustment for WHR and HTN. While the latter study supports the findings in the present study, associations in the literature to date between hostility and IR have been inconsistent (Philip & Facchini, 1995).

One reason for the inconsistency may be the use of different measures of hostility between studies. Both of the aforementioned studies used the full-scale CMHo index making it more difficult to make an even comparison to the present study. Despite inconsistent findings in the literature between hostility and MetS factors, a recent meta-analysis found that full-scale CMHo scores were significantly related to BMI, WHR, and IR leading the authors to conclude that these factors appear to be particularly important mediators of the relationship between hostility and CHD (Bunde & Suls, 2006).

Given findings from this and other studies identifying a link between various measures of hostility, metabolic dysfunction, and adverse outcomes, it seems apparent that interventions aimed at reducing cynical hostility would be beneficial for all individuals, perhaps even more so for those with manifest CHD. Interventions incorporating health education, CBT, and relaxation training may help individuals reduce negative health behaviors and alter long-established patterns of biological hyper-responsivity. A recent study of men and women participating in a cardiac rehabilitation program featuring an integrated mind/body approach that included components such as smoking cessation, moderate aerobic exercise, nutrition counseling, relaxation response training, and CBT reported significant improvements in patients' medical (blood pressure, lipids, weight, exercise conditioning, frequency of symptoms of chest pain and shortness of breath) and psychological (general severity index, depression, anxiety, and hostility) outcomes (Casey, Chang, Huddleston, Virani, Benson, et al., 2009).

There are several notable limitations associated with the present study. One of the most important limitations is the cross-sectional design of the study which precludes inferring causality among the associations identified. Future studies should investigate the relationships identified in this model employing a longitudinal design, ideally over a period of time greater than one year given research suggesting that cardiac remodeling can occur beyond one year (St John Sutton et al., 1997). It is conceivable that such remodeling could degrade cardiac function despite improvements in MetS factors. Another limitation of the

present study involves the use of different MetS and cardiac variables in some instances relative to those tested in the Klaus et al. (2009) study. Beyond an inability to make direct comparisons between certain specified associations, the present study employed variables that may lack the precision of those used in the Klaus et al. (2009) study. An example is the use of HOMA-IR to measure IR instead of more sensitive measures such as the euglycemic clamp method. While the euglycemic clamp method is considered the gold standard in the measurement of IR, it was not employed in the present study due to cost considerations and the inclusion of patients with DM2 in the sample which generally precludes use of the procedure.

The inclusion of post-MI patients with DM2 in the present study may itself be an important limitation. It is possible that including both diabetic and non-diabetic patients in the same study could confound the results if DM2 status differentially impacts the values of the biological indices measured. Given this possibility, it is important to note that DM2 status was statistically associated with only a limited number of variables employed in the present study. Future studies should assess and compare associations between variables in post-MI patients with and without DM2 to learn whether the present study's findings are generalizeable. Other limitations of the current study are the use of continuous wave Doppler imaging to measure E/A ratio instead of the more technologically advanced tissue Doppler imaging method and a relatively low N.

Despite these limitations, findings from the present study have several implications. Importantly, the current study corroborates many of the

relationships identified in the Klaus et al. (2009) study of healthy individuals between MetS factors and cardiac structure and function and extends them to a post-MI population. The use of SEM techniques to investigate these relationships in a single comprehensive model provides compelling support for the identification of the MetS components having the greatest impact on CV structure and function in this cohort. This is particularly evident for central adiposity and IR which, separately or together, exhibit robust associations with the MetS and cardiac structure and function indices investigated. Given the primary roles played by central adiposity and IR in MetS pathophysiology, coupled with the fact that each of these factors are modifiable, the present study suggests that adverse outcomes may be reduced and/or the progression of CHD halted or perhaps even reversed in post-MI patients. Results from the present study suggest that interventions in post-MI patients should target WC and IR to impact cardiac structure and function. Results from the present study also suggest that CynHo should be addressed in post-MI patients given the association identified between CynHo and IR. Cardiac rehabilitation interventions like the one studied by Casey and colleagues (2009) appear to benefit both psychological and physiological health.

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Table 1

Demographic, Personality, and Behavioral Characteristics of Sample

Variable	N (%)	Mean	SD	Range
Age (years)	186	53.31	8.79	27 - 72
Education (years)	186	11.88	3.17	3 - 21
Annual household income[a]	136	17.30	14.80	0 - 80
Female	57 (30.6)			
Ethnicity/Race				
Hispanic	152 (81.7)			
Black (non-Hispanic)	26 (14.0)			
Other	8 (4.3)			
Married	99 (53.2)			
Employed	112 (60.2)			
Smoking history				
Previous smoker	139 (74.7)			
# of years smoked		28.10	13.80	2 - 63
Current smoker	40 (21.5)			
Cigarettes per day		3.17	8.44	0 - 60
Hostility score				
Total	186	23.43	9.36	4.08 - 43
Cynicism subscale	186	7.51	3.38	0 - 13

Abbreviations: SD, standard deviation.

[a] Represents annual household income in thousands of U.S. dollars.

Table 2
Medical Characteristics of Sample

Variable	N (%)	Mean	SD	Range
Medical characteristics				
Family history of CHD	87 (46.8)			
Prior MI	41 (22.0)			
Prior angina	42 (22.6)			
Prior CABG surgery	14 (7.5)			
Prior PTCA	18 (9.7)			
MetSyn	147 (79.0)			
4 or 5 symptoms[a]	92 (49.5)			
Diabetes mellitus[b]	70 (37.6)			
Insulin treated	20 (10.8)			
Oral hypoglycemic	46 (24.7)			
Diet controlled	20 (10.8)			
Impaired glucose tolerance[c]	62 (33.3)			
HTN	104 (55.9)			
Hypercholesterolemia	104 (55.9)			
Ejection fraction		50.17	5.51	25.9 - 65.1
BMI		29.60	5.20	19.8 - 43.8
Days from MI to baseline		62.25	33.24	28 - 188
Characteristics of index MI				
Infarct type				
Q wave	89 (47.8)			
Infarct location				
Anterior	84 (45.2)			
Inferior	116 (62.4)			
Killip class				
I	125 (67.2)			
II	34 (18.3)			
III	23 (12.4)			
IV	4 (2.2)			
Current medications				
Antihypertensive	184 (99.5)			
Anticoagulant	172 (92.5)			
Lipid lowering	163 (87.6)			

N=186 unless indicated.
Abbreviations: BMI, body-mass index; CABG, coronary artery bypass graft; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; SD, standard deviation.
[a] using the NCEP-ATP III criteria.
[b] defined as fasting plasma glucose values ≥ 126 mg/dL or 2-hour OGTT values ≥ 200 mg/dL.
[c] defined as fasting plasma glucose values from 100-125 mg/dL or 2-hour OGTT values from 149-199 mg/dL.

Table 3

Descriptive Statistics for Metabolic Syndrome Variables

Variable	N	Mean	SD	Range
Central Adiposity				
WC (cm)	186	98.47	13.28	71.12 - 135.26
Insulin Resistance				
Fasting glucose (mg/dL)	183	110.05	55.87	40.20 - 401.00
Fasting insulin (μU/mL)	183	13.06	9.45	2 - 54.90
HOMA-IR	181	3.78	3.56	0.49 - 21.11
Glucose AUC (mg/dL/120 min.)	119	149.60	44.69	68.93 - 455.63
Lipidemia				
HDL-C (mg/dL)	184	40.01	10.33	22 - 81
TRIG (mg/dL)	184	132.45	78.83	24 - 572
Blood Pressure				
SBP (mmHg)	186	124.01	21.41	84.67 - 198.33
DBP (mmHg)	186	75.01	11.74	51.33 - 111.33
Inflammation				
CRP (mg/L)	183	5.69	9.19	0.15 - 63.16
CRP[a] (mg/L)	156	2.85	2.57	0.15 - 9.87
IL-6 (pg/mL)	183	4.16	3.92	0.38 - 22.39
Fibrinolysis				
PAI-1 (ng/mL)	184	39.13	33.30	4 - 220.10

Abbreviations: AUC, area under the curve; CRP, C-reactive protein; DBP, diastolic blood pressure; HDL-C, high density lipoprotein cholesterol; HOMA-IR, homeostatic model of insulin resistance; IL-6, interleukin-6; PAI-1, plasminogen activator inhibitor-1; TRIG, triglycerides; WC, waist circumference.

[a] CRP values > 10 were removed from data to calculate values.

Table 4

Descriptive Statistics for Cardiac Variables

Variable	N	Mean	SD	Range
Cardiac Mass				
LVMI ($g/m^{2.7}$)	167	93.86	11.97	71.54 - 134.43
LVPWTd (cm)	167	1.52	0.20	1.14 - 2.38
IVSTd (cm)	167	1.19	0.14	0.90 - 1.89
Cardiac Compliance				
E/A ratio	167	1.18	0.53	0.49 - 3.43
Cardiac Contractility				
FS (%)	167	19.70	4.79	9.06 - 32.77
Myocardial Oxygen Demand				
RPP[a]	186	87.65	21.12	51.00 - 152.53

Abbreviations: E/A, early to late diastolic filling; FS, fractional shortening; IVSTd, interventricular septal thickness at diastole; LVMI, left ventricular mass index; LVPWTd, left ventricular posterior wall thickness at diastole; RPP, rate-pressure product.

[a] RPP =[resting systolic blood pressure (mmHg) x resting heart rate (beats/minute)]/100

Table 5

Intercorrelation Matrix of Metabolic Syndrome and Cardiovascular Variables

Variable[a]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1. WC	1														
2. HOMA-IR	.39**	1													
3. G-AUC[b]	.21*	.50**	1												
4. HDL-C	-.30**	-.08	.15+	1											
5. TRG	.09	.22**	.09	-.21**	1										
6. DBP	.16*	.15*	.08	-.05	.02	1									
7. CRP	.32**	.18*	.08	-.12+	.10	.11	1								
8. IL-6	.20*	.12	.10	-.12	.02	-.05	.53**	1							
9. PAI-1	.29**	.28**	.25**	-.17*	.08	.08	.20**	.16*	1						
10. LVMI	.30**	.13+	.15	-.09	-.01	.16*	.13+	.10	.06	1					
11. LVPWTd	.51**	.22**	.15	-.19*	.05	.29**	.08	.08	.12	.39**	1				
12. IVSTd	.48**	.24**	.19*	-.16*	.01	.22*	.05	.02	.12	.35**	.85**	1			
13. FS	-.08	-.14+	-.20*	-.04	-.29**	.05	-.20**	-.19*	.02	-.12	.02	.05	1		
14. E/A	.04	-.21**	-.22*	-.28**	-.19*	.05	.06	.04	-.04	-.13	-.03	.01	.15*	1	
15. RPP	.14+	.23**	.22**	.01	.03	.65**	.08	.05	.15*	.22**	.29**	.21**	.05	-.08	1

Abbreviations: AUC, area under the curve; CRP, C-reactive protein; DBP, diastolic blood pressure; HDL-C, high density lipoprotein cholesterol; HOMA-IR, homeostatic model of insulin resistance; IL-6, interleukin-6; PAI-1, plasminogen activator inhibitor-1; TG, triglycerides; WC, waist circumference; E/A, early to late diastolic filling; FS, fractional shortening; IVSTd, interventricular septal thickness at diastole; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LVPWTd, left ventricular posterior wall thickness at diastole; RPP, rate-pressure product.

[a] N = 167 – 186; [b] N = 119.

* $p < .05$; ** $p < .01$; + p > .05 but < .10.

Table 6

Significant Correlations between Selected Demographic, Behavioral, Metabolic Syndrome and Cardiovascular Variables

Variable[a]	Age	Sex	Hispanic[c]	Education	Smoking Hx	Smoking - Current
1. WC		.34**		.14+	.14+	
2. HOMA-IR						
3. G-AUC[b]	.30**					
4. HDL-C	.21**	-.43**	-.21**		-.20**	
5. TRIG			.31**		.14*	
6. DBP						
7. CRP						.13+
8. IL-6	.22**					
9. PAI-1						
10. LVMI						
11. LVPWTd		.30**				
12. IVSTd		.28**				
13. FS	-.15*					
14. E/A	-.25**	.16*				
15. RPP	.14*					

Abbreviations: WC, waist circumference; HOMA-IR, homeostatic model of insulin resistance; G-AUC, glucose - area under the curve; HDL-C, high density lipoprotein cholesterol; TRIG, triglycerides; DBP, diastolic blood pressure; CRP, C-reactive protein; IL-6, interleukin-6; PAI-1, plasminogen activator inhibitor-1; LVMI, left ventricular mass index; LVPWTd, left ventricular posterior wall thickness at diastole; IVSTd, interventricular septal thickness at diastole; FS, fractional shortening; E/A, early to late diastolic filling; RPP, rate-pressure product; Hx, history.

[a] N = 167 – 186 unless otherwise indicated.

[b] N = 119.

[c] Given the high percentage of Hispanics in the study, a dichotomous ethnicity variable was created (i.e., Hispanic and non-Hispanic)

* $p < .05$; ** $p < .01$; + $p > .05$ but $< .10$

Table 7

Correlations between Hostility Scales and Selected Demographic, Behavioral, MetSyn, and Cardiovascular Variables

Variable[a]	CM Hostility (total)	CM Cynical Hostility
Demographic variables		
Age	.041	.081
Sex	.079	-.018
Education	-.266**	-.233**
Hispanic	.068	.039
DM2 status	.134+	.206**
Behavioral variables		
Smoking history	.170*	.100
Current smoking	.092	.040
Cigarettes per day	.048	.001
MetSyn variables		
Waist circumference	-.056	-.058
HOMA-IR	.143*	.188*
Glucose AUC[b]	.069	.087
HDL cholesterol	.066	.051
Triglycerides	.158*	.134+
Diastolic blood pressure	-.025	-.028
C-reactive protein	.126+	.094
Interleukin-6	.079	.044
PAI-1	.061	.065
Cardiac variables		
LVMI	.034	.016
LVPWTd	-.021	-.056
IVSTd	-.004	-.062
Fractional shortening	-.041	-.063
E/A ratio	-.007	-.099
Rate-pressure product	.117	.161*

Abbreviations: HOMA-IR, homeostatic model of insulin resistance; AUC, area under the curve; PAI-1, plasminogen activator inhibitor-1; LVMI, left ventricular mass index LVPWTd, left ventricular posterior wall thickness at diastole; IVSTd, interventricular septal wall thickness at diastole.

[a] N = 167 – 186.

[b] N = 119.

* $p < .05$; ** $p < .01$; + p > .05 but < .10.

Table 8

Variance Explained (R^2) By Variables in Models

Variable	Model 1	Model 2
Insulin Resistance[a]	.30	.27
Glucose Tolerance	.31	.41
Lipidemia[b]	.44	
HDL-C		.29
TRIG		.14
Diastolic Blood Pressure	.30	.08
Inflammation	.60	.17
Fibrinolysis	.32	.11
Cardiac Mass	.49	.33
Cardiac Contractility	.17	.06
Cardiac Compliance	.25	.13
Myocardial Oxygen Demand	.82	.45

Abbreviations: HDL-C, high density lipoprotein cholesterol; TRIG, triglycerides.

[a] Value reflects insulin sensitivity (M) in Model 1.

[b] Variable comprised of triglycerides, HDL cholesterol, and ratio of total cholesterol to HDL cholesterol.

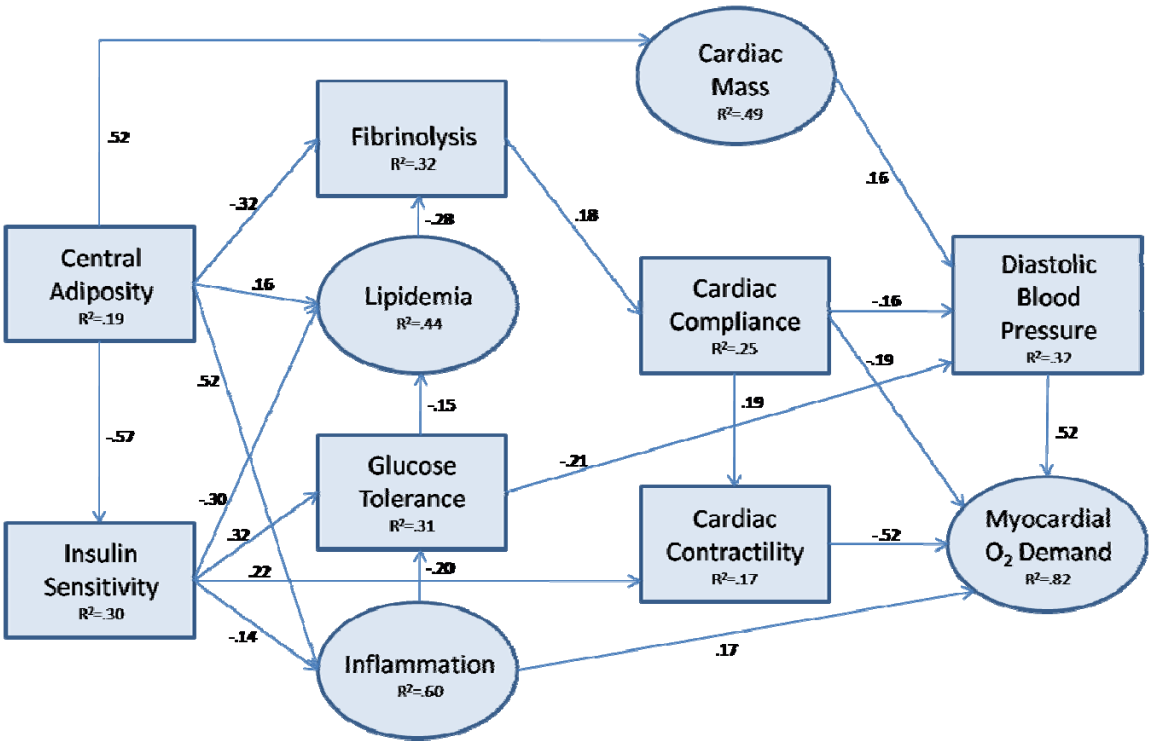

Figure 1 – Structural model proposed by Klaus et al. (2009) delineating associations between metabolic syndrome indices and cardiovascular structure and function in healthy individuals. All model variables are adjusted for age, sex, and Hispanic ethnicity.

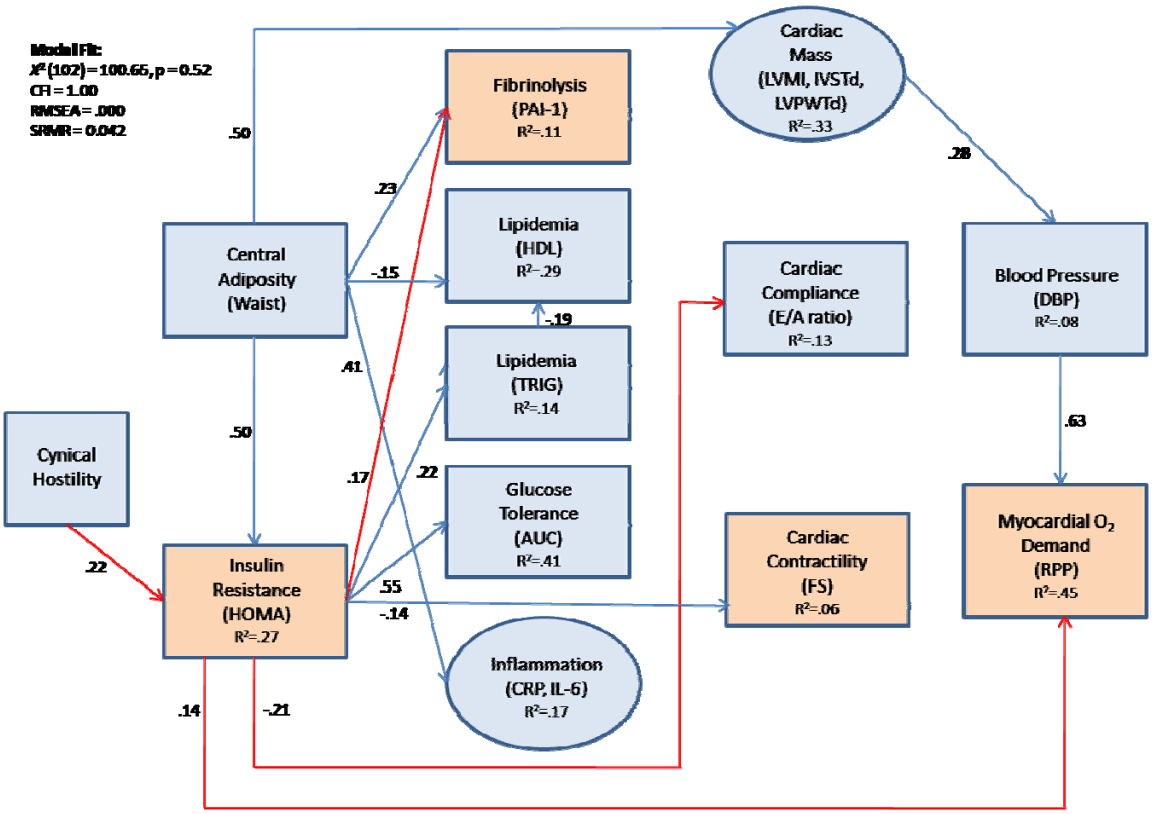

Figure 2 – Structural model delineating associations between cynical hostility, metabolic syndrome indices, and cardiovascular structure and function in post-MI patients. All model variables are adjusted for age, sex, and Hispanic ethnicity. Cynical Hostility and Inflammation are also adjusted for smoking history.

APPENDIX

Selected Abbreviations

BMI	Body mass index
CBT	Cognitive behavioral therapy
CHD	Coronary heart disease
CMHo	Cook-Medley hostility scale
CRP	C-reactive protein
CVD	Cardiovascular disease
CynHo	Cynical hostility subscale
DBP	Diastolic blood pressure
E/A	Ratio of early to late diastolic filling velocity
FS	Fractional shortening
GL-AUC	Area under the curve for glucose during OGTT
HDL-C	High-density lipoprotein cholesterol
HOMA-IR	Homeostatic model assessment of insulin resistance
HTN	Hypertension
IL-6	Interleukin-6
IR	Insulin resistance
IVSTd	Inter-ventricular septal thickness at end-diastole
LV	Left ventricular
LVEF	Left ventricular ejection fraction
LVMI	Left ventricular mass index
LVPWTd	Left ventricular posterior wall thickness at end-diastole
mESS	Meridional end systolic stress
MetS	Metabolic syndrome
OGTT	Oral glucose tolerance test
PAI-1	Plasminogen activator inhibitor-1
RPP	Rate-pressure product
SBP	Systolic blood pressure
SNS	Sympathetic nervous system
TRIG	Triglycerides
Vcf_c	Velocity of circumferential shortening, corrected
WC	Waist circumference