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Cardiac Autonomic Control in Patients with Metabolic Syndrome

Jonathan Mitchell
University of Central Florida

CARDIAC AUTONOMIC CONTROL IN PATIENTS WITH METABOLIC SYNDROME

by

JONATHAN CLOVIS MITCHELL
B.M. University of Miami, 2007
M.A. University of Central Florida, 2010
M.S. University of Central Florida, 2013

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ABSTRACT

Metabolic syndrome (MetS) encompasses metabolic abnormalities that substantially increase risk for chronic illnesses. MetS and stress are closely related; the pathophysiology of MetS involves dysregulated stress response in both the physiological and psychological domains. In an effort to further clarify the relationship between metabolic abnormalities and autonomic dysregulation, we used ambulatory impedance cardiography (ICG) to examine indicators of cardiac autonomic control (CAC) in a sample of 50 adult primary care patients with and without MetS. Indices of sympathetic and parasympathetic influences on cardiovascular functioning were assessed in the context of psychological stressors and compared across experimental groups and examined in relation to self-reported health measures. Primary results suggest that while our experimental groups did not differ significantly on baseline measures, patterns of responses to experimentally induced stressors were largely consistent with our predictions, and demonstrate that individuals with MetS responded to stress cues with more maladaptive CAC scores. Moreover, in line with previous work, we found that elements of CAC in our sample were predictive of both cardiovascular disease and self-reported environmental quality of life. Overall, our results suggest that maladaptive physiological manifestations of the stress response are evident among individuals with MetS and may also be related to long-term health outcomes. The present study carries implications for both evaluation and assessment as well as treatment delivery and monitoring. In addition, the ambulatory nature of data collection demonstrated here supports trends toward mHealth and related initiatives in emerging modes of healthcare delivery.

Dedicated to Kayla

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I would like to recognize my entire family, particularly my mother and father, whose enduring and unfailing love enable me to undertake daily the challenges that I face.

Above all, I thank my wife. None of this is possible without you.

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LIST OF ACRONYMS

Ag/AgCl	Silver/Silver chloride
ANCOVA	Analysis of covariance
ANS	Autonomic nervous system
ApEn	Approximate entropy
AUDIT	Alcohol Use Disorders Identification Test
AV	Arterioventricular
BMI	Body mass index
BP	Blood pressure
CAB	Cardiac autonomic balance
CAC	Cardiac autonomic control
CAR	Cardiac autonomic regulation
CNS	Central nervous system
CO	Cardiac output
CV	Cardiovascular
CVD	Cardiovascular disease
CVR	Cardiovascular reactivity
CVS	Cardiovascular system
DBP	Diastolic blood pressure
DM2	Diabetes mellitus, Type 2
DV	Dependent variable
ECG	Electrocardiography

fBG	Fasting blood glucose
FIML	Full information maximum likelihood
HADS-A	Hospital Anxiety and Depression Scale – Anxiety subscale
HADS-D	Hospital Anxiety and Depression Scale – Depression subscale
HC	Healthy Control
HDL	High-density lipoprotein
HF	High Frequency
HPA	Hypothalamic-pituitary-adrenal
HR	Heart rate
HRV	Heart rate variability
HWI	Health and wellness interview
ICG	Impedance cardiography
IPAQ-S	International Physical Activity Questionnaire – Short Form
LA	Left atrium
LV	Left ventricle
LVET	Left ventricular ejection time
MA	Mental arithmetic
MANCOVA	Multivariate analysis of covariance
MAP	Mean arterial pressure
MAR	Missing at random
MetS	Metabolic Syndrome
MI	Myocardial infarction

MMAS-8	Morisky Medication-Taking Assessment Scale – 8-item Version
NHLBI	National Heart, Lung and Blood Institute
OBP	Oscillometric blood pressure
PEP	Pre-ejection Period
PNS	Parasympathetic nervous system
QLE	WHO Quality of Life–Brief–Environmental Domain
QLPH	WHO Quality of Life–Brief–Physical Domain
QLPS	WHO Quality of Life–Brief–Psychological Domain
QLS	WHO Quality of Life–Brief –Social Domain
RA	Right atrium
RSA	Respiratory sinus arrhythmia
RV	Right ventricle
SA	Sinoatrial
SBP	Systolic blood pressure
SNS	Sympathetic nervous system
SV	Stroke volume
TPR	Total peripheral resistance
UCFH	University of Central Florida Health Clinic
WHO	World Health Organization
WHOQOL-B	World Health Organization Quality of Life Questionnaire – Brief Form

CHAPTER ONE: INTRODUCTION AND LITERATURE REVIEW

Metabolic syndrome (MetS; also labeled "insulin resistance syndrome," DeFronzo, & Ferrannini, 1991) represents a constellation of metabolic abnormalities that substantially increase risk for cardiovascular disease (CVD) and diabetes mellitus, type 2 (DM2). MetS is related closely to lifestyle factors (Grundy et al., 2006; Tentolouris, Argyrakopoulou, & Katsilambros, 2008), but stress also contributes to the development and maintenance of MetS (Blumenthal et al., 2012; Hjemdahl, 2002; Rosmond, 2005; Schwartz et al., 2003; Vitaliano et al., 2002). Moreover, embodied psychological phenomena during periods of stress are important determinants of illness (Adler, 2002; Blascovich & Mendez, 2000; Burke, Davis, Otte, & Mohr, 2005; Cacioppo & Tassinary, 1990; Carroll et al., 2012; Celano et al., 2013; Lambert, Straznicky, Lambert, Dixon, & Schlaich, 2010; Prkachin, Williams-Avery, Zwaal, & Mills, 1999). In MetS, one unresolved issue involves the extent to which these determinants are pathophysiological, and how these determinants relate to disease progression. The purpose of this investigation is to examine cardiovascular responses to stress among individuals with MetS and to explore the impact of these responses on health behavior and treatment adherence.

Metabolic Syndrome

Clinical Features

MetS is not a new condition (Kylin, 1923), and a growing body of research has dramatically improved our understanding of its role in chronic illness. In an effort to reconcile discrepant diagnostic criteria, The American Heart Association and the National Heart, Lung, and Blood Institute (NHLBI; Grundy et al., 2006), issued a joint report clarifying the five clinical

features of MetS. They include (1) elevated waist circumference, (2) elevated triglycerides (3) reduced high-density lipoprotein (HDL) cholesterol, (4) elevated blood pressure (BP) and (5) elevated fasting blood glucose (fBG). Table 1 outlines MetS criteria as defined by the NHLBI.

Table 1. Metabolic Risk Measurement and Diagnostic Criteria for Metabolic Syndrome

Measure	**Clinical Threshold/Cutoff**	**Normal Range**
1. Waist circumference	≥ 102 cm in men ≥ 88 cm in women	< 102 cm in men < 88 cm in women
2. Triglycerides	≥ 150 mg/dL *– or –* On drug treatment for elevated triglycerides	< 150 mg/dL
3. High-density lipoprotein	< 40 mg/dL in men < 50 mg/dL in women *– or –* On drug treatment for reduced HDL	40-49 mg/dL in men 50-59 mg/dL in women *– or –* 60 mg/dL and above
4. Blood pressure	≥ 130 mm Hg systolic *– or –* ≥ 85 mm Hg diastolic *– or –* On antihypertensive drug treatment in a patient with a history of hypertension	≤ 120 mm Hg systolic ≤ 80 mm Hg diastolic
5. Fasting glucose	≥ 100 mg/dL *– or –* On drug treatment for elevated glucose	70-99 mg/dL

Note: Adapted from Grundy et al. (2006) Reprinted with permission, Circulation.2005;112:2735-2752, ©2005, American Heart Association, Inc.; Additional sources: The Mayo Clinic,

These risk factors are all interrelated, and while visceral adiposity (Carr et al., 1994) and insulin resistance (Ferrannini, Haffner & Mitchell, 1991) are thought to underlie metabolic abnormalities, there is most likely not a single cause for the syndrome (Grundy et al., 2006; Canale et al., 2013).

Developmental Features

Onset of MetS is difficult to determine because the component features develop gradually, and can wax and wane in the early stages of the syndrome. Genetic factors predispose individuals to some degree of metabolic dysregulation. There is evidence that genetically moderated hormonal hypersensitivity along the hypothalamic-pituitary-adrenal (HPA) axis is important in the maintenance of MetS (Rosmond, 2005). It appears also that metabolic and biochemical processes differ as a function of race (Anderson, McNeilly, & Myers 1993; Haffner et al., 1996), corroborating genetic contributions. Such biological and genetic influences become amplified by lifestyle factors including physical inactivity and poor diet.

Lifestyle factors increase the propensity for obesity and insulin resistance, the two underlying risk factors for MetS. Park et al. (2003) studied lifestyle and physiological variables that contribute to MetS in a sample of 12,363 individuals drawn from the Third National Health And Nutrition Examination Survey (NHANES III). Findings indicate that men (who are at an increased risk for metabolic syndrome, Katano et al., 2010), were significantly more likely to develop MetS if they were inactive and consumed high quantities of carbohydrates. Other lifestyle variables (e.g., smoking, alcohol use) are linked to increased odds of developing MetS (Katano et al., 2010; Park et al., 2003; Zhu, St. Onge, Heshka, & Heymsfield, 2004). Therefore, treatment for MetS first and foremost incorporates behavior change and lifestyle modification.

Stress and Metabolic Risk

Stress increases metabolic risk, and has been associated with MetS and other chronic conditions on theoretical and empirical grounds (Blumenthal et al., 1995; Brunner et al., 2002; Canale et al., 2013; Koivistoinen et al., 2010; Novak et al., 2013; Rosmond, 2005; Tentolouris et

al., 2008; Thayer, Yamamoto, & Brosschot, 2010). Several trends in the literature support this conclusion.

First, prevalence rates of MetS are higher among individuals facing chronic psychosocial stressors compared to those who are not. It has been estimated that between 6% and 23% of the variance in MetS can be attributable to chronic stress (Vitaliano et al. 2002). Chandola, Brunner, and Marmot (2006) analyzed data from over ten thousand individuals in the Whitehall II study and found that the accumulation of chronic work stress over a 14-year period increased odds for MetS development by 125 percent.

Second, physiological mechanisms underlying insulin resistance and obesity have been linked to autonomic activation (Canale et al., 2013; Flaa et al., 2008; Hjemdahl, 2002; Lambert et al., 2010). Masuo, Mikami, Ogihara, and Tuck (1997) concluded that heightened physiological activation was predictive of obesity and hypertension over a 10-year period among both hypertensive and normotensive adults. This association has been argued on conceptual grounds as well. Julius, Valentini, and Palatini (2000) proposed that physiological activation in response to stress impacts obesity directly through altering beta-adrenergic sensitivity, and indirectly through increasing insulin resistance.

Finally, several studies have concluded that autonomic dysregulation precedes development of MetS (DeCouck, Mravec, & Gidrron, 2012; Koivistoinen et al., 2010; Masi, Hawkley, Rickett, & Cacioppo, 2007; Tentolouris et al., 2008, Thayer et al., 2010). Notably, Chang et al. (2010) examined a sample of pre-disease participants at risk for MetS and found that those with more risk factors evidenced maladaptive physiological stress patterns in response to

standardized stressors. In addition, Licht and colleagues (2013) found that in a sample of 1933 adults, measures of autonomic dysregulation were predictive of MetS risk factors two years later.

A core theme in the investigations described above is cardiovascular reactivity (CVR). The physiology of CVR and the anatomy of the cardiovascular system (CVS) are central indicators of the body's typical stress response and can help clarify why stress becomes pathogenic for these patients (Curtis & O'Keefe, 2002; Lambert et al., 2010; Soares-Miranda et al., 2012; Tentolouris et al., 2008).

The Cardiovascular System

The heart, arteries, veins, and capillaries constitute the CVS – a system highly responsive to biological and environmental changes. The CVS is under the control of both intrinsic and extrinsic mechanisms (Berntson, Quigley, & Lozano, 2007; Andreassi, 2007).

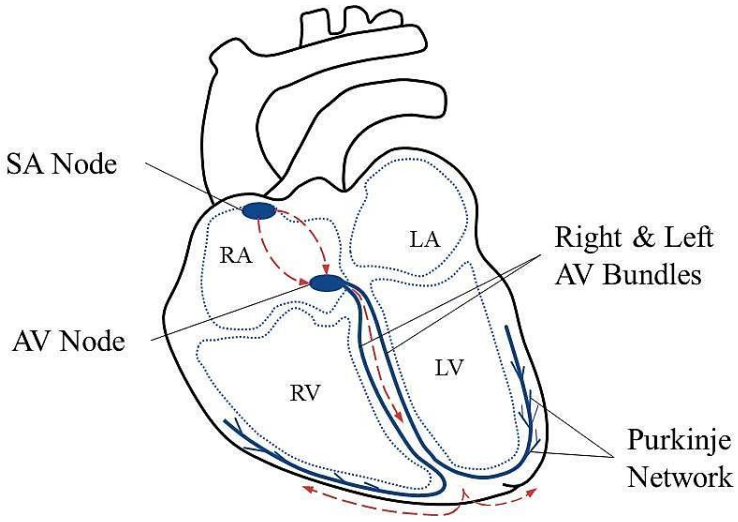

Figure 1. Anatomy and Physiology of Electrical Elements Controlling the Cardiac Cycle. Adapted from Berntson et al. (2007). Note: Dotted lines denote direction of depolarization; RA = Right Atrium; LA = Left Atrium; RV = Right Ventricle; LV = Left Ventricle.

Intrinsic Control

Electrochemical activity within the myocardium controls the cardiac cycle. The cardiac cycle refers to the sequence of events in the heart that occur from one beat to another. The cycle consists of two epochs: systole, during which myocardium contracts and pumps blood, and diastole, during which the myocardium relaxes and the chambers fill with blood (Berntson et al., 2007; Andreassi, 2007).

Systole and diastole occur through depolarization of electrically active muscle fibers within the heart beginning in the sinoatrial (SA) node located in the right atrium (see Figure 1). Depolarization travels downward to the atrioventricular (AV) node, initiating contraction of the atria, and completely filling the ventricles. The electrical impulse propagates down the right and left bundle branches terminating in the Purkinje network. This final sequence of depolarization causes ventricular contraction, which ejects blood toward the periphery and lungs. Polarization occurs during the diastolic epoch as negative pressure builds in the ventricles, causing an inflow of blood to the atria (Andreassi, 2007).

Electrocardiogram (ECG) is a common method used to assess cardiac function (Andreassi, 2007; Berntson et al., 2007). ECG records electrical fluctuations on the surface of the skin caused by myocardial depolarization. This electrical fluctuation translates to a specific waveform, characterized by upward and downward deflections over time. In the ECG signal, the QRS complex denotes depolarization down the AV bundle and corresponds to ventricular contraction. This signal is used to derive measures of cardiac activity including heart rate (HR) and heart rate variability (HRV). Figure 2 depicts the standard ECG waveform (including the QRS complex) and identifies corresponding physiological features of the cardiac cycle.

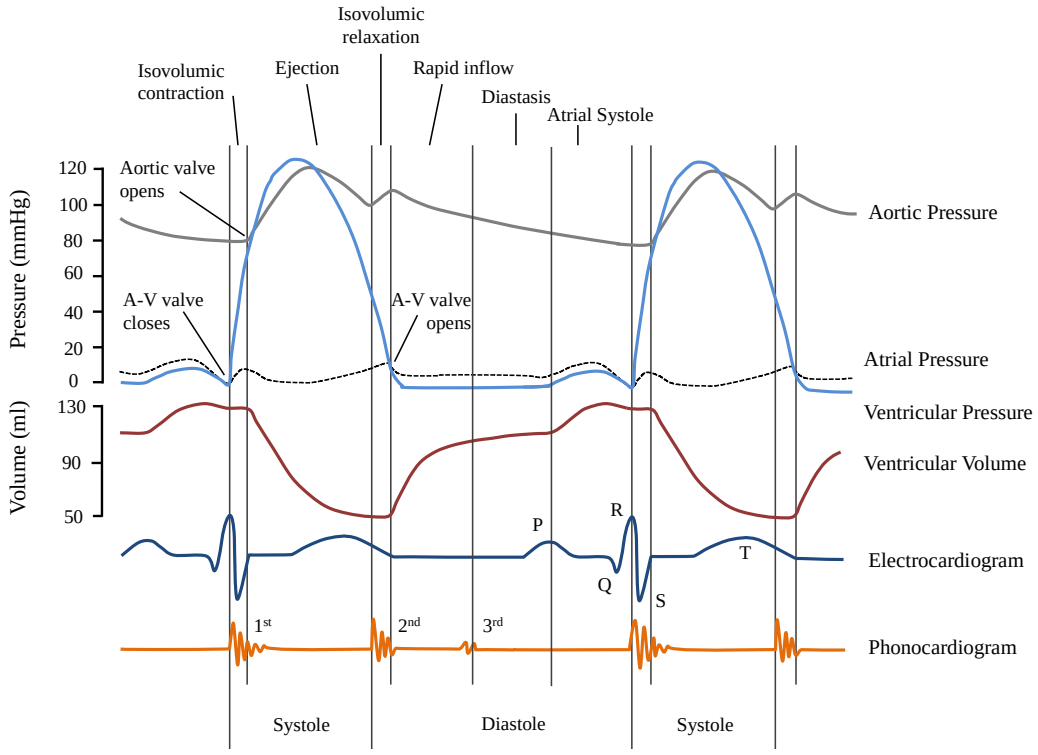

Figure 2. Comparison of Physiological, Electrical, and Phonographic Features of the Cardiac Cycle Over Time. (Adapted from Berntson et al., 2007).

Impedance cardiography (ICG) is a non-invasive procedure that permits measurement of physiological features in the heart. ICG records the voltage differential between opposing pairs of dorsal and ventral sensors by applying a high-frequency, constant-current electrical flow to the torso. Contrary to ECG's measurement of electrical activity, ICG facilitates computation of systolic (pre-ejection period) and volumetric indices (e.g., stroke volume) of cardiac functioning. There is some evidence that hemodynamics in individuals with MetS may be compromised (i.e., irregular; Wahba & Mak, 2007) due to the significant impact of metabolic dysregulation on the cardiovascular system. However, in a thorough investigation involving approximate entropy

(ApEn) analysis, Guerra et al. (2011) did not detect differences in systolic or volumetric ICG indices between MetS patients and healthy controls.

The vasculature is also under control of intrinsic mechanisms that regulate blood flow and pressure. Blood flow (F) within a vessel is a function of the pressure differential along a gradient (i.e., between point 1 and point 2; P_1-P_2) and the inverse of the resistance (R) to that flow, such that $F = (P_1-P_2)/R$. That is, along a constant pressure gradient, flow decreases as resistance increases. Whereas resistance depends on persistent factors such as blood viscosity and local intravascular conditions (e.g., atherosclerosis), blood pressure (BP) depends on transient factors such as cardiac output (CO) and vasoconstriction/dilation (Andreassi, 2007). Therefore, regulation of BP is the most efficient means of manipulating momentary blood flow in the periphery.

Vascular functioning is more challenging to quantify at a given point because blood pressure fluctuates greatly throughout the circulatory system. For instance, BP in the aorta and large arteries is markedly greater than in the venae cavae and large veins, due to their location within the circulatory system and their ability to distend (Berntson et al., 2007). Oscillometric blood pressure monitoring (OBP) is a measurement approach that enables peripheral vasculature to be monitored remotely (Berntson et al., 2007). OBP can provide estimates of systolic, diastolic and mean arterial pressure (MAP; Berntson et al., 2007; Babbs, 2012).

Extrinsic Control

Extrinsic control of the CVS occurs through interdependent mechanisms in the central nervous system (CNS), autonomic nervous system (ANS), and HPA axis. The majority of CNS control is automatic and is housed in primitive brain stem structures including the medulla and

cerebellum (Andreassi, 2007; Berntson et al., 2007). Additionally, baroreceptors in the carotid sinus provide reflexive feedback to these brain structures, increasing HR when blood pressure decreases. These lower-level mechanisms give rise to higher-level central and autonomic control (Berntson & Cacioppo, 2007; Berntson et al., 2007).

Synergistic coactivation of the HPA axis and the ANS provides much of the extrinsic control for the CVS. Hormonal substrates initiate activity along the two branches of the ANS, providing electrochemical impulses for local alterations in muscle and tissue (Andreassi, 2007; Berntson & Cacioppo, 2007; Berntson et al., 2007). The sympathetic nervous system (SNS) maximizes blood flow to large muscle groups, constricts peripheral vasculature, and increases cardiac output, thereby energizing the body. The parasympathetic nervous system (PNS) opens channels of blood flow, dilates peripheral vasculature, and slows heart rate (HR) and respiration, thereby conserving energy.

Hormonal facilitation in the CVS is important because it provides impetus for SNS and PNS projections to alter heart rate (chronotropic effects; primarily related to PNS activation), muscle contractility (inotropic effects; primarily related to SNS activation) and peripheral vasoconstriction (also sympathetically moderated). The speed of SNS and PNS effects are considerably different (Berntson et al., 1997; Berntson et al., 2007). PNS activation can produce significant chronotropic effects almost immediately, whereas SNS activation has a longer, more cumulative impact on cardiovascular function (Andreassi, 2007, Somsen et al., 2004). Accordingly, the SNS and PNS play a central role in determining how the CVS adapts (or fails to adapt) to demands placed upon it. This process is known as cardiac autonomic control (CAC). Empirical evidence suggests that dysregulated CAC within these branches may place an

individual at risk for health complications (Chang et al., 2010; Hemmingway et al., 2005; Lambert et al., 2010; Masuo et al., 1997). One explanation for this relationship lies in the physiological stress response.

Physiological Stress Response

Selye (1956) described stress as a physical state that manifests via stereotypic responses in the face of a particular demand on the body. This definition highlights two important elements of the stress construct. First, stress is not a discrete external condition, but rather an internal state that arises in context of external demands (i.e., stressors). Second, the body's response is *stereotypic*; it has a predictable and consistent temporal sequence when triggered.

Biological Self-Regulation

In the presence of internal or external demands, activity across body systems fluctuates to maintain *homeostasis* (i.e., equilibrium around a particular set point). This process was referred to initially as *homeostatic regulation* (Berntson & Cacioppo, 2007). Cannon (1939) formulated a number of initial concepts related to autonomic processes in homeostatic regulation that have had a lasting impact on the understanding of physiological stress response. Namely, that regulatory effects of the SNS and PNS are balanced (Wenger, 1941), reflexive (Randall, Wurster, Randal, & Xi-Moy, 1996), and characterized by reciprocal central control (Berntson & Cacioppo, 2007). Seyle (1973) refined the conceptualization of this process by suggesting that the regulatory level is necessarily flexible to compensate for changing demands. The term *allostasis* or *allodynamic regulation* (Sterling & Eyer, 1988) encompasses the notion that

stability must be achieved through change and reflects the finding that autonomic regulation of the body is subject to constantly changing internal and external criteria (Dworkin, 1993).

Autonomic Space

Consistent with broad models of biological self-regulation, early conceptualizations of autonomic regulation also held that SNS and PNS activity was reciprocal, existing along a continuum from sympathetic to parasympathetic dominance. Findings pertaining to this continuum support the notion that SNS activation occurred with PNS inhibition, and vice versa (Malliani, 1999).

However, other empirical investigations revealed differences in the specific modes of ANS activation during times of stress (Iwata & LeDoux, 1988; Koizumi & Kollai, 1981; Quigley & Berntson, 1990). These findings suggested separation of SNS and PNS activity that appeared to override tendencies toward reciprocity. In turn, Berntson and colleagues (Berntson, Cacciopo & Quigley, 1991; 1993a; Berntson, Cacciopo, Quigley & Fabro, 1994) formulated the *doctrine of autonomic space*, which accounts for fluidity in autonomic activation. This model holds that ANS activity is best understood within orthogonal two-dimensional space enabling SNS and PNS activation to be reciprocal, coactive, or uncoupled (see Table 2).

Table 2. A Matrix Depicting Modes of Autonomic Control

Sympathetic Response	**Parasympathetic Response**		
	Increase	*No Change*	*Decrease*
Increase	**Coactivation**	Uncoupled sympathetic activation	**Reciprocal sympathetic activation**
No Change	Uncoupled parasympathetic activation	**Baseline**	Uncoupled parasympathetic withdrawal
Decrease	**Reciprocal parasympathetic activation**	Uncoupled sympathetic withdrawal	**Coinhibition**

In support of this model, Bernston, Norman, Lawkley, and Cacioppo (2008) provide evidence that cardiovascular changes related to autonomic control reflect multiple configurations of SNS and PNS activity. The research team collected numerous CVS measures from a sample of 229 adult participants in the community during a three-year epoch of the Chicago Health, Aging, and Social Relations Study. The team used data from ECG and ICG recordings to derive measures of CAC (see Figure 3), which they labeled cardiac autonomic balance (CAB; based on SNS and PNS reciprocity) and cardiac autonomic regulation (CAR; based on SNS and PNS co-activity).

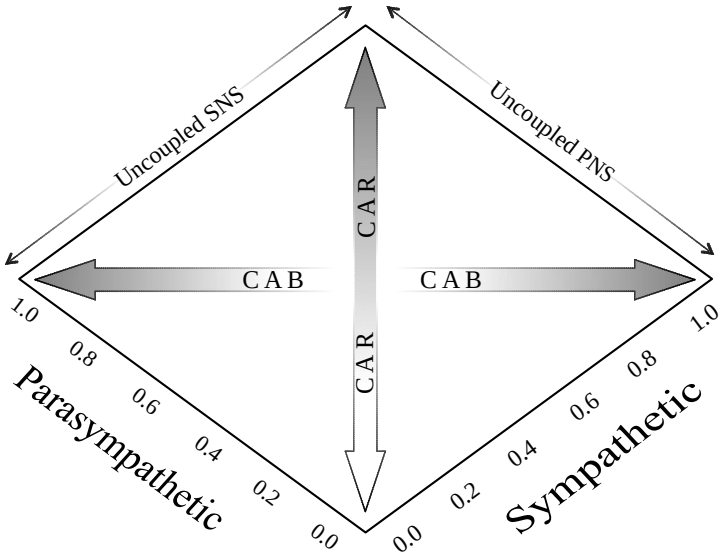

Figure 3. Relationship Between CAB and CAR within the Doctrine of Autonomic Space.

The team compared these and other markers of SNS and PNS activity (e.g., HR and HRV) to various subjective and objective health outcomes including DM2, myocardial infarction (MI), and quality of life. The results further indicated that those with low CAR scores were more likely to have a history of MI, where as those with low CAB scores were more likely to have a history of DM2. Moreover, the authors concluded that CAR (but not CAB) was predictive of global health, physical well-being, and pain as measured through self-report after controlling for demographic variables. These findings not only support the notion that SNS and PNS activation may occur in a variety of configurations, but also indicate that each carries implications for physical health. The findings are also consistent with literature suggesting dysregulated autonomic activity is associated with chronic illness.

Licht et al. (2010) developed a separate study to demonstrate that CAC has unique etiological implications for MetS. Working from the doctrine of autonomic space, the authors

utilized longitudinal data to examine CAC and HPA activity among a cohort of participants in the Netherlands Study of Depression and Anxiety (NESDA) over a three-year period. The authors monitored CAB, CAR, and salivary cortisol levels among 1,883 adults who presented with varying degrees of metabolic risk, ranging from none (0 risk factors) to severe (all 5 factors). The authors then compared response patterns across participants to determine the extent to which autonomic (as opposed to hormonal) activity relates to metabolic abnormalities. Results indicated not only that individuals with MetS show lower CAB and CAR, but also that these variables were linearly related to the number of metabolic abnormalities. The authors determined that hormonal measures did not have metabolic implications, pointing to the specific effect of ANS activity in the development of MetS. These findings lend support to the notion that across individuals, patterns of CAC are related to distinct physical outcomes.

The doctrine of autonomic space offers an effective description of CAC, but does not clearly explain the ways in which this process can lead to MetS. Furthermore, these studies are limited by a failure to monitor psychosocial features of the stress response. This limitation is particularly important because the psychological stress response may help explain the relationship between CAC and MetS.

Psychological Stress Response

Psychological variables are known to play a crucial role guiding patterns in allodynamic regulation during times of stress (Berntson & Cacioppo, 1999; Curtis & O'Keefe, 2002; Jorgensen & Kolodziej, 2007; Lambert et al., 2010). Current theory suggests the extent and intensity of the stress response is mediated by the psychological response to the stressor. This

response is commonly labeled *appraisal* (Lazarus, 1993; Lazarus & Folkman, 1984; Schwartz et al., 2003).

Appraisal is built upon two complementary processes: primary (or *demand*) appraisal and secondary (or *resource*) appraisal (Blascovich & Mendes, 2000; Blascovich & Tomaka, 1996). Primary appraisal refers to the judgment of situational danger and/or required effort. Secondary appraisal refers to the judgment of personal skills or knowledge relevant to performance in light of the situation (Blascovich & Mendes, 2000). The resolution of the primary-secondary appraisal process establishes a particular motivational state that leads to cognitive and behavioral tendencies intended to cope with the stressor.[1] This motivational state is highly relevant physiologically; it ensures the body responds to the external demand in a manner consistent with primary and secondary appraisals.

The Biopsychosocial Model of Challenge and Threat

Blascovich and colleagues' biopsychosocial model of challenge and threat (Blascovich, 2008; Blascovich & Mendez, 2000; Blascovich & Tomaka, 1996) outlines how differences in primary and secondary appraisals underlie specific motivational states and describes how these states manifest in the body. The model stipulates that in the context of motivated performance

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[1] A fundamental distinction with regard to coping strategies involves whether the strategy moves the individual toward (approach) or away (avoidance) from a particular target, object, or goal (Elliot & Fryer, 2008). It has been suggested that approach-avoidance dichotomy can be mapped on to the challenge-threat model; however, one particular motivational state does not universally precede one particular behavioral coping strategy. The concordance between these two concepts is complicated further by mediating and moderating variables including gender, dispositional traits, and sociocultural norms. A more accurate parallel concept may be active vs. passive coping, which relates to the individual's perceived resources as opposed to objects, targets, or goals.

situations (i.e., those that require instrumental cognitive or behavioral performance), an interaction between affective and cognitive evaluations during the appraisal process determines whether the individual enters a challenge or threat motivational state (see Figure 4a).

(a) (b)

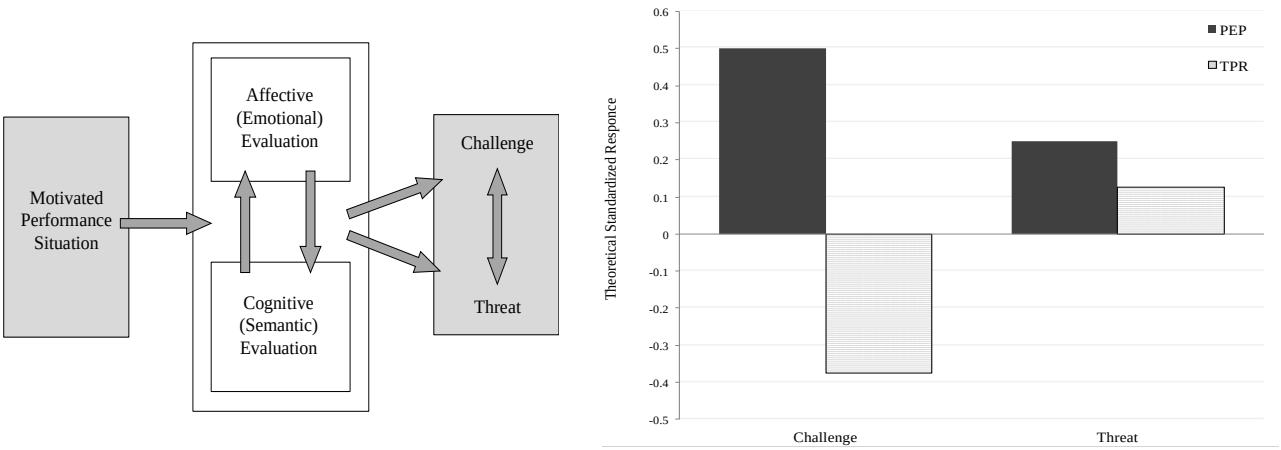


Figure 4. Blascovich & Colleagues' (a) Biopsychosocial Model of Challenge and Threat and (b) Theoretical Cardiovascular Patterns Associated with Each Motivational State.
Note: Adapted from Blascovich & Mendes (2000); PEP = Pre-ejection Period (cardiac contractility); TPR = Total Peripheral Resistance (vascular response)

Challenge states occur when the available resources are judged to be equivalent to or outweigh the perceived demand. *Threat* states occur when situational demands are judged to be greater than the available resources. The authors theorize that certain variables moderate processes of demand and resource appraisal including uncertainty, physical and psychological danger, skills, knowledge and support; they also propose that these states tend to carry hedonic valance, noting threat is more likely to elicit negative affect.

The authors submit that challenge and threat motivational states are associated with distinct cardiovascular patterns, consistent with the concept of cardiac-somatic coupling as well

as previous work by Obrist (1981) and Dienstbier (1989). The model suggests that challenge states are marked by decreases in total peripheral resistance in conjunction with increased cardiac output (cardiac-somatic coupling), producing little change in blood pressure. Conversely, threat states are associated with minimal increases in total peripheral resistance in conjunction with increased cardiac output (cardiac-somatic uncoupling), which has the effect of increasing blood pressure (see Figure 4b). This theoretical model gained support through experimental studies that confirm expected cardiovascular patterns among individuals in challenge and threat motivational states (Tomaka, Kibler, Blascovich, & Ernst, 1997; Blascovich, Seery, Mugridge, Norris, & Weisbuch, 2004).

Challenge, Threat, and Illness

Blascovich (2008) suggests that challenge states tend to be adaptive (synchronous cardiac activation and vasodilation that facilitate effective performance), while threat states tend to be maladaptive (asynchronous cardiac activation and vasoconstriction that inhibit effective performance). The initiation of threat states leads to cardiovascular strain in non-metabolically demanding situations. Therefore, the direct relationship between challenge/threat states and health is one that can be defined and tested.

Blascovich and Katin (1993) note that vascular contractility in conjunction with increased cardiac output (i.e., threat state) precipitates blood turbulence within coronary arteries and acute hypertension. This process can produce lesions in the endothelial lining of these arteries increasing the likelihood of scarring and arteriosclerosis. In addition, Manuck, Kamarck, Kasprowicz, and Waldstein (1993) concluded that repeated elevations in blood pressure consistent with threat states impede intrinsic hemoregulatory mechanisms, potentially

precipitating clinical hypertension. Indeed, persistent activation of this pattern of appraisal is associated with an increase in *allostatic load* (i.e., a systemic failure of regulatory mechanisms brought on by chronic stress), which leads to heightened baseline activation in body systems under hormonal and autonomic control (McEwen & Stellar, 1993).

Challenge and threat states can impact physical health in other ways. An intriguing extension of this model yet to be tested suggests that particular patterns of PNS and SNS activation along with the cardiovascular profiles of challenge and threat states create an indirect line of influence on MetS by attenuating health behavior and treatment adherence. Treatment non-adherence is related strongly to increased disease progression, particularly in CVD and DM2 (Asche, LaFleur & Conner, 2011; Bodenheimer, Lorig, Holman & Grumbach, 2002; Dunbar-Jacob & Mortimer-Stephens 2001; Gonzalez et al., 2008; Lerman, 2005). It is possible that perceiving insufficient resources in motivated performance situations both (1) increases negative affect (e.g., worry, fear, depression; Blascovich & Mendes, 2000) and (2) inhibits tendencies toward health behavior and/or adhering to treatment recommendations, thereby minimizing illness-based stress. Indeed, theories of treatment adherence such as the Health Compliance Model-II (HCM-II; Heiby & Frank, 2003) suggest motivational state and emotional experience are chief determinants of treatment adherence and health behavior (Heiby & Lukens, 2006).

The Proposed Investigation: Aims and Hypotheses

Based on current literature and unresolved questions, we have developed four study aims and corresponding hypotheses.

Table 3. Study Aims and Hypotheses**.**

Aim		
1	**Validate the relationship between CAC and MetS**	
	H_1	Consistent with findings from Berntson et al. (2008), both CAB and CAR will predict concurrent diagnosis of DM2 and CVD. CAC will be positively related to self-reported well-being and negatively related to depression and anxiety.
	H_2	Patients with metabolic syndrome will evidence lower baseline CAB & CAR scores.
2	**Examine the patterns of CAC among patients with MetS during a standardized stressor.**	
	H_3	Patients with metabolic syndrome will evidence lower CAB & CAR scores during standardized stressors.
3	**Examine the patterns of CAC among individuals with MetS during a health and wellness interview.**	
	H_4	Patients with metabolic syndrome will evidence lower CAB & CAR scores during the health and wellness interview.
	H_5	During the experimental tasks, responding with a cardiovascular "threat" configuration will be associated with MetS.
4	**Examine the influence of cardiac autonomic control on health behaviors & treatment adherence among individuals with MetS.**	
	H_6	Low CAB & CAR scores will be associated with increased BMI, decreased physical activity, increased smoking behavior, increased drinking, and decreased self-reported medication adherence.

CHAPTER TWO: METHODOLOGY

Participants

Participants were 51 primary care patients at the University of Central Florida Health Clinic (UCFH) who were identified as study candidates by having any number of metabolic abnormalities consistent with NHLBI guidelines. Within this full sample, 25 individuals met diagnostic criteria for MetS as confirmed by their referring physician, and 26 individuals were identified as "healthy controls" (HC; presented with two or fewer metabolic abnormalities). One individual in the HC group was removed form the initial sample due to failure of the ambulatory monitoring device. The final sample (*N*=50*)* was predominantly female (68%) with a mean age of 56.32 years (*SD*=16.74). The majority of the final sample identified as Caucasian (64%) with a smaller proportion identifying as Latino/a (16%), Black/African American (12%) and Asian (8%). Table 4 (see Results section, below) provides more specific information about the final sample, including demographic and medical characteristics of each of the experimental groups as well as analysis of group differences along these characteristics.

Measures

Metabolic Syndrome

The NHLBI guidelines (Grundy et al., 2006) stipulate that three of five risk factors must be present for diagnosis of MetS (see Table 1). These criteria have been adjusted from previous guidelines to reconcile differences in interpretive ranges and the complication of frequently prescribed medications targeting metabolic abnormalities. Assessment of these abnormalities were be conducted through measurement of waist circumference in the case of risk factor 1, and

using current medical records, laboratory tests, and vital signs in the case of factors 2-5. Following diagnostic guidelines, waist circumference was measured using a measuring tape placed around the abdomen on a horizontal plane (parallel to the floor) at the level of the iliac crest. The research team consulted medical records, laboratory tests, vital signs, and medication prescription records to confirm the existence of metabolic risk factors.

Cardiac Autonomic Control

Accurate and reliable measurement of CAC necessitates an ensemble of measures that include ECG, ICG and OBP. We utilized ambulatory measurement for each of these signals. Participants were seated for all data collection procedures.

ECG and ICG

ECG and ICG were recorded simultaneously using a series of adhesive sensors affixed to the participant's skin. ECG was recorded using two Ag/AgCl spot electrodes in standard Lead-II configuration. The typical reference, or "ground," electrode in ECG monitoring was assigned to one of the ICG electrodes. ICG was recorded using four Ag/AgCl adhesive spot electrodes placed in corresponding dorsal and ventral sites (see Figure 5). These sensors were connected via touchproof snap leads to an ambulatory monitoring device (MindWare Mobile) provided by MindWare Technologies (Gahannah, OH). Offline, data were subjected to a band pass and notch filters to remove movement and electrical (60 Hz) artifact, respectively. All data collection and analysis procedures followed best practice guidelines (Berntson et al., 1997; Sherwood et al., 1990).

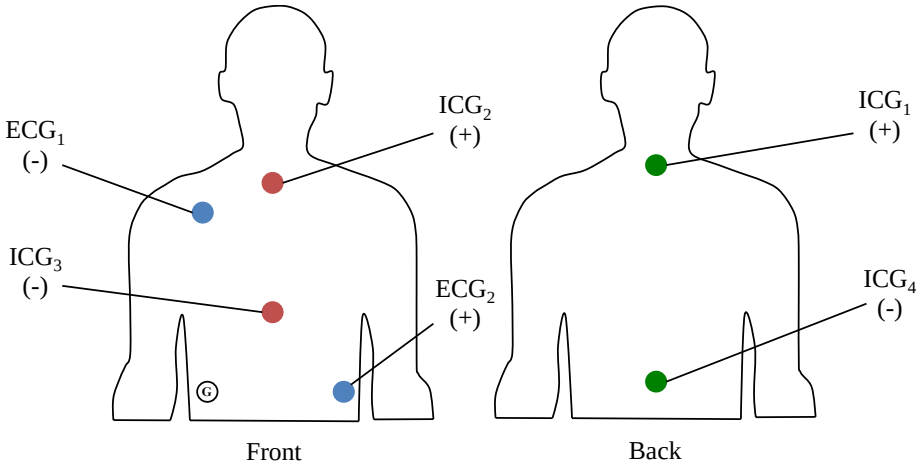


Figure 5. Sensor Placement and Electrical Configuration (+/-) for ECG and ICG Recording. Note: Subscripts indicate lead number. G = Ground, omitted in this investigation.

Analysis of the ECG waveform produces estimates of HR and HRV. HR is defined as the average number of beats over a period of time (e.g., beats per minute) measured using a count of R waves observed in that period. In contrast, HRV is defined as the variability in the inter-beat interval (IBI) between R waves measured using either time or frequency domains. The frequency domain (expressed in Hz) is most appropriate for assessing changes over shorter periods of time (Berntson et al., 1993b). HRV requires a minimum of number of breath cycles (typically 10), which takes between 30 seconds and 60 seconds for most individuals. This method produces two main frequency 'bands' that represent differing levels of autonomic control.[2] The low-frequency band (LF; 0.05-0.15 Hz) is associated with combined sympathetic and parasympathetic influences (coactivation), whereas the high-frequency band (HF; 0.15-0.4 Hz) is associated with parasympathetic control of the heart (Berntson et al., 1997). The HF band is the metric of an

[2] A third band exists at the very low-frequency range (VLF; 0.003-0.05 Hz), which represents primarily thermoregulatory mechanisms associated with circadian rhythm (Berntson et al., 1993b, 1997)

chronotropic phenomenon called respiratory sinus arrhythmia (RSA), a feature of independent parasympathetic control of the heart.

ICG necessitates ECG (Berntson et al., 2007, Sherwood, 1993). The Q and R waves in the ECG signal establish cardiac landmarks that can be fitted to the two ICG waveforms, Z0 (basal thoracic impedance) and dZ/dt (1st derivative of Z0). Figure 6 presents prototypical examples of ICG waveforms as they relate to the QRS complex.

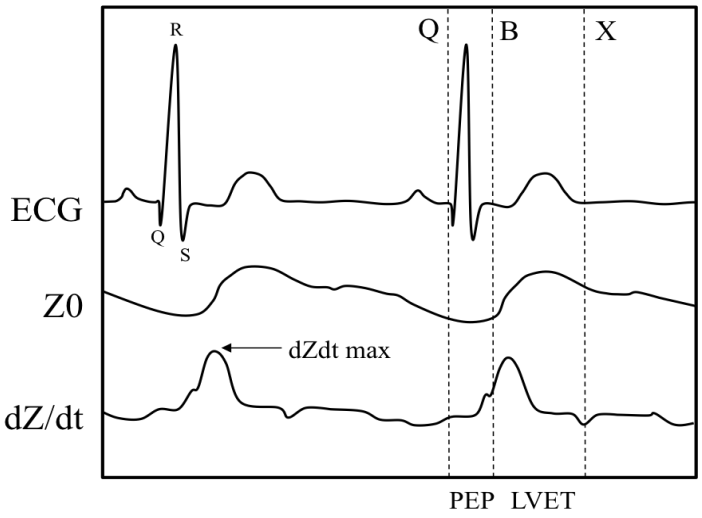


Figure 6. Relationships Among ECG and ICG Signals and Corresponding Landmarks
Note: PEP = Pre-ejection Period; LVET = Left Ventricular Ejection Time; Adapted from Berntson et al. (2007).

There are two landmark points in the dZ/dt signal (i.e., B and X points) from which physiological cardiac function can be derived. The B point is located at the primary inflection in the waveform marking ventricular ejection (Lozano et al., 2007). Pre-ejection period (PEP) is calculated as the time between Q onset and the B point. The X peak is the lowest point in the dZ/dt signal and marks closure of the aortic valve and the end of ventricular ejection. Left ventricular ejection time (LVET) is calculated as the time between the B and X points. Both PEP and LVET are indices of cardiac contractility and thus relate to sympathetic control.

In the present study, RSA and PEP were used to calculate indices of CAB and CAR as defined by Berntson et al. (2008). Specifically, the CAB dimension is quantified as the difference between normalized (z-score transformed) indices of SNS and PNS activation at a given point in time, such that CAB = zHF – [(-1)zPEP]. Conversely, the CAR dimension is quantified as the sum of normalized indices of SNS and PNS activation at a given point in time, such that CAR = zHF + [(-1)zPEP]. In these calculations, normalization is required due to scaling differences between these measures. Inversion of PEP is required due to the negative correlation between this measure and SNS activity. Although CAB and CAR enable delineation of SNS and PNS reactivity, a more fine-grained method for measuring SNS responses is warranted due to the mounting evidence for SNS dysregulation in MetS (e.g., Licht et al., 2013).

Oscillometric Blood Pressure (OBP)

While measures of cardiac reactivity are available from ECG and ICG, measures of vascular reactivity can only be obtained by recording peripheral BP. Peripheral PB was recorded oscillometrically using an Oscar 2 Ambulatory Blood Pressure Monitor provided by SunTech Medical (Morrisville, NC). This technique records pressure oscillations in an inflated pneumatic cuff produced by a depressed artery (Babbs, 2012). An adjustable, inflatable nylon cuff was placed around the patient's left upper arm at the level of the heart. OPB was measured once at baseline and at 5-minute intervals through out the experimental procedure. The Oscar 2 device automatically monitors and calculates systolic (SBP) and diastolic blood pressure (DBP), from which mean arterial pressure (MAP) and total peripheral resistance (TPR) can be determined. MAP is calculated from systolic and diastolic estimates such that MAP = 2(DBP/3) + SBP/3. TPR is calculated as the quotient of MAP and cardiac output (Berntson et al., 2007).

Health Measures

Psychosocial Health

Anxiety and Depression

The Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983) is a 14-item measure of anxiety and depression that has been used extensively in medical and primary care settings. Items on the scale address current physiological and psychological symptoms (e.g., *I get a sort of frightened feeling like 'butterflies' in the stomach*). Respondents provide ratings on a four-point Likert scale with variable anchors based on the extent to which they have experienced that symptom within the past week. The instrument contains two subscales of even length, including anxiety (HADS-A) and depression (HADS-D). Raw scores are summed to represent normal (0-7) borderline abnormal (8-10) and abnormal (11-21) levels of anxiety and depression, respectively. The psychometric properties of the HADS have been scrutinized in a number of populations and have been found to be excellent. Bjelland, Dahl, Haug and Neckelmann (2002) concluded that the internal consistency of the two subscales are very good to excellent (HADS-A α = .68-.93, HADS-D α = .67-.90) and that estimates of convergent validity indicate strong positive correlations with similar measures (*r*'s = .49-.83). Sensitivity and specificity of the instrument were in optimal balance at a score of 8 or above.

Coping Style

The Brief Coping Scale (Brief COPE; Carver, 1997) is a 28-item measure of coping style that has been used in both stress and health outcome research. Items on the scale represents a method for coping with life stress (e.g., *I've been taking action to try to make the situation better*). Respondents rate the extent to which they use each method on a five-point Likert scale (1

= *I haven't been doing this at all*, 4 = *I've been doing this a lot*). Scoring yields 14 two-item subscales with higher scores indicating greater use of that strategy. Subscales include Behavioral Disengagement, Denial, Self-distraction, Self-blame, Substance Abuse, Active Coping, Positive Reframing, Planning, Humor, Acceptance, Religion, Emotional Support, Instrumental Social Support, and Venting. No procedure exists for creating second-order composite or factor scores; however, the author indicates that these scales can be organized within a second-order structure based on patterns evident in the observed responses. Such efforts have been undertaken in previous research to identify patterns in passive, active, and avoidant coping (Litman, 2006; Marroquín, Fontesc, & Scilletta, 2010; Mitchell, MacLeod, & Cassisi, in press). The Brief COPE has demonstrated adequate to very good internal consistency (all but one subscale $\alpha \geq .60$) and test-retest reliability (*r*'s = .46-.86).

Quality of Life

The World Health Organization Quality of Life – Brief Version (WHOQOL-BREF; The WHOQOL Group, 1996) is a 26-item quality of life measure in adults that has been implemented in a variety of settings internationally. It was developed as a short form for the longer 100-item version. Items on the scale (e.g., *To what extent do you feel your life to be meaningful?*) address current level of functioning across four biopsychosocial domains (Physical, Psychological, Social, Environmental). Respondents provide ratings on a five-point Likert scale with variable anchors based upon their experience within the previous two weeks. Scoring yields four domain scores with higher scores indicating higher quality of life in that domain. These scores may then be standardized using a 0-100 scale for ease of comparison. The WHOWOL-BREF has demonstrated adequate to very good psychometric properties, with α's ranging from 0.68 to .82

across all domains. The discriminant and construct validity have been judged to be very good. The WHOQOL-BREF is correlated highly with similar measures of quality of life and can differentiate those with high and low quality of life as defined by independent criteria.

Health Behavior and Treatment Adherence

To account for personal and contextual factors in illness, measurement of health behavior and treatment adherence is necessary. Measuring health behavior and treatment adherence is challenging for a number of reasons. First, the nature of medical interventions means the specific treatment recommendations and needs for each individual will be different. Additionally, the progression of an illness means treatment recommendations change over time; whereas one line of treatment may be easy to follow (i.e., early in the progression of an illness), a different line of treatment may present more extensive challenges. Despite these challenges, several themes in health behavior and adherence can be reliably quantified throughout one's treatment. Current perspectives on measuring treatment adherence underscore the need for multiple methods of measurement that include combined objective and patient-reported measures (Riekert, 2006; WHO, 2003).

Body Mass Index

Participant's body mass index (BMI) was recorded as a marker of relative weight. BMI is defined as the quotient of mass in kilograms (kg) and height in meters squared (m^2). Height and weight were collected from patient medical records obtained on the day of data collection.

Physical Activity

Participant's level of physical activity was measured with The International Physical Activity Questionnaire – Short Form (IPAC-S; Ainsworth et al., 2000). The IPAC is an eight-

item self-report inventory that measures recent patterns in physical activity in a number of domains (e.g., work, leisure, exercise). Items on the scale include questions that address frequency of physical activity (e.g., *During the last 7 days, on how many days did you do vigorous physical activities like heavy lifting, digging, aerobics, or fast bicycling?*). Scoring protocol provides both categorical measures across individuals (low, moderate, high activity individuals) and continuous measures of physical activity across activity intensity (walking, moderate, vigorous activity). The continuous measures are in the unit of Metabolic Equivalent of Task-minutes (MET-minutes) per week. MET-minutes are useful to quantify physical activity because they are standardized to account for the intensity of activity. Higher MET-minute scores are indicative of greater physical activity. A number of studies support the psychometric properties of the IPAC-S. Estimates of internal consistency and test-retest reliability of the categorical outcomes are very good (Spearman's ρ = .64-.79) and the measure also correlates highly with objective measures of physical activity (Craig et al., 2003).

Smoking Status

Participant's smoking history was assessed by self-report. Smoking behavior was quantified categorically by status (current smoker, previous smoker, never smoked) and continuously by a count the number of cigarettes smoked per day for current smokers.

Alcohol Use

Participant's use of alcohol was assessed with The Alcohol Use Disorders Test (AUDIT; Saunders, Aasland, Babor, de la Fuente, & Grant, 1993). The AUDIT is a 10-item instrument developed by the World Health Organization to assess drinking behavior in health care settings. Items on the scale address frequency, amount and problems in drinking behaviors (e.g., *How*

often do you have a drink containing alcohol?). Respondents provide ratings on a five-point Likert scale with variable anchors based on their typical use of alcohol. The AUDIT yields a single score ranging from 0 to 40, with higher scores indicating maladaptive alcohol use. The authors suggest that a score of 8 can be used as a cut-off for problematic drinking. The AUDIT has demonstrated good internal consistency (α = .62-.78), and very good test-retest reliability (*r* = .86).

Medication Adherence

The Morisky Medication-Taking Adherence Scale – Eight Item Version (MMAS-8; Morisky et al., 2008) is a widely used revised version of an earlier four-item scale used to assess adherence to medication regimens. Each item on the scale asks the respondent about his or her typical use of medication (e.g., *Over the past two weeks, were there any days when you did not take your medicine?*). Respondents answer either "yes" or "no" to each item. A composite score of summed positive responses is then calculated. Morisky et al. (2008) report the MMAS-8 demonstrated good internal consistency (α = 0.83) and can discriminate between clinical outcomes in hypertension (i.e., those who demonstrate BP control, versus those who do not). Although it was developed originally for hypertensive medication adherence, the MMAS-8 has been utilized in diabetic populations with similar levels of success (Wang, Lee, Tang, Toh, & Ko 2012). The MMAS-8 has been shown to correlate highly with pharmacy refill rates (Krousel-Wood et al., 2009).

Procedure

The experimental procedure was developed to take place in the context of a primary care clinic and included three phases: *intake* (consent documentation and sensor placement),

physiological recording (baseline period, two counterbalanced stressor tasks, and recovery periods following each task), and *checkout* (sensor removal, self-report assessment, and debriefing).

Participants were recruited from the patient population at UCFH. Eligible patients were identified prior to their arrival at the clinic during routine clinical consultations between the investigator, attending physicians, and medical assistants. This consultation is a standard of practice for integrated healthcare services. Upon presenting for treatment and completing clinic check-in procedures, patients were escorted to the examination area where the medical assistant collected routine medical data (height, weight, vital signs).

At that time, the investigator notified the patient about the study, provided an abridged study description, and invited the patient to participate. Regardless of the participant's decision to participate, the patient's healthcare appointment progressed as usual. In most cases, patients interested in participating were scheduled for a follow-up appointment to accommodate scheduling and availability restrictions.

Phase I: Informed Consent and Preparation

The first element of Phase I was provision of a full description of the study procedures and potential risks and benefits of participation. This conversation occurred at the time of intake and included a broad overview of the topic of the study. This conversation did not include specific information about the study hypotheses. Following this description, participants were asked to provide their verbal consent to participate. Each participant was assigned a three-digit number to serve as an anonymous identifier throughout data collection and analysis. Each participant was randomized to one of two experimental conditions, which determined the order

in which stressor tasks were administered (see Phase II, below). Random assignment was completed using an virtual random number generator (www.random.org).

The second element of the intake phase was the preparation of the surface recording sites for ECG and ICG sensors and the attachment of the OBP cuff. Site preparation included a thorough cleansing of the skin using an alcohol pad. Next, sensors were placed on the skin and connected to the MindWareMobile device, which was secured to a belt containing the OBP monitor. Finally, the OBP cuff was placed around the participant's arm and the device belt is secured to the participant's waist.

Phase II: Physiological Measurement

Physiological measurement began with a habituation period lasting five minutes. This period facilitated physiological habituation to the experimental environment and stabilization of physiological signals. The final minute of the habituation was used as a baseline for data analyses. This approach is generally superior to calculating change scores (Berntson, 2014, personal communication). The habituation period was tracked with a stopwatch, and start and end times were recorded using a standardized external timepiece. These times were then converted to a cumulative run-time to permit synchronization of event markers and signals collected in the experiential procedure.

Physiological measurements were recorded during two counterbalanced stressor tasks: a mental arithmetic task and a semi-structured health and wellness interview (see Appendices A and B, respectively). Counterbalancing of the stressors was used to help attenuate order effects in physiological activation. The mental arithmetic task involved two standardized procedures (i.e., Serial 7s and Mental Multiplication), each of which lasted one minute. In Serial 7s, participants

were asked to subtract seven from 100 and continue to subtract seven from each subsequent answer. In Mental Multiplication, participants were asked to multiply three by four and continue multiplying by three each subsequent answer. In both tasks, the investigator provided corrective feedback for incorrect answers and the participant was instructed to begin again. The health and wellness interview comprised five topics including medication adherence, diet, exercise, stress, and coping strategies. Each topic was discussed for approximately two minutes. The series of questions in each topic of conversation in this interview was uniform for each participant, but the specific content of each discussion was different, by necessity. The entire interview task lasted approximately 10 minutes. A five-minute recovery period followed each stressor task to encourage physiological signals to stabilize. As with the baseline period, stressor duration was tracked with a stopwatch, and start and end times were recorded using a standardized external timepiece.

Phase III: Checkout

Sensor removal was the first element of the checkout phase. The researchers removed the sensors and provided participants with cleansing wipes to remove any adhesive residue from their skin. The second element of the checkout phase was collection of self-report measures administered in paper-and-pencil format. The final element of the checkout phase was debriefing of the purpose and objectives of the experiment. Participants were provided more specific information about the research questions and were provided the opportunity to ask questions of the investigators. All participants received a debriefing form containing an additional written description and contact information for the research team and university review board.

Data Examination, Screening and Replacement

The investigator examined the entire data set prior to initiating data analyses in accordance with recommendations by Tabachnick and Fidell (2013). During this process, it was discovered that several data points were missing or unavailable for analysis. The majority of these observations were related to medical data collected from patient records. These observations generally included measures of blood lipid and/or glucose levels, and were unavailable because either (1) routine collection of these values were not medically necessary as determined by the treating physicians, or (2) the values were no longer current (i.e., collected longer than 2 weeks prior to the visit). In light of these missing values, between-group comparison of these variables and examination of MetS as a continuous indicator was not feasible in the present study. The remaining missing data points were identified in self-report measures. Specifically, 11 cases contained missing values, with 1-7 observations missing per case (approximately 0.9% of the self-report data). These data, missing at random (MAR), were estimated and replaced via maximum likelihood (FIML) procedures in Mplus (Version 7.11, Muthén & Muthén; Los Angeles, California). In Mplus, multiple imputation for a set of variables with missing values is carried out using Bayesian analysis, creating a full dataset that can be used in subsequent analyses (Muthén & Muthén, 2012). FIML estimation is the preferred method for data replacement because it is built upon robust procedures that incorporate casewise likelihood estimation, thereby reducing standard error values (Enders & Bandalos, 2001).

The resulting data set was then checked visually and statistically for multivariate normality and for violations of the assumptions of the general linear model. Several of the self-report independent variables were positively skewed. Specifically, all MET-minute variables and

the AUDIT total score demonstrated positive skewness, with values of 2.31–5.44. To correct for these findings, we discarded the continuous scores derived from these measures and relied on categorical scoring, as described in the Measures section, above. All dependent variables were observed to be approximately normal (skewness < |1|). Examination of normal Q-Q plots and residual scatter plots suggested that these variables did not violate the assumptions of the general linear model.

Physiological Signal Processing

Signals were processed visually and digitally on a desktop computer using MindWare's BioLab, ICG, and HRV Analysis software version 3.1.1. Prior to processing, event markers corresponding to the beginning and end of each of the baseline, recovery, and experimental periods were inserted manually into the data file. ECG and dZ/dt signals were digitized using a band pass filter with a low cutoff of .50 Hz and a high cutoff of 45.0 Hz. The Z0 signal was digitized using a low pass filter with a cutoff of 10 Hz. Data were obtained and recorded by examining the signal between the start and end event markers inserted via synchronized, cumulative run-time of each individual's unique experimental procedure. For the Health and Wellness task, we utilized data from the full two-minute epoch of each interview segment. For the Mental Arithmetic task, we utilized data calculated from the one-minute epoch for each stressor.

With regard to HRV calculation, spectral analysis followed a Hamming windowing function, with the VLF (.003-.04 Hz), LF (.040-.12 Hz) and HF (.12-.42 Hz) bands pre-set across all participants. The Z0 signal from ICG recording was used as a respiration signal for all HRV analysis in order to confirm that respiratory sinus arrhythmia occurred in the appropriate HF

frequency band. HRV analysis involved assessment of mean R-R peak variability (HF HRV, or RSA) as well as the standard deviation of normal R-R intervals (SDNN).

With regard to ICG calculation, metrics of Z0 and dZ/dt were calibrated at .10 volts/Ohm and 1.00 Volts/Ohm/Second, respectively, with a blood resistivity constant of 135. The Q point calculation method was minimum value of the K-R interval where K=35. LVET windowing followed the Farmingham method with minimum and maximum offset threshold of 200 and 600 milliseconds, respectively. B-point calculation was executed using the 55% plus a constant of 4 procedure, as recommended by Lozano et al. (2007). Stroke volume was calculated using the Kubicek method. A 60 Hz notch filter was used during all signal processing procedures.

Initially, signal processing involved removal of movement artifact from the raw ECG signal. Movement artifact was confirmed through examination of X-, Y-, and Z-axis actigraphy housed within the mobile monitoring unit. As a component of artifact removal, R-peak accuracy was assessed and corrected as needed. Upon verification of accurate R-peak placement for all data segments, automated analyses of HRV and ICG signals were initiated. All output variables from these automated analyses were then verified manually based on recommendations from Lozano et al. (2007).

CHAPTER THREE: RESULTS

Sample Characteristics

Within the final sample, we examined several characteristics of each experimental group that have the potential to impact physiological performance. These variables were selected on the basis of theoretical mechanisms underlying physiological performance or because previous research has indicated that particular variable may have such an effec. Table 4 contains descriptive and demographic characteristics for the full sample (*N*=50), stratified by experimental group. Table 4 also contains between-group comparisons on variables not directly included in establishment of MetS diagnosis.

Table 4. Sample Characteristics by Experimental Group.

	Experimental Group			
	Healthy Control (*N*=25)	Metabolic Syndrome (*N*=25)	F (*df*)	*p*
Mean Age (*SD*)	52.04 (18.37)	60.60 (14.00)	3.43 (1,49)	.075
Female Sex (*N*, %)	20, 80%	14, 56%	–	–
Race				
Caucasian (*N*, %)	19, 76%	13, 52%	–	–
Latino/a (*N*, %)	3, 12%	5, 20%	–	–
Black (*N*, %)	2, 8%	4, 16%	–	–
Asian (*N*, %)	1, 4%	3, 12%	–	–
Mean BMI (*SD*)	25.99 (5.17)	31.81 (6.60)	12.09 (1,49)	.001
Mean # Medical Problems (*SD*)	5.64 (0.82)	9.28 (1.01)	7.73 (1,49)	.008
Mean # CV Medications (*SD*)	0.32 (0.75)	1.28 (0.98)	15.15 (1,49)	<.001

Note: BMI = Body mass index; CV = Cardiovascular

With regard to race, we examined the relative proportions of race within the experimental groups using chi-square test of independence and found no difference between the HC and MetS groups, χ^2 (3)=3.29, *p*=.349. With regard to sex, there is considerable evidence that rate of MetS diagnosis varies by sex and that sex influences patterns of cardiovascular responses (Ordaz &

Luna, 2012; Stoney, Davis, & Matthews, 1987). As such, we chose to include sex as an independent between-subjects variable or, unless otherwise noted, as a covariate in analyses examining either experimental group membership or CV activity. We also controlled for medical complexity (i.e., number of medical problems) in analyses that examined between-subject differences. This decision was based on the observed between-group differences, and findings in the literature that suggest individuals with chronic or advanced medical diagnoses may present with unique physiological profiles (Manganelli et al., 2002; Wakkee, Thio, Prens Sijbrands, & Neumann, 2006).

In the process of data collection, we tracked the use of medications known or intented to alter or adjust CV functioning, including the broad class of antihypertensive medications. The majority of the sample (52%) were not on any CV medication with smaller proportions prescribed one (24%), two (16%), and three (12%) CV medications. Table 5 provides an overview of medication prescription in both the HC and MetS groups.

Table 5. Number of Individuals Prescribed CV Medications by Experimental Group

	Experimental Group			Experimental Group	
Medication	HC	MetS	Medication	HC	MetS
ACE Inhibitors	0	7	NDH CCB	0	0
A2R Blockers	3	7	DH CCB	0	4
Diuretics	–	–	Beta Blocker	0	5
Thiazide	1	6	Alpha Blocker	1	3
Loop	0	0	Antiarrythmics	0	0
Aldasterone Blocker	2	0	Stimulants	1	0

Note: HC = healthy control; ACE = angiotensin converting enzyme; A2R = angiotensin II receptor; NDH = non-dihydropyridine; DH = dihydropyridine; CCB = calcium channel blocker

Whereas several of these drugs work primarily on the physiology of the vascular system (e.g., ACE inhibitors), others work primarily on the heart cycle (e.g., beta blockers). In addition, several of these medications (e.g., diuretics) bring about systemic changes that comprehensively

alter the cardiovascular system, making it difficult to control for the global impact of these various agents. Therefore, in analyses examining either cardiac (e.g., CAB, CAR, PEP), or vascular functioning (e.g., TPR), we used as covariates only those medications that have direct cardiac or vascular implications, respectively.

Examination of Study Aims and Tests of Experimental Hypotheses

Aim 1: Validate the Relationship Between CAC and MetS

Hypothesis 1: CAC will predict concurrent medical and mental health concerns

Following Berntson et al. (2008), binary logistic regression was employed to predict diagnosis of DM2 and CVD from baseline CAB and CAR scores. The DM2 group (N=11) included all individuals with a current diagnosis. The CVD group (N=9) included all individuals with recorded diagnosis of coronary artery disease, congestive heart failure, or arrhythmia, as described by the American Heart Association. Both baseline CAB and CAR scores and an interaction term (CAB $\times$ CAR) were entered into the regression equation in a hierarchical fashion, with CAB preceding CAR in the prediction of DM2 diagnosis, and CAR preceding CAB in the prediction of CVD. To avoid multicolinearity, the individual components of the CAB and CAR variables were not included in these models. Observed groups and predicted probabilities plots were generated to identify potential outliers; none were detected. Findings from the final model blocks are described in-text. Findings form the full models are presented in Table 6.

Table 6. Full Model Logistic Regression Analysis Predicting Diagnosis of Diabetes and Cardiovascular Disease from CAB and CAR Scores.

Type 2 Diabetes Diagnosis (*N*=11)

Predictor	β	*SE* β	Wald	*df*	*p*	e^{β}
(Constant)	-1.319	0.375	13.646	1	.000	0.267
CAB	-0.003	0.226	0.000	1	.991	0.997
CAR	0.074	0.315	0.054	1	.816	1.076
CAB × CAR	-0.315	0.271	1.354	1	.245	0.730
Test			χ^2	*df*	*p*	
Overall Model Evaluation			1.505	3	.651	
H-L Goodness of Fit			11.848	8	.158	

Cardiovascular Disease Diagnosis (*N*=9)

Predictor	β	*SE* β	Wald	*df*	*p*	e^{β}
(Constant)	-2.040	0.556	13.451	1	.000	0.130
CAR	-0.786	0.388	4.115	1	.042	0.456
CAB	-0.562	0.355	2.501	1	.114	0.570
CAB × CAR	-0.426	0.333	1.633	1	.201	0.653
Test			χ^2	*df*	*p*	
Overall Model Evaluation			8.275	3	.041	
H-L Goodness of Fit			8.745	8	.364	

Note: H-L = Hosmer-Lemeshow

None of the logistic models predicting diagnosis of Type 2 Diabetes was significant; however, the final model iteration predicting diagnosis of CVD was significant, Nagelkerke R^2=.250, and correctly classified 86% of all CVD cases. In this model, CAR was a significant negative indicator (β=-0.562), suggesting decreased CAR scores are associated with an increased likelihood of being diagnosed with CVD. The Hosmer-Lemeshow goodness-of-fit test was non-significant for this model, indicating that this model is appropriately specified, and observed group membership did not deviate from the expected count predicted by the model. This finding

is consistent with previous research provided by Berntson and colleagues that indicate diminished CAR scores are associated with previous MI.

Subsequently, a series of hierarchical linear regression analyses was employed to determine if CAC variables, including CAB, CAR, and individual measures of the cardiac cycle predict self-reported quality of life, anxiety and depression scores. We chose to include individual cardiac measures in the model to account for independent activation of sympathetic and parasympathetic branches, as CAB and CAR capture reciprocity and co-activation of these branches, respectively. To account for potential experimental group differences (HC vs. MetS), a dummy-coded dichotomous variable was entered into the first block of the regression. Baseline CAB and CAR were included in the second block, and baseline measures of PEP, RSA, LVET, and CO were included in the final block. Although SV was originally included in the model, it was removed to avoid multicolinearity. Mahalonobis distances were computed to identify outliers; none were detected. Table 7 contains descriptive statistics and zero-order Pearson correlations among all observed variables in this model. Additional descriptive statistics for study variables are presented in Appendix A.

Table 7. Descriptive Statistics and Zero-order Correlations Among Physiological and Self-report Health Measures in the Full Sample**.**

	1	2	3	4	5	6	7	8	9	10	11	12	13
1. CAB	–												
2. CAR	.00	–											
3. PEP	.80***	-.59***	–										
4. RSA	.81***	.59***	.29*	–									
5. LVET	-.13	.12	-.17	-.03	–								
6. SV	-.14	.08	-.16	-.07	-.50***	–							
7. CO	-.27*	.02	-.23	-.21	.41**	.93***	–						
8. ANX	-.26	.05	-.24	-.18	-.10	.09	.12	–					
9. DEP	-.09	-.03	-.06	-.09	-.01	.04	.05	.63***	–				
10. QLPH	.14	.14	.03	.19	.11	.06	-.06	-.48***	-.51***	–			
11. QLPS	.10	.03	.06	.09	.07	-.12	-.17	-.73***	-.70***	.59***	–		
12. QLS	.11	-.05	.12	.06	.09	-.11	-.18	-.51***	-.49***	.44**	.63***	–	
13. QLE	.26	.00	.21	.21	.20	-.14	-.26	-.56***	-.34*	.47***	.59***	.65***	–

Descriptives	CAB	CAR	PEP	RSA	LVET	SV	CO	ANX	DEP	QLPH	QLPS	QLS	QLE
Mean	0.00	0.00	92.76	4.86	304.80	257.64	17.85	6.94	4.44	14.33	14.33	13.38	16.04
SD	1.61	1.19	24.00	1.15	71.94	106.73	7.05	3.55	2.98	3.22	2.84	3.55	2.86
Minimum	-3.13	-3.78	50.00	2.66	158.00	94.47	6.20	1.00	0.00	7.43	7.33	6.67	9.00
Maximum	3.85	2.92	142.00	7.58	410.00	553.33	37.38	14.00	13.00	20.00	19.33	20.00	20.00

Note: *** < .001; ** < .01; * <.05; CAB = Cardiac Autonomic Balance; CAR = Cardiac Autonomic Control; PEP = pre-ejection period; RSA = respiratory sinus arrhythmia; LVET = left ventricular ejection time; SV = stroke volume; CO = cardiac output; ANX = Hospital Anxiety and Depression – Anxiety Scale Score; DEP = Hospital Anxiety and Depression – Depression Scale Score; QL-PH = WHO Quality of Life–Brief–Physical Domain; QLPS = WHO Quality of Life–Brief–Psychological Domain; QLS = WHO Quality of Life–Brief –Social Domain; QLE = WHO Quality of Life–Brief–Environmental Domain.

With regard to quality of life, only one model reached significance. In the prediction of the Quality of Life-Environment Domain, both LVET (β=0.369) and CO (β=-0.353) significantly predicted total scores on this subscale, R^2=.25, adjusted R^2=.14, F(5,44)=2.558, p=.041. These findings indicate that individuals with longer LVET and lower CO scored higher in this domain of QOL. Models predicting Physical Domain scores, F(5,44)=1.097, p=.375, Psychological Domain scores, F(5,44)=0.988, p=.436, and Social Domain scores, F(5,44)=1.676, p=.160 failed to reach significance. These findings indicate that the CAB, CAR, and individual measures of cardiac functioning did not predict these quality of life domains, while controlling for diagnosis of MetS.

Regression models predicting anxiety, F(5,44)=1.056, p=.728, and depression, F(5,44)=0.674, p=.645, failed to reach significance. These findings indicate that the CAB, CAR, and individual measures of cardiac functioning did not predict these self-reported anxiety or depression scores, while controlling for diagnosis of MetS. Collectively, these results provide only partial support to our first experimental hypothesis.

Hypothesis 2: Individuals with MetS will evidence lower CAC at baseline

Prior to examination of baseline CAB and CAR, we performed a 2 (experimental group) × 2 (sex) multivariate analysis of covariance (MANCOVA) to determine differences in baseline PEP and RSA. We controlled for number of medical problems and for medication use by entering as a dummy-coded variable patients who were and were not prescribed beta-blockers. In reviewing multivariate results, we failed to detect main effects for group, Λ=.958, F(2, 43)=0.933, p=.401, or sex, Λ=.991, F(2, 43)=0.189, p=.828, suggesting that neither baseline PEP nor RSA were significantly different between these sets of participants.

Subsequently, we performed a 2 (experimental group) × 2 (sex) MANCOVA to identify differences in baseline CAB and CAR scores. We controlled statistically for baseline PEP and RSA scores as well as number of medical problems and medication use, as noted above. We failed to detect main effects for group, Λ=.979, F(2, 43)=0.464, p=0.632, or sex, Λ=.993, F(2, 43)=0.153, p=.859, suggesting that neither baseline CAB nor baseline CAR scores were significantly different between these groups, even when controlling statistically for medical problems and medication use. These findings do not support experimental hypothesis 2.

Aim 2: Examine CAC among patients with MetS during a standardized stressor.

Hypothesis 3: Patients with MetS will display lower CAC scores during standardized stressors.

Prior to examining group differences in calculated CAC scores during any of the experimental stressors, our first task was to verify that group differences exist in the constituent variables that comprise the computed CAB and CAR scores. These analyses also helped us verify the effectiveness of our experimental manipulation. To this end, we executed paired-sample *t*-tests across the full sample to examine differences in PEP and RSA between baseline and each segment of the experimental manipulation. We also conducted a 2 (experimental group) × 2 (sex) MANCOVA to determine differences in PEP and RSA scores during both the mental arithmetic and health and wellness stressors. In the MANCOVA analysis, we controlled for number of medical problems and medication use by entering as a dummy-coded variable patients who were and were not prescribed beta-blockers. We also included baseline PEP and RSA scores as covariates during examination of experimental stressors, following Bernston et al. (2008). Descriptive statistics for variables included in these analyses are presented in Appendix A.

Findings from paired-sample *t*-tests suggested that across the full sample, our experimental manipulations were associated with significantly lower PEP values relative to baseline, providing evidence that our experimental manipulation was effective in eliciting a physiological stress response (see Table 8).

Table 8. Tests of Differences in PEP and RSA Between Baseline and Experimental Task Segments Across the Full Sample (N = 50).

	t	***df***	***p***
Health and Wellness Interview			
Medication Segment			
Baseline – Task Δ PEP	2.216	49	.031
Baseline – Task Δ RSA	-1.193	49	.239
Diet Segment			
Baseline – Task Δ PEP	3.314	49	.002
Baseline – Task Δ RSA	-1.087	49	.282
Exercise Segment			
Baseline – Task Δ PEP	1.436	49	.157
Baseline – Task Δ RSA	-0.494	49	.632
Stress Segment			
Baseline – Task Δ PEP	1.866	49	.068
Baseline – Task Δ RSA	-0.693	49	.492
Coping Segment			
Baseline – Task Δ PEP	1.770	49	.083
Baseline – Task Δ RSA	0.140	49	.889
Mental Arithmetic			
Serial 7s Segment			
Baseline – Task Δ PEP	2.393	49	.021
Baseline – Task Δ RSA	1.946	49	.057
Multiplication Segment			
Baseline – Task Δ PEP	2.665	49	.010
Baseline – Task Δ RSA	0.580	49	.565

Note: PEP = Pre-ejection period; RSA = Respiratory sinus arrhythmia

Multivariate results by experimental group revealed a significant main effect for group, Λ=.469, F(14, 29)=2.348, p=.025, partial η^2=.531, but not for sex, Λ=.624, F(14, 30)=1.250, p = .295. Findings from planned comparisons within this set of analyses are presented in Table 9.

Table 9. Tests of Between-subject Differences in PEP and RSA During Individual Segments of the Experimental Task.

	F	*df*	*p*	Partial η^2
Health and Wellness Interview				
Medication Segment				
PEP	6.763	1, 42	.013	.139
RSA	1.011	1, 42	.320	.024
Diet Segment				
PEP	8.562	1, 42	.006	.169
RSA	0.102	1, 42	.751	.002
Exercise Segment				
PEP	0.333	1, 42	.567	.008
RSA	1.137	1, 42	.292	.026
Stress Segment				
PEP	0.919	1, 42	.343	.021
RSA	3.591	1, 42	.065	.079
Coping Segment				
PEP	0.187	1, 42	.668	.004
RSA	0.061	1, 42	.806	.001
Mental Arithmetic				
Serial 7s Segment				
PEP	0.000	1, 42	.984	.000
RSA	0.636	1, 42	.481	.012
Multiplication Segment				
PEP	0.147	1, 42	.704	.003
RSA	0.871	1, 42	.356	.020

Note: PEP = Pre-ejection period; TPR = Total peripheral resistance

After accounting for covariates described above, estimated marginal mean PEP values in the HC group were higher during the medication and diet segments, as compared to the MetS group, suggesting a greater sympathetic response in MetS during these segments. The group-by-sex interaction failed to reach significance, Λ=.614, $F(14, 29)$=1.301, p=.263.

We then performed a 2 (experimental group) × 2 (sex) repeated measures MANCOVA to determine differences in CAB and CAR scores during the two mental arithmetic stressors. We controlled statistically for baseline CAB and CAR scores as well as number of medical problems and beta-blocker medication (dummy coded). We failed to detect main effects for group, Λ=.981, $F(2, 41)$=0.392, p=.678, or sex, Λ=.984, $F(2, 41)$=0.337, p=.716, suggesting that

contrary to our hypothesis, CAB and CAR scores during all segments of the standardized stressor tasks did not differ by experimental group or as a function of sex, when controlling for medication. Figure 7 depicts group CAB and CAR scores during the mental arithmetic stressors.

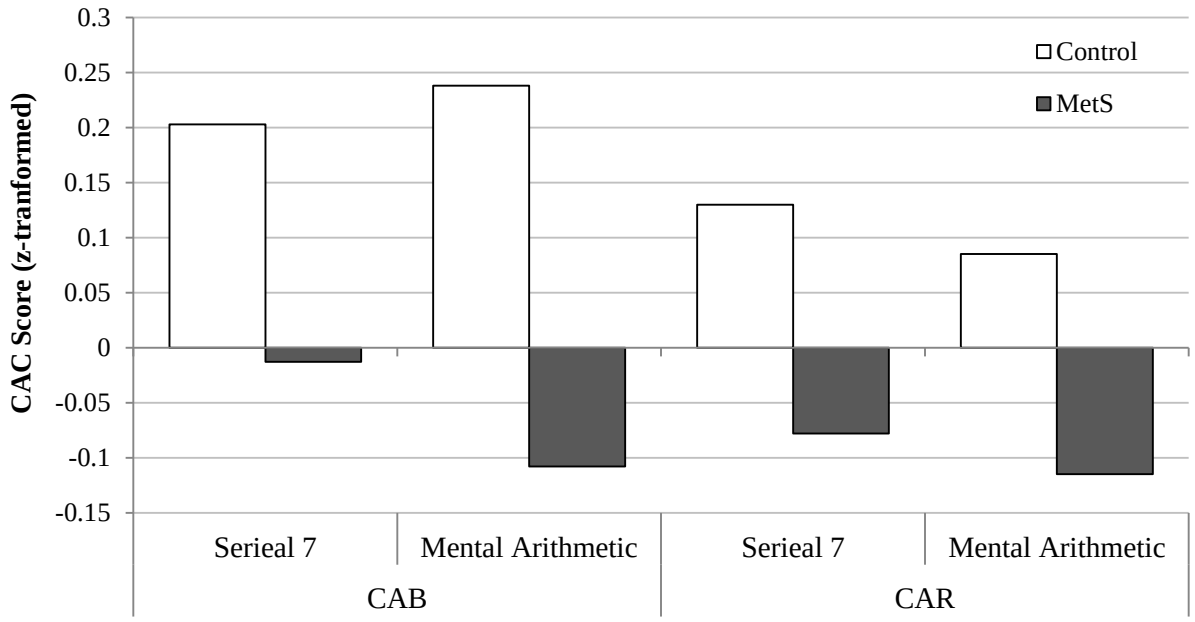


Figure 7. Between-group Estimated Marginal Means of CAB and CAR Scores During the Mental Arithmetic Stressors

Aim 3: Examine CAC Among Patients with MetS During a Health and Wellness Interview

Hypothesis 4: Patients with MetS will display lower CAC scores during health interview.

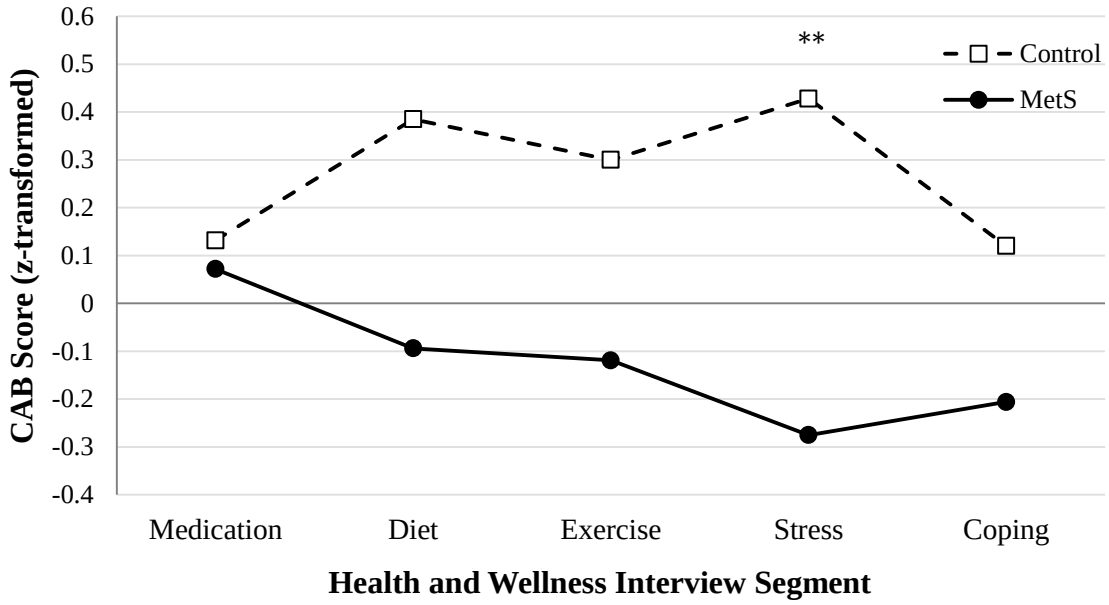
We performed a 2 (experimental group) × 2 (sex) MANCOVA to determine differences in CAB and CAR scores during the five health and wellness interview segments. We controlled statistically for baseline CAB and CAR scores as well as number of medical problems and medication use (dummy-coded), as noted above. Overall, we failed to detect main effects for group, Λ=.931, $F(2, 42)$=1.561, p=.222, or sex, Λ=.928, $F(2, 42)$=1.634, p=.207, suggesting that the CAB and CAR were statistically equivalent across experimental group and participant sex,

even when controlling for medication use that has the potential to alter sympathetic cardiac control. Nonetheless, we did detect a segment-by-group interaction, Λ=.496, F(2, 42)=4.573, p=.001, partial η^2=.504, suggesting CAC scores during interview segments differed as a function of experimental group.

Follow-up multivariate tests of within-subjects effects confirmed this interaction, Λ=.893, F(8, 334)=2.440, p=.004, and univariate tests of within-subjects contrasts (i.e., changes over time) revealed that CAB scores across the HWI interview segments were significantly different between the MetS group and the HC group, F(1, 42)=11.974, p=.001, partial η^2=.222. In addition, we found that CAR scores across the HWI interview segments were significantly different between the MetS group and the HC group, F(1, 42)=9.495, p = .004, partial η^2=.184. Collectively, this pattern of findings permitted additional inspection of differences in CAB and CAR at each individual segment.

Planned between-subjects comparisons (paired-samples *t*-tests corrected for multiple comparisons using the Bonferoni adjustment) across interview segments confirmed that CAB scores during the stress segment were significantly higher in the HC group as compared to the MetS group, p=.049. We also observed that CAR scores during the medication segment were significantly higher in the MetS group as compared to the HC group, p=.051. MetS and HC groups did not respond differently during other interview segments, providing partial support for this hypothesis. Figures 8a and 8b depict CAB and CAR scores, respectively, across each of the health and wellness interview segments as a function of experimental group.

(a)



(b)

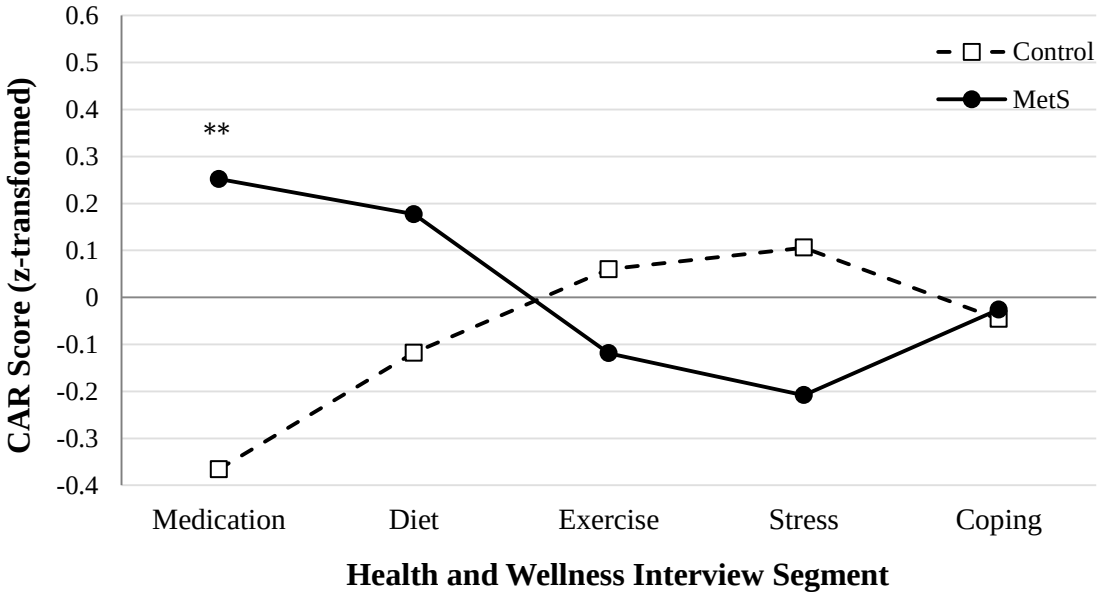


Figure 8. Between-group Estimated Marginal Means of (a) CAB and (b) CAR Scores Across All Health and Wellness Interview Segments.
Note: ** $p < .05$

Hypothesis 5: During experimental tasks, a CV "threat" response will be associated with MetS.

Binary logistic regression was used to predict MetS diagnosis from CV variables. Unanticipated discrepancies in the initiation of the Mental Arithmetic and Health and Wellness Interview tasks across participants limited our ability to verify that a particular BP measurement and TPR value was representative of physiological reactions to that task. Therefore, we used sequential points of measurement as an alternative method of estimation, serving as a proxy for on-going task engagement. We entered PEP, TPR, and an interaction term (PEP × TPR) hierarchically in blocks representing each of the measurement points, such that each block only contained the observed variables for that point in time (i.e., 300 [baseline], 600, 900, 1200, 1500 and 1800 seconds). The interaction term was intended to depict the simultaneous cardiac and vascular changes that characterize the "threat" response. In the initial block, we also included dummy-coded variables accounting for medication prescriptions (beta-blocker and ACE inhibitor). Each block in the model included previous blocks to estimate the cumulative effect of these observations in the prediction of MetS.

Table 10. Omnibus Chi-Square, Goodness-of-fit, and Classification Accuracy Derived from the Full Logistical Model Predicting Metabolic Syndrome through PEP and TPR.

	Nagelkerke R^2	% correct	χ^2	*df*	*p*
Block 1, Omnibus Model Test	**.000**	**52.4**	**.008**	**3**	**.998**
H-L Goodness-of-Fit			10.556	8	.228
Block 2, Omnibus Model Test	**.225**	**54.8**	**7.730**	**6**	**.258**
H-L Goodness-of-Fit			6.558	8	.585
Block 3, Omnibus Model Test	**.457**	**78.6**	**17.631**	**9**	**.040**
H-L Goodness-of-Fit			8.682	8	.370
Block 4, Omnibus Model Test	**.538**	**78.6**	**21.665**	**12**	**.041**
H-L Goodness-of-Fit			5.962	8	.651
Block 5, Omnibus Model Test	**.594**	**83.3**	**24.746**	**15**	**.053**
H-L Goodness-of-Fit			10.155	8	.254
Block 6, Omnibus Model Test	**.804**	**92.9**	**38.747**	**18**	**.003**
H-L Goodness-of-Fit			3.110	8	.927

Note: H-L = Hosmer-Lemeshow

Table 10 provides omnibus chi-square model tests as well as goodness-of-fit tests for each block in the model. Table 11 provides parameter estimates of all indicators entered into the full model.

Table 11. Logistical Regression Parameter Estimates, Standard Errors, and Odds Ratio for the Full Logistical Model in the Prediction of Metabolic Syndrome from Measures of PEP and TPR.

	β	***SE* β**	**Wald**	***df***	***p***	e^{β}
Null Model (Constant)	22.231	30.890	0.518	1	.472	4.516
Block 1 (Baseline)						
PEP, 300 seconds	0.241	0.290	0.687	1	.407	1.272
TPR, 300 seconds	-0.291	4.067	0.005	1	.943	.748
PEP × TPR 300 seconds	-0.054	0.045	1.464	1	.226	.947
Block 2						
PEP, 600 seconds	-1.209	0.678	3.179	1	.075	.298
TPR, 600 seconds	-6.414	5.643	1.292	1	.256	.002
PEP × TPR 600 seconds	0.166	0.109	2.350	1	.125	1.181
Block 3						
PEP, 900 seconds	-0.761	0.490	2.241	1	.120	.467
TPR, 900 seconds	-14.564	8.527	2.917	1	.088	.000
PEP × TPR 900 seconds	0.168	.099	2.846	1	.092	1.183
Block 4						
PEP, 1200 seconds	-0.871	0.657	1.760	1	.185	.418
TPR, 1200 seconds	-9.001	8.763	1.055	1	.304	.000
PEP × TPR 1200 seconds	0.103	0.116	0.779	1	.377	1.108
Block 5						
PEP, 1500 seconds	0.414	0.329	1.586	1	.208	1.513
TPR, 1500 seconds	-7.018	4.486	2.448	1	.118	.001
PEP × TPR 1500 seconds	0.077	0.049	2.455	1	.117	1.080
Block 6						
PEP, 1800 seconds	1.859	1.067	3.034	1	.082	6.416
TPR, 1800 seconds	29.617	16.870	3.082	1	.079	7.285
PEP × TPR 1800 seconds	-0.353	0.205	2.977	1	.084	.702

Note: PEP = Pre-ejection Period; TPR = Total Peripheral Resistance

Overall model chi-square tests reached significance, suggesting that the full model predicted diagnosis of MetS. Nonetheless, when individual indicators were examined, none of the Wald estimates in this model reached significance and therefore cannot be interpreted. This

pattern suggests that no single indicator variable significantly contributed to the full model, but that collectively, this series of variables adequately predicted group membership.

The independent variables in this analysis were intended to serve as indicators of the "threat" response. Because they failed to reach significance, the interpretation of this model is not feasible. As such, an alternative method to understand the association between MetS and cardiovascular responses involves visual and statistical examination of group differences in PEP and TPR change scores at each point of measurement. To this end, we compared the experimental groups on change-from-baseline PEP and TPR at each point of measurement using 2 (experimental group) X 2 (sex) repeated measures MANCOVA controlling number of medical problems and medication use (beta blocker, ACE inhibitor). Time points were used as the within-subjects factor in the same fashion as noted above (i.e., at 600, 900, 1200, 1500 and 1800 seconds). The 300-second point of measurement of PEP and TPR was used in the calculation of change scores and therefore was not included in the analysis.

Contrary to expectations, findings from the MANCOVAs did not reveal a within-subjects main effect for group, Λ=.965, F(2, 31)=0.561, p=.357. The main effect for sex was also non-significant, Λ=.936, F(2, 31)=1.066, p=.278. There was no within-subject main effect for measurement point, Λ=.804, F(8, 25)=0.761 p=.639, and neither the time-by-group interaction, Λ=.661, F(8, 25)=1.604, p=.174, nor the time-by-sex interaction reached significance, Λ=.719, F(2, 28)=1.223, p=.326. Collectively, these findings do not support our fifth experimental hypothesis.

Aim 4: Examine the Impact of CAC on Health Behavior and Treatment Adherence

Hypothesis 6: CAC scores will be associated with health behavior and medication adherence

Prior to analyses, we examined the self-report outcome variables to address concerns related to violations of the general linear model, as described above. We determined that even when utilizing the well-supported AUDIT cut off score of '8' to denote problematic drinking, cell size of the problematic drinking group was too small ($N = 4$) to analyze statistically. In conjunction with the significant skewness observed in the continuous AUDIT score, we removed this variable from the analytic plan. Additionally, we created a dichotomous variable from the physical activity group assignment due to initial findings revealing singularities in the multinomial regression Hessian matrix, typically indicating statistical separation in the DV. Separation is sometimes referred to as 'perfect prediction,' and occurs when one of the categorical outcome groups is explained entirely by one level of an indicator variable. In this case, the recommended approach is to re-specify the model by merging categories of the outcome variable or creating fewer groups (Gill & King, 2003). Because the groups were approximately equal in size, we created a dichotomous (median-split) variable based on the continuous physical activity scale, resulting in low- and high-activity groups. Finally, as described in the AUDIT scores, we found similar differences in smoking classification, with separate groups of current smokers ($N = 5$) and previous smokers ($N = 11$) creating too few cases in each cell for analysis. In this case, we collapsed responses to the smoking status question creating two groups, one comprising current and previous smokers and one comprising non-smokers.

We then performed a series of logistic regression analyses predicting smoking group (yes vs. no) and activity group (low vs. high) using sex and experimental group as initial covariates in block 1. Both baseline CAB and CAR as well as a CAB × CAR interaction term scores were entered into the regression equation in a hierarchical fashion in block 2. Subsequently, we performed a series of linear regressions predicting BMI and medication adherence score using sex and experimental group as initial covariates in block 1. As above, baseline CAB and CAR and a CAB × CAR interaction term were entered into the regression equation in block 2. Findings from the final model blocks are described in-text. Findings form the full models are presented in Tables 12 and 13.

Table 12. Full Model Logistic Regression Analysis Predicting Smoking Status and Low Physical Activity from CAB and CAR Scores

Positive Smoking Status (*N*=16)

Indicator	β	*SE* β	Wald	*df*	*p*	e^{β}
(Constant)	0.199	0.753	.070	1	.791	1.221
Sex	-2.114	0.780	7.175	1	.007	.121
Group	0.421	0.783	0.289	1	.591	1.524
CAB	-0.305	0.272	1.259	1	.262	.737
CAR	-0.687	0.356	3.730	1	.053	.503
CAB × CAR	-0.041	0.307	0.018	1	.894	.960

Test			χ^2	*df*	*p*	
Overall Model Evaluation			15.671	5	.008	
H-L Goodness of Fit			6.799	8	.558	

Low Physical Activity (*N*=25)

Indicator	β	*SE* β	Wald	*df*	*p*	e^{β}
(Constant)	0.545	0.671	0.661	1	.416	1.725
Sex	-0.250	0.663	0.142	1	.707	.779
Group	-0.756	0.620	1.483	1	.223	.470
CAB	-0.295	0.195	2.279	1	.131	.745
CAR	-0.083	0.264	0.100	1	.752	.920
CAB × CAR	0.071	0.223	0.101	1	.751	1.073

Test			χ^2	*df*	*p*	
Overall Model Evaluation			4.704	5	.448	
H-L Goodness of Fit			8.498	8	.386	

The full logistic model predicting physical activity failed to reach significance; however, as noted in Table 11, the full model predicting smoking status was significant, Nagelkerke R^2=.269, and correctly classified 78% of all cases with affirmative smoking status. In this model, both participant sex (β=-2.114) and CAR (β=-0.687) were significant negative indicators, suggesting male gender and decreased CAR scores are associated with an increased likelihood of smoking status. The Hosmer-Lemeshow goodness-of-fit test was non-significant for this model,

indicating that this model is appropriately specified, and observed group membership did not deviate from the expected count predicted by the model.

Table 13. Multiple Regression Estimates Predicting BMI and Medication Adherence from CAB and CAR Scores.

	β	***SE* β**	**B**	***t***	***p***
Body Mass Index					
(Constant)	**21.449**	**3.651**	**–**	**5.992**	**.000**
Sex	6.448	1.923	.162	1.177	.246
Group	2.263	1.794	.496	3.594	.001
CAB	0.126	0.542	.031	0.233	.817
CAR	0.428	0.761	.077	0.562	.577
CAB × CAR	0.254	0.613	.056	0.400	.691
Medication Adherence					
(Constant)	**2.421**	**1.132**	**–**	**1.966**	**.054**
Sex	-0.099	0.596	-.024	-0.165	.869
Group	1.009	0.556	.265	1.813	.077
CAB	-0.273	0.168	-.229	-1.628	.111
CAR	0.256	0.236	.158	1.083	.285
CAB × CAR	0.177	0.190	.139	0.931	.357

Note: CAB = cardiac autonomic balance; CAR = cardiac autonomic regulation

With regard to BMI, the omnibus test of the full model was significant, $F(5,44)=2.825$, $p=.027$, $R^2=.24$, adjusted $R^2=.16$. Within this model, only group membership (β=2.263) was a significant predictor of BMI. With regard to medication adherence, the omnibus test of the full model in the prediction failed to reach significance, $F(5,44)=1.562$, $p=.191$. These findings should be interpreted with caution, however, because in both instances the null model remained significant with the inclusion of the hypothesized indicator variables. As such, we cannot conclude that these variables enhance prediction of BMI or medication adherence.

CHAPTER FOUR: DISCUSSION

The purpose of this investigation was to further clarify the relationship between metabolic abnormalities and autonomic dysregulation as measured by variations in CAC. In support of this purpose, we used ambulatory ICG to measure physiological changes during engagement in psychosocial stressors among 50 patients with and without metabolic syndrome. We then compared these groups on a variety of cardiovascular measures to identify the extent to which patterns of sympathovagal reactivity may be implicated in MetS, and whether such a relationship may also impact health behavior and treatment adherence. To our knowledge, this is the first study to examine whether individuals with and without MetS differ in regard to CAC in the context of experimentally induced stress. We developed four aims to address our core research questions. Each of these aims will be discussed in turn.

Our first aim was to verify the association between CAC and health status. In particular, we set out to replicate previous findings that suggest CAB and CAR are related to certain chronic conditions that develop as a result of MetS (i.e., type 2 diabetes and cardiovascular disease). We hypothesized that CAC indices would predict diagnosis of these conditions in our sample; this hypothesis gained partial support. As expected, CAR was a significant predictor of cardiovascular disease, lending support to the original work by Berntson et al. (2008). This finding indicated that within the full sample, individuals who evidenced a lower degree of co-activation between sympathetic and parasympathetic systems were more likely to be diagnosed with cardiovascular disease. This association is conceptually and empirically well-supported, as diminished sympathovagal co-activation may restrict the dispositional nature with which one adapts to a stressor, and facilitating a cycle of maladaptive responding (Sloan et al, 1995).

Despite this significant outcome, CAB was not a significant predictor of type 2 diabetes, a finding that does not replicate the original work. There are likely several reasons for this null finding, the most salient of which may be related to consistency of diabetes management across the sample. While many measurements of HbA1C were missing from this sample, most of the existing values were below 7.5, suggesting a relatively high degree of control of this chronic condition and potentially decreased burden on the cardiovascular system.

In an effort to further examine the relationship between CAC and health status, we also tested whether cardiovascular measures (including CAB and CAR) could predict self-reported measures of psychosocial distress and quality of life while controlling for MetS diagnosis. Contrary to our expectations, our models predicted only one of the quality of life domains (environmental). We found higher LVET scores and lower CO scores were associated with greater environmental quality of life. Higher LVET scores are often cited as a marker of decreased sympathetic cardiac control; likewise, CO, which is largely related to myocardial contractility[3], may also serve as an indicator of sympathetic activation. These variables not only predicted quality of life in this domain, but also did so in an expected direction, such that lower sympathetic activation is associated with increased perceived environmental quality of life. Items in this scale pertain to physical safety and security, accessibility and quality of health care, and quality of physical environment, among others. It may be that individuals who respond with decreased sympathetic cardiac control are more likely to engage in practices that support this

[3] There are a host of additional variables that influence and/or change CO including pre-load, after-load and heart rate (Vincent, 2008). However, because contractility is often indicative of sympathetic cardiac control in non-exertive situations, it frequently denotes degree of sympathetic activation.

domain of quality of life. Our models did not predict anxiety or depression scores, however, running contrary to our hypothesis. Failure to detect differences in these models may be due to a relatively low degree of reported symptoms (i.e., restricted range) within these measures.

Our second hypothesis within this aim was to examine baseline differences in CAC and related indices of sympathovagal activation between the MetS and HC groups. We hypothesized that the MetS and HC groups would differ both on individual measures of sympathetic (PEP) and parasympathetic (RSA) cardiac control, but also on the computed measures of CAB and CAR. Contrary to expectations, baseline CAB and CAR scores did not differ between groups, even when controlling for medication use and number of medical problems. Though unanticipated, this finding nonetheless provides important information with regard to reactivity of the experimental groups during experimentally induced stress. That is, this finding argues against the notion that cardiovascular status individuals with MetS are fundamentally different at rest. Instead, we submit that it is in the process of appraising and responding to external demands that meaningful alterations emerge. These alterations, in turn, may provide the foundation for negative health outcomes.

Our second and third experimental aims were directed at understanding this possibility and were focused on examining CAC among patients with MetS during the two distinct experimental tasks. These tasks comprised standardized mental arithmetic as well as a structured, but flexible health and wellness interview. Prior to proceeding with these tests, we first verified the effectiveness of our experimental relationship by examining changes in key psychological variables across the full sample during the experimental task. We identified decreases in PEP

during a number of the task segments, providing initial indication that our experimental task elicited the expected response across the entire sample.

We hypothesized that individuals with MetS would evidence lower CAB and CAR scores during the standardized Mental Arithmetic stressor. By virtue of the standardization, this stressor was intended to provide a point-of-comparison for subsequent experimental tasks. Our findings revealed that configuration of CAB and CAR responses to the arithmetic tasks were consistent with expectation, but these differences failed to reach statistical significance. It is unlikely that this null finding is an artifact of practice effects. Counterbalancing of experimental tasks was crucial in order to verify group differences were due not to passage of time, but to the specific experimental manipulation. The utility of using this stressor as a point-of-comparison is therefore crucial in the context of examining hypothesized between-group differences during the other stressors tasks.

Indeed, we observed such differences during distinct segments of the health and wellness interview. These differences occurred both in PEP and RSA as well as the computed CAC variables. Specifically, PEP among HC participants became longer during the medication and diet segments, as compared to those with MetS. This difference was in the expected direction, suggesting that HC participants responded with decreased sympathetic activity in response to these segments.

Moreover, we found significant group-by-segment interaction in both CAB and CAR scores that highlight how patterns of responses between experimental groups differed in the context of distinct interview segments. CAB scores in the HC group generally increased across the interview segments, peaking during the stress segment. The opposite pattern was observed in

the MetS group, which evidenced generally decreasing CAB scores, with the lowest value observed during the stress segment. That is, MetS participants demonstrated poorer sympathovagal balance when discussing their daily stress as compared to HC patients. This finding points to maladaptive psychological responses to an externally presented stressor (i.e., the interview questions), and it is potentially meaningful given its relevance to stress cues. It is possible that patterns of appraisal observed here may become chronic and can therefore place an individual at greater risk for negative health outcomes either by limiting the extent to which the individuals maintains allostasis, or by increasing allostatic load. It may also be the case that the topic presented during this experimental task provides a context in which the patient with MetS may avoid stress cues.

Patterns of CAR scores during the interview segments were slightly different relative to the corresponding pattern of CAB scores. Among HC participants, CAR scores were the lowest in response to questions about medication adherence and trended upward thereafter, peaking during the stress segment. Again, the opposite pattern was seen in MetS patients with highest CAR scores observed during the medication segment. CAR scores then decreased gradually to their lowest point, observed during the stress segment. This pattern indicates coactive sympathovagal responses among MetS patients discussing medication adherence, in comparison to HC participants, who responded with a lesser degree of sympathovagal co-activation to the same questions. This finding, though unexpected, may support the notion that as medical complexity increases, so too does the likelihood of a holding multiple medications prescription. The MetS group, who evidenced more medical problems, may have a greater demand for regular medication adherence, thereby demonstrating a greater degree of coactive autonomic control in

response to this perceived demand. Conversely, HC participants who likely had fewer medication concerns may not have appraised this segment in the same way, leading to a less dramatic autonomic response.

We also set out to assess whether dominant motivational states (i.e., "challenge" vs. "threat") could be associated with MetS by examining variations in cardiac and vascular reactivity to our experimental manipulation. Unfortunately, due to technological limitations of the monitoring equipment, we were unable to verify that TPR readings corresponded to the distinct start- and end-points of our stressor tasks, and therefore, we could not test whether changes in TPR corresponded to experimental manipulation. Instead, we examined whether PEP and TPR across the full experimental task (approximately 30 minutes) as an analogue. Initial findings suggested that PEP, TPR, and an interaction term representing their combined effect was predictive of MetS; however, we were unable to determine that specific indicators were statistically associated with our outcome, so these models could not be interpreted. We then attempted to compare MetS groups on PEP and TPR at each point of measurement to further determine if distinct CV patterns underlying motivational state varied between HC and MetS groups. Our primary hypothesis was not supported, however, as we were unable to detect differences in PEP or TPR at sequential points of measurement. This null finding is most likely due to the temporal staggering in both task engagement and baseline recovery across the sample.

Our final aim was to examine the influence of cardiac autonomic control on health behaviors and treatment adherence among individuals with MetS. We hypothesized that lower CAC would predict poorer health behaviors, higher BMI and poorer medication adherence. Indeed, the hypothesis gained partial support. Across the whole sample, decreased CAR scores

and male gender were associated with an increased likelihood of smoking, while controlling for experimental group. This pattern may be representative of attempts to behaviorally regulate sympathovagal activity. None of the other models suggested that CAB or CAR were predictive of poor treatment adherence. Because these models failed to adequately predict the identified outcomes, the indicator variables we measured cannot be used to explain patterns of disease progression in MetS. It is possible that with a larger sample, these hypotheses could be addressed with greater cogency and more vigorous conclusions may be drawn.

Limitations

A primary limitation of the present investigation pertains to experimental power and external validity given current sample size. Most notably, statistical control of potentially confounding variables becomes problematic in small samples, as inclusion of covariates expends degrees of freedom. This concern was particularly relevant as we attempted to account for the impact of CV medications on our outcome variables. For more robust hypothesis testing and replication of the present findings, collection of data in a larger sample is warranted. Second, we observed a number of missing data, primarily within the patients' laboratory findings maintained in their medical record. These particular data could not be imputed because they were not missing at random; rather, they were collected (or not collected) based on best practice guidelines of clinical care, which are directly related to disease status and progression. Indeed, if these data were to be imputed, it would likely lead to biased estimates. Nonetheless, inclusion of these observations would have allowed for a number of analyses that were not feasible in the present data set (e.g., examination of MetS as a continuous variable thereby permitting estimation of illness severity). A third limitation, as noted above, involved technological issues

in BP measurement. Obtaining a non-continuous measure was the most logistically appropriate option for this investigation but it presented a significant barrier when comparing cardiovascular reactivity across experimental groups. Without a continuous measure of BP, and in view of the necessarily variable boundaries of the experimental tasks, we could not compare participants' TPR responses during task engagement. This circumstance limited out ability to test differences along the domain of TPR reactivity, and by extension, to draw conclusions about how such differences may potentiate the relationships described here. Finally, due to time restrictions we were unable to collect objective measures of diet. Given the role of diet in MetS, these measurements would have offered the opportunity to conduct additional analyses pertaining to disease etiology and maintenance, which were not feasible in this study. This limitation is also related to the problem of using the health behaviors measures here as an analogue of treatment adherence.

Future Directions

The most important extension of this work would be to develop longitudinal, prospective studies to examine the extent to which CAC and its constituent indicators may be implicated in the etiology of MetS. Within this type of study design, longer periods of monitoring (e.g., over a period of hours) across many days, weeks, or months may be helpful to clarify the timeline along which etiological mechanisms operate. A particular strength of this kind of study could be examination of other stressors types (e.g., medical visits vs. family interactions) to better understand the circumstances within which stress is pathogenic. Additionally, our findings are consistent with the notion that direct engagement in stress cues is associated with potentially maladaptive responses among individuals with metabolic abnormalities. One implication of such

findings is that certain patterns of reactivity contributes to disease maintenance, given the established influence of stress in MetS; it is therefore possible that prototypical 'profiles' can be observed among subgroups of individuals with MetS. Cluster or latent class analysis could help uncover these subgroups of individuals. Similarly, understanding protective factors in this population would offer an important perspective on minimizing the damaging effects of dysregulated CAC. Coping may prove to be one such factor that could safeguard against progression of MetS. Given the emphasis on behavioral interventions in managing stress, examination of coping skills would serve as a crucial component of programmatic research in the physiology of illness. Finally, repercussions of autonomic reactivity may be evident in other systems, such as immune and endocrine reactivity (e.g., HPA-axis). Given the emerging emphasis on inflammation as a cross-cutting feature of a number of diseases, including MetS (Lee & Pratley, 2005), it would be valuable also to evaluate the extent to which autonomic tendencies identified here contribute to patterns of immune functioning and/or inflammation.

Conclusions

As reviewed above, previous findings have supported the notion that psychological appraisal in response to external demands are associated with physiological changes that may have deleterious effects over time. Such evidence has been used to advance current etiological models of MetS (Aubert & Raemaekers, 1999; Bellavere et al., 1992; Krzesinski, Gielerak, & Kowal, 2013; Malliani, 2005; McGrady, 2010). The findings of the present study also contribute to this existing body of evidence, supporting psychological contributions to physical illness and may offer additional information about the conditions under which psychological reactivity is involved in disease progression.

Though limitations exist, this study has implications both for assessment and treatment monitoring, especially given the potential relationship between CAC and health and wellness ques presented here. On-going hemodynamic evaluation of individuals with MetS would allow application of basic physiological concepts to relevant real-world settings in order to predict patient outcomes and response to treatment. Notably, the ambulatory nature of these monitoring procedures is consistent with ongoing efforts to enhance mobile health (mHealth) and can even inform remote delivery of clinical interventions such as biofeedback. Crucially, our results can be applied to preventative efforts to help individuals at risk for metabolic syndrome identify and thereby alter responses to stress.

APPENDIX A: DESCRIPTIVE STATISTICS FOR STUDY VARIABLES BY EXPERIMENTAL GROUP

Appendix A: Descriptive Statistics for Study Variables by Experimental Group

	Healthy Control (*N*=25)		Metabolic Syndrome (*N*=25)	
	M (SD)	Range	*M (SD)*	Range
Baseline PEP	89.36 (22.04)	50.00–126.00	96.16 (25.80)	68.00–142.00
Baseline RSA	4.75 (1.20)	2.66–7.23	4.97 (1.11)	2.87–7.58
Baseline CAB	-0.24 (1.59)	-3.13–2.61	0.24 (1.63)	-1.91–3.85
Baseline CAR	0.05 (1.16)	-1.99–2.92	-0.05 (1.24)	-3.78– 1.73
HWI, Medication	–	–	–	–
PEP	88.40 (25.77)	54.00–134.00	91.12 (25.93)	64.00–148.00
RSA	4.95 (1.20)	2.72–7.59	5.12 (1.43)	2.46–7.74
CAB	-0.12 (1.44)	-3.02–2.65	0.12 (1.55)	-2.34–3.79
CAR	-0.01 (1.28)	-2.94–2.25	0.01 (1.42)	-3.92–2.50
HWI, Diet	–	–	–	–
PEP	87.68 (24.14)	56.00–128.00	88.56 (28.06)	46.00–146.00
RSA	5.04 (1.27)	2.60–7.74	5.02 (1.36)	2.61–7.10
CAB	-0.01 (1.56)	-2.75–2.46	0.01 (1.40)	-2.12–2.43
CAR	0.02 (1.10)	-1.78–2.08	-0.02 (1.59)	-3.94–2.36
HWI, Exercise	–	–	–	–
PEP	86.88 (26.36)	50.00–132.00	92.56 (29.12)	62.00–146.00
RSA	5.15 (1.30)	1.46–7.44	4.73 (1.41)	2.50–7.84
CAB	0.05 (1.49)	-2.54–2.78	-0.05 (1.58)	-2.43–2.32
CAR	0.26 (1.19)	-2.56–1.83	-0.26 (1.37)	-3.06–2.63
HWI, Stress	–	–	–	–
PEP	86.72 (24.21)	54.00–132.00	91.44 (28.60)	64.00–142.00
RSA	5.34 (1.22)	2.79–8.08	4.60 (1.23)	2.59–6.85
CAB	0.20 (1.48)	-2.30–3.07	-0.20 (1.47)	-2.57–2.68614
CAR	0.38 (1.16)	-2.14–2.42	-0.39 (1.45)	-3.79–1.53452
HWI, Coping	–	–	–	–
PEP	86.56 (24.92)	52.00–130.00	92.00 (28.36)	64.00–144.00
RSA	4.85 (1.46)	1.21–7.73	4.84 (1.17)	2.99–7.00
CAB	-0.10 (1.61)	-2.81–2.54	0.10 (1.39)	-1.99–2.35
CAR	0.10 (1.28)	-2.87–2.08	-0.10 (1.39)	-3.25–1.95
MA, Serial 7s	–	–	–	–
PEP	84.48 (24.58)	54.00–132.00	90.56 (28.63)	64.00–148.00
RSA	4.72 (1.36)	1.59–7.31	4.34 (1.40)	1.86–6.89
CAB	0.02 (1.54)	-2.29–2.60	-0.02 (1.63)	-2.77–2.75
CAR	0.25 (1.13)	-2.15–2.43	-0.25 (1.31)	-3.23–2.30
MA, Multiplication	–	–	–	–
PEP	84.88 (22.91)	54.00–124.00	91.12 (28.64)	62.00–144.00
RSA	5.01 (1.22)	2.96–6.86	4.52 (1.56)	1.98–7.88
CAB	0.05 (1.40)	-2.13–2.80	-0.05 (1.55)	-2.90–2.78
CAR	0.29 (1.06)	-1.90–2.29	-0.29 (1.59)	-3.97–2.75

Appendix Table A (continued)

	Healthy Control (*N*=25)		Metabolic Syndrome (*N*=25)	
	M (SD)	Range	*M (SD)*	Range
TPR (dyn·s·cm^{-5})	–	–	–	–
300 sec	6.05 (2.39)	2.84–10.07	6.05 (3.23)	2.51–17.06
600 sec	5.44 (1.87)	2.75–9.65	6.75 (3.99)	3.11–16.81
900 sec	5.79 (2.71)	2.75–14.42	6.36 (3.35)	2.29–15.64
1200 sec	5.56 (2.09)	2.13–10.40	5.63 (2.37)	2.38–11.22
1500 sec	6.17 (2.93)	2.26–12.94	5.98 (3.09)	2.51–14.34
1800 sec	5.88 (2.18)	2.88–9.67	6.63 (3.41)	2.97–15.03
PEP (milliseconds)	–	–	–	–
300 sec	86.56 (23.86)	48.00–132.00	90.16 (27.11)	58.00–146.00
600 sec	90.42 (24.22)	52.00–126.00	94.40 (29.42)	58.00–148.00
900 sec	82.00 (24.69)	48.00–128.00	98.40 (27.09)	58.00–150.00
1200 sec	84.64 (22.78)	42.00–134.00	98.40 (28.48)	60.00–152.00
1500 sec	85.76 (24.30)	50.00–132.00	98.88 (27.56)	58.00–144.00
1800 sec	87.75 (23.34)	44.00–122.00	95.23 (26.11)	58.00–150.00
Self-Report Measures	–	–	–	
HADS-A	6.76 (3.42)	1.00–13.00	7.12 (3.74)	2.00–14.00
HADS-D	3.76 (2.44)	0.00–8.00	5.12 (3.34)	1.00–13.00
QOL – Physical	15.09 (3.36)	7.43–20.00	13.58 (2.95)	8.57–18.29
QOL – Psychological	14.96 (2.49)	11.33–19.33	13.70 (3.07)	7.33–17.33
QOL – Social	14.45 (3.52)	8.00–20.00	12.32 (3.32)	6.67–20.00
QOL – Environmental	16.21 (2.78)	9.00–20.00	15.88 (2.63)	10.50–20.00
MMAS	2.36 (1.73)	1.00–7.00	3.16 (2.06)	2.00–8.00

Note: CAB = PEP = pre-ejection period; RSA = respiratory sinus arrhythmia; Cardiac Autonomic Balance; CAR = Cardiac Autonomic Control; HWI – Health and Wellness Interview; MA = Mental Arithmetic; TPR = total peripheral resistance; PEP = pre-ejection period; HADS-A= Hospital Anxiety and Depression – Anxiety Scale Score; HADS-D= Hospital Anxiety and Depression – Depression Scale Score; QOL – Physical = WHO Quality of Life–Brief–Physical Domain; QOL – Psychological = WHO Quality of Life–Brief–Psychological Domain; QOL – Social = WHO Quality of Life–Brief –Social Domain; QOL – Environmental = WHO Quality of Life–Brief–Environmental Domain; MMAS = Morisky Medication Adherence Scale Total Score.

APPENDIX B: MENTAL ARITHMETIC TASK

Mental Arithmetic

Directions:

I am interested in how you perform a couple of metal math calculations. In a moment, I will ask you to perform some subtraction problems. When I say to, I want you to subtract 7 from 100 and continue subtracting 7 from each subsequent answer. Please continue until I tell you to stop. Do you have any questions?"

"Ready? Begin" Begin timing for 1 minute.

Start Time: _____: _____: _____

End Time: _____: _____: _____

Correct answers (left to right):

NOTE: For each incorrect answer, instruct the participant: *"Incorrect. Please begin again."*

100	93	86	79	72	65
58	51	44	37	30	23
16	9	2	-5	-12	-19
-26	-33	-40	-47	-54	-61
-68	-75	-82	-89	-96	-103

"Thank you. Next, I would like you to multiply 4 by 3 and continue multiplying each answer by 3 until I tell you to stop. Do you have any questions?"

"Ready? Begin" Begin timing for 1 minute.

Start Time: _____: _____: _____

End Time: _____: _____: _____

NOTE: For each incorrect answer, instruct the participant: *"Incorrect. Please begin again."*

12	36	108	324	972	2,916
8,748	26,244	78,732	236,196	708,588	2,125,764

APPENDIX C: HEALTH AND WELLNESS INTERVIEW

Health and Wellness Interview

Directions:

"I am interested in understanding any difficulties you have had with your health and wellness. In particular, I would like to know about your experience taking medication, following a healthy diet, being physically active, stress patterns and coping."

I. Medical Adherence Start Time: _____: _____: _____ End Time: _____: _____: _____

"Are you taking your prescription medication regularly?" ☐Yes ☐No

"What barriers do you perceive to taking your medication?"

☐Inconvenient ☐Cost ☐Side Effects ☐Not Important ☐Not Motivated ☐Forget

Other/Notes:_____

II. Nutrition Start Time: _____: _____: _____ End Time: _____: _____: _____

"Are you following a healthy diet?" ☐Yes ☐No

"What barriers do you perceive to following a healthy diet?"

☐Inconvenient ☐Cost ☐Time/Energy ☐Not Important ☐Not Motivated ☐Forget

Other/Notes:_____

III. Exercise Start Time: _____: _____: _____ End Time: _____: _____: _____

"Are you getting regular exercise?" ☐Yes ☐No

"What barriers do you perceive to getting regular exercise?"

☐Inconvenient ☐Pain ☐Time/Energy ☐Not Important ☐Not Motivated ☐Forget

Other/Notes:_____

IV. Stress Start Time: _____: _____: _____ End Time: _____: _____: _____

"Are you feeling stress from everyday hassles?" ☐Yes ☐No

"What areas in particular do you find most stressful"

☐Finances ☐Employment ☐Home Life ☐Health ☐Relationships ☐Housing ☐School

Other/Notes:_____

"On a scale of 0 to 10, with 10 being the most stress, how much stress do you feel on a daily basis?

0 1 2 3 4 5 6 7 8 9 10

V. Coping Start Time: _____: _____: _____ End Time: _____: _____: _____

"Are you managing your stress very well?" ☐Yes ☐No

"What barriers do you perceive to managing your stress?"

☐Knowledge ☐Ability ☐Relationships ☐Responsibilities ☐Not Motivated ☐Unimportant

Other/Notes:_____

APPENDIX D: IRB APPROVAL LETTER

University of Central Florida Institutional Review Board
Office of Research & Commercialization
12201 Research Parkway, Suite 501
Orlando, Florida 32826-3246
Telephone: 407-823-2901 or 407-882-2276
www.research.ucf.edu/compliance/irb.html

Approval of Human Research

From: **UCF Institutional Review Board #1**
FWA00000351, IRB00001138

To: **Jonathan Mitchell** and Co-PIs: **Daniel Lee Paulson, Jeffrey E. Cassisi, Joyce Ann Paulson, Maria Louise Cannarozzi, Sandra M. Neer**

Date: **November 26, 2014**

Dear Researcher:

On 11/26/2014 the IRB approved the following modifications to human participant research until 11/02/2015 inclusive:

Type of Review:	Submission Response for IRB Addendum and Modification Request Form Expedited Review
Modification Type:	Protocol revision; Added a new recruitment brochure and poster
Project Title:	Cardiac Autonomic Control in Medical Patients
Investigator:	Jonathan Mitchell
IRB Number:	SBE-14-10663
Funding Agency:	UCF College of Medicine(UCF COM)
Grant Title:	
Research ID:	N/A

The scientific merit of the research was considered during the IRB review. The Continuing Review Application must be submitted 30days prior to the expiration date for studies that were previously expedited, and 60 days prior to the expiration date for research that was previously reviewed at a convened meeting. Do not make changes to the study (i.e., protocol, methodology, consent form, personnel, site, etc.) before obtaining IRB approval. A Modification Form **cannot** be used to extend the approval period of a study. All forms may be completed and submitted online at https://iris.research.ucf.edu .

If continuing review approval is not granted before the expiration date of 11/02/2015, approval of this research expires on that date. When you have completed your research, please submit a Study Closure request in iRIS so that IRB records will be accurate.

Use of the approved, stamped consent document(s) is required. The new form supersedes all previous versions, which are now invalid for further use. Only approved investigators (or other approved key study personnel) may solicit consent for research participation. Participants or their representatives must receive a copy of the consent form(s).

All data, including signed consent forms if applicable, must be retained and secured per protocol for a minimum of five years (six if HIPAA applies) past the completion of this research. Any links to the identification of participants should be maintained and secured per protocol. Additional requirements may be imposed by your funding agency, your department, or other entities. Access to data is limited to authorized individuals listed as key study personnel.

In the conduct of this research, you are responsible to follow the requirements of the Investigator Manual.

On behalf of Sophia Dziegielewski, Ph.D., L.C.S.W., UCF IRB Chair, this letter is signed by:

Signature applied by Patria Davis on 11/26/2014 09:56:23 AM EST

IRB Coordinator

APPENDIX E: COPYRIGHT PERMISSION NOTIFICATIONS

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Inv. # P03B 24413

September 16, 2014

Jonathan Mitchell
4111 Pictor Lane
Department of Psychology
Orlando, Florida 32816

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ahirschberg@cambridge.org

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September 16, 2014

Jonathan Mitchell
4111 Pictor Lane
Department of Psychology
Orlando, Florida 32816

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Authorization: Adam Hirschberg

Adam Hirschberg
Rights and Permissions Associate
ahirschberg@cambridge.org

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September 20, 2014

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Jonathan Mitchell
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EXHIBIT A

Publication Name— *Circulation.2005;112:2735-2752*
AHA/NHLBI Scientific Statement: Diagnosis and Management of the Metabolic Syndrome

Specifically:
Page 2739, Table 2. Criteria for Clinical Diagnosis of Metabolic Syndome

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