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Individual differences in the prediction of metabolic dysfunction from physiological responses to stress: A target for intervention?

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Résumé

Approximativement un Canadien sur quatre rapporte se sentir extrêmement stressé quotidiennement. Le stress a été associé avec l'incidence et la progression de la maladie cardiovasculaire (MCV), qui est la cause principale de mortalité mondiale parmi les hommes et les femmes. Une explication de la manière dont le stress peut contribuer aux MCV est l'impact du stress sur les facteurs de risque intermédiaires, tel que le syndrome métabolique. Le syndrome métabolique représente une constellation de facteurs de risque pour les MCV, qui ont été regroupés en un construit cliniquement significatif; la présence du syndrome métabolique double le risque de souffrir d'une MCV, indépendamment des composantes présentes. Avant la préparation de cette thèse, peu était connu concernant le lien entre notre façon de répondre au stress psychologique et le risque de développer un syndrome métabolique. Cette thèse a examiné l'impact des réponses physiologiques au stress sur le risque de développer un disfonctionnement métabolique, d'une manière transversale et longitudinal (Articles 1 & 2). Elle a aussi investigué l'effet modérateur du sexe et de l'âge sur ces associations.

Les résultats démontrent que les réponses du système nerveux autonome sont associées avec des anomalies métaboliques, bien que ses associations soient modérées par le sexe. Plus précisément, parmi les hommes (Étude 1) et les femmes (Étude 2), des réponses exagérées du système nerveux autonome au stress interpersonnel, ont été associé avec davantage de dysfonction métabolique. Des réponses émoussées du système nerveux autonome (absence de réponse ou retrait vagal minimal pendant le stress) et l'augmentation de l'activité vagale durant le stress ont été aussi liées aux anomalies métaboliques plus importantes chez les femmes. En outre, dans l'étude 2, une fréquence cardiaque élevée au repos, combinée avec une plus grande réactivité au stress et une récupération différée, a aussi été associée avec une probabilité accrue de satisfaire aux critères du syndrome métabolique.

Cette thèse a aussi inclut une étude pilote examinant la faisabilité et l'acceptabilité d'un programme de réduction du stress par la pleine conscience (MBSR) chez les personnes âgées atteintes du syndrome métabolique, actuellement ou dans le passé. Les résultats (Chapitre 3) ont été favorables à cet égard; l'étude était modérément faisable et très acceptable selon les participants. Nous avons également étudié si les élévations des paramètres métaboliques pourraient être inversées à travers le MBSR, et si le MBSR pourrait influencer l'ampleur des réponses au stress chez ceux qui démontraient des réponses exagérées ou émoussées au départ. Bien que les résultats soient préliminaires et doivent être répliqués dans une étude à plus grande échelle, les données initiales suggèrent la réversibilité de conséquences physiologiques induites par le stress dans le profil métabolique, soulignant en outre le rôle des réponses au stress dans la pathogenèse de ce syndrome. Le MBSR s'est également révélé prometteur dans la normalisation des réponses du système nerveux autonome au stress.

Les implications théoriques et cliniques de ces résultats sont discutées en détail dans la dernière partie de la thèse. Des directions futures ainsi que des stratégies de transfert de connaissances sont également fournies.

Mots-clés: stress, syndrome métabolique, maladie cardiovasculaire, variabilité du rythme cardiaque, pleine conscience, la réduction du stress

Abstract

Nearly one in four Canadians reports feeling significantly stressed on a daily basis. Stress has been associated with the onset and progression of cardiovascular disease, which is the leading cause of death in men and women worldwide. One pathway by which stress may contribute to CVD is through its impact on intermediary risk factors of CVD, such as the metabolic syndrome. Metabolic syndrome represents a constellation of CVD risk factors that have been grouped into a clinically meaningful construct; its presence doubles risk of CVD, independent of its individual components. Prior to the preparation of this thesis, little was known regarding the relation between our responses to psychological stress and metabolic syndrome risk. This thesis specifically examined the contribution of physiological stress responses to metabolic dysfunction, both concurrently and prospectively (Articles 1 & 2). It also investigated the potential moderating effect of sex and age.

Results suggested that non-normative autonomic stress responses are associated with metabolic abnormalities, though these associations are moderated by sex. Specifically, in men (Study 1) and women (Study 2), exaggerated autonomic reactivity to interpersonal stressors was associated with metabolic dysfunction. Non-normative autonomic responses such as a blunted response (lack of or minimal vagal withdrawal during stress) and stress-related increase in vagal activity were linked to greater metabolic abnormalities in women. Additionally, a stress response pattern including high basal HR, greater HR reactivity, and delayed HR recovery, was also associated with increased odds of meeting metabolic syndrome criteria in Study 2.

This thesis also included a pilot proof-of concept study examining the feasibility and acceptability of mindfulness-based stress reduction as an adjunct to usual treatment for older adults with current or past metabolic syndrome. Results (summarized in Chapter 3) were favorable in this regard; the study was moderately feasible and largely acceptable to participants.

We also investigated whether elevations in metabolic parameters could be reversed through MBSR and tested whether MBSR influenced the magnitude of stress responses in both heightened and blunted responders. Although results need to be replicated in large-scale research before conclusions can be drawn, initial evidence suggests the reversibility of stress-induced changes in metabolic profile, further highlighting the role of stress responses in the pathogenesis of metabolic syndrome. MBSR also showed promise in normalizing autonomic stress responses.

The theoretical and clinical implications of these findings are discussed in detail in the final section of this thesis. Future directions as well as strategies for transfer of knowledge are also provided.

Keywords: stress, metabolic syndrome, cardiovascular disease, heart rate variability, mindfulness-based stress reduction, sex differences

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List of Abbreviations

ANS: autonomic nervous system

BP: blood pressure

BMI: body mass index

CAD = coronary artery disease

CVD: cardiovascular disease

DBP: diastolic blood pressure

ES : effect size

HR: heart rate

HRV: heart rate variability

HF: high frequency

HDL: high-density lipoprotein

LF: low frequency

LDL: low-density lipoprotein

MB: metabolic burden

MB-EAT: mindfulness-based eating awareness program

MBSR: Mindfulness-Based Stress Reduction

MetS: metabolic syndrome

OR: odds ratio

PASAT: Paced Auditory Serial Addition Test

RCT: randomized-controlled trial

SBP: systolic blood pressure

This thesis is dedicated to my parents,

who taught me empathy and compassion,

and to my patients,

who gave me the strength to keep going.

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INTRODUCTION

Stress is often referred to as the epidemic of the Western World. It is estimated that 23 percent of Canadians describe their everyday life as being quite a bit or extremely stressful, with rates reaching 30 percent in adults aged 35 to 54 (Statistics Canada, 2014). The financial burden associated with stress is significant in North America: in Canada, it is estimated that stress-related mental health issues cost the economy nearly 50 billion dollars a year as a result of diminished work productivity (Southerland, & Stonebridge, 2016) In the United States, at least 42 billion dollars is spent yearly on stress-related health problems while workplace stress costs the government an additional 125 to 190 billion dollars a year (Goh, Pfeffer, & Zenios, 2015; Kalia, 2002). Approximately 43 percent of American adults experience adverse health consequences as a result of stress and it is estimated that workplace stress contributes to at least 120 000 deaths per year (Boone & Anthony, 2003; Goh et al., 2015). Stress is a major health concern.

Stress Defined

Despite its common use in everyday vernacular, researchers have attempted to define the term "stress" for decades. This has resulted in numerous models and definitions, only some of which will be discussed here. One of the most influential researchers in this regard was Hans Selye. Known as the "father of stress", Selye first described it as a non-specific response to any physical or psychological demand (Selye, 1936). As was later demonstrated, the demand itself is neutral; our perceptions, individual characteristics, and environment influence the way that event is interpreted. Thus, the same event can cause either distress (negative stress) or positive arousal in different individuals. Lazarus and Folkman (1984) expanded upon this model and posited that we only experience negative stress when we *perceive* that the demands (pressures or threats) of a situation exceed what we view as our available resources to cope. These coping resources may be internal to us (e.g. our personal attributes such as resilience, intelligence, strength) or external (e.g. finances, social support, our available time). Thus, the larger the discrepancy between the demands of a *stressor* and our perceived capacity to cope with it, the more subjective stress we will experience (Lazarus & Folkman, 1984). In this context, an acute stressor refers to a specific, novel, and/or unpredictable event that threatens our sense of control (Lepore & Evans, 1996). Stressors have been classified in research into four general categories: a) *cataclysms*; sudden, irrevocable, large-scale stressors in our natural environment (e.g. natural disasters, terrorist attacks), b) *major life events* (e.g. death of loved one, loss of job, birth of a child), c) *daily hassles* (e.g. interpersonal conflicts, meeting deadlines, work demands) and d) *ambient stressors*; characteristics of the environment that are ongoing and difficult to change (e.g. overcrowding, noise pollution, traffic) (Lepore & Evans, 1996). Chronic stress refers to repeated exposure to similar or novel stressors for a prolonged period of time.

The experience of psychological stress has also been defined as any uncomfortable emotional experience that causes predictable biochemical, physiological, behavioral, and cognitive changes (Baum, 1990; Vaccarino & Bremner, 2012). For example, when we become stressed, we may experience reactions including but not limited to muscle tension, rapid breathing (or even hyperventilation), increased heart rate, and/or gastrointestinal disturbance. While all aspects of the stress experience are of import, this thesis will focus primarily on the acute physiological changes that take place in response to stress, particularly those of the cardiovascular and autonomic systems. These physiological responses evolved millions of years ago in order to facilitate adaptation to acute threats to our survival, such as attacks from animals or dangerous environmental conditions (Taylor et al., 2000). These threats to life required mobilization of significant amounts of energy and surviving usually entailed the ability to fight or flee the danger. Cannon (1932) was the first to coin the term "flight or fight", which represents an immediate cascade of reactions triggered by the sympathetic nervous system when faced with a life-threatening stressor, in order to maximize chance of survival. Specifically, hormones such as adrenaline and noradrenaline are secreted in order to prepare the body for immediate and strenuous muscular action (Cannon, 1932). Energy stores of fat and glycogen are also liberated to order to facilitate increased speed and strength, while blood pressure, heart rate, and respiration are accelerated to increase blood flow and oxygen to muscles. Blood flow to non-essential systems is temporarily inhibited (e.g. digestion and sexual function) so as to maximize resources available for fight or flight. However, according to Selye (1936), chronic exposure to stress or prolonged and repeated activations of the stress response can lead to illness or even death, as a result of vital exhaustion and full depletion of resources.

Although the stressors most individuals encounter in the industrialized world today are not life-threatening, these "stress responses" are still triggered to varying degrees, depending on the nature of the situation as well as the characteristics of the individual and of his or her environment (Boone & Anthony, 2003). Although the ability to physiologically adapt to stressors is vital for survival, repeated mobilization of resources required to deal with acute and chronic stressors may have damaging effects on health, including cardiovascular health (McEwen & Seeman, 1999).

Stress and Cardiovascular Disease

Cardiovascular disease (CVD) is the leading cause of death in both men and women worldwide (Roth et al., 2015). The yearly economic burden of CVD is approximately 21 billion dollars in Canada alone (Tarride et al., 2009). Traditional risk factors for CVD include cigarette smoking, diabetes, obesity, hypertension, hyperlipidemia, and a sedentary lifestyle (Boone & Anthony, 2003; Khot et al., 2003). There is also an abundance of evidence suggesting that the experience of both *acute and chronic stress* contribute to CVD development, progression, and mortality (for meta-analytic reviews, see Richardson et al., 2012; Steptoe & Kivimaki, 2012; Steptoe & Kivimaki, 2013).

The mechanisms through which stress impacts cardiovascular health remain to be fully understood. One hypothesis is that stress increases risk of CVD through its influence on health behaviors. Research shows that stressed individuals tend to consume foods that are higher in fats and carbohydrates, resulting in greater caloric intake and weight gain; this may account, in part, for stress' relationship with obesity (Dallman, 2010; Epel, Lapidus, McEwen, & Brownell, 2001; Roberts, Campbell, Troop, 2013; Tomiyama, Dallman, & Epel, 2011; Torres & Nowson, 2007). Stress and cigarette smoking are also associated. A cohort study of 46 190 employees revealed that high stress in the workplace was associated with a greater likelihood of being a current smoker and with higher intensity of smoking (Kouvonen, Kivimäki, Virtanen, Pentti, & Vahtera, 2005). In addition, stress has been associated with less exercise adherence in a small study (Stetson, Rahn, Dubbert, Wilner, & Mercury, 1997). However, the association of stress with disease has generally been shown to be independent of health behaviors, suggesting that other mechanisms also play a role.

The Stress Reactivity Hypothesis

In addition to its impact on health behaviours, stress may increase risk for negative cardiovascular outcomes through activation of heightened or prolonged physiological responses to stress (Cohen, Panguluri, Na, & Whooley, 2010; Nelson, Palmer, & Pedersen, 2004; Rosmond, 2005). This will be the focus of this thesis.

Individuals differ in the way they react to stressful situations, such that some exhibit greater physiological arousal in response to stress compared to others. Physiological *reactivity* to stress refers to the changes that occur from a resting state within one or several body systems (e.g. cardiovascular system) in response to a stressful situation. According to the *stress reactivity hypothesis*, those who are more physiologically reactive (i.e. hyper-reactors) to acute stress may be more at risk for negative cardiovascular endpoints, particularly hypertension (Obrist, 1981). A possible explanation for this phenomenon is that since hyper-reactors tend to experience more frequent increases in blood pressure (BP) to various stressors throughout their daily lives, their resting BP eventually increases, leading to hypertension (Chida & Steptoe, 2010). This may be due to damage caused to the arteries as a result of these frequent hemodynamic disturbances. Reactivity has been associated to the thinning of arterial lumen (the cavity inside blood vessels) in both coronary and peripheral arteries (Blascovich & Katkin, 1993; Matthews et al., 2004). Moreover, Folkow (1978) reported that repeated peripheral vasoconstriction as a result of exposure to recurring psychological stressors leads to arterial muscle hypertrophy (thickening of arterials walls). This, in turn, results in decreased arterial lumen and increased peripheral resistance, which, over time, is associated with risk of hypertension.

A meta-analysis conducted by Chida and Steptoe (2010) is considered to provide the greatest support for the stress reactivity hypothesis to date (Lovallo, 2010). The authors included studies from 41 separate cohorts and examined a total of 169 associations between indices of reactivity and various cardiovascular disease outcomes. The most consistent relationship was that between reactivity and high blood pressure/hypertension (Chida & Steptoe, 2010). Specifically, reactivity to stress accounted for approximately one percent of the variance in predicting high blood pressure across studies (Chida & Steptoe, 2010). Furthermore, exaggerated reactivity was associated with a 23 percent increase in risk of hypertension (Chida & Steptoe, 2010). Although this represents a small effect size, a 23 percent increase in hypertension risk as a result of reactivity is comparable to that of a 20 mm Hg increase in resting BP (Lovallo, 2010). The largest effect sizes were observed in a longitudinal study examining the relation between systolic blood pressure (SBP) reactivity and myocardial infarction or stroke (ES = .85) in patients with a history of myocardial infarction (Manuck, Olsson, Hjemdahl, & Rehnqvist, 1992). Similarly, diastolic blood pressure (DBP) reactivity predicted myocardial infarction in hypertensive patients in a 14 year follow-up study (ES = .89) (Alderman, Ooi, Madhavan, & Cohen, 1990). Heightened reactivity has also been associated with cardiovascular mortality over a 16 year period in more recent research (Carroll et al., 2012). In a sample of 431 older adults, increased SBP and DBP reactivity to a mental arithmetic task was associated with mortality from cardiovascular disease even when controlling for independent risk factors such as age, sex, socioeconomic status, body mass index (BMI), exercise habits, and resting BP (Carroll et al., 2012). The hazard ratios were 1.03 and 1.05 for SBP and DSP reactivity, respectively.

Despite its general support, the stress reactivity hypothesis does not in its original formulation address the extent to which individuals appear to be able to *recover* from stress and its associated physiological disturbances (Brosschot, Pieper, & Thayer, 2005). In the laboratory, physiological *recovery* from stress is typically operationalized in two ways, either a) the time required to return to pre-stress levels of a particular physiological parameter once exposure to a stressor has subsided, or b) the extent to which an individual has returned to his or her pre-stress state following a given time period (Stewart & France, 2001). The latter is usually characterized by a change score, notably the difference between a parameter during the recovery phase and that parameter at baseline (Rutledge, Linden, & Paul, 2000). For instance, heart rate (HR) may increase in response to a stressful situation, but will eventually decrease back to the level at which it was prior to the stressor occurring. To quantify the extent to which the individual has recovered, the average HR at baseline is calculated and this value is subtracted from the average HR obtained during the recovery period. Values closer to zero would indicate greater recovery. Similar to reactivity, individuals differ in their ability to physiologically recover from a stressful event. Rapid or greater return to baseline levels is thought to be a marker of good adjustment to a stressor, whereas delayed recovery once a stressor has subsided may reflect a difficulty of the person to adequately adapt to a situation and then return to a homeostatic state.

Until more recently, physiological recovery from stress had been largely ignored in the literature examining stress responses and cardiovascular health. Indeed, in their comprehensive meta-analysis examining the relation between stress responses and cardiovascular outcomes, Chida and Steptoe (2010) found 169 analyses (from 36 articles) on reactivity to stress, but only 30 (from 5 articles) on recovery. Poor cardiovascular recovery was associated not only with higher resting SBP and DBP (both *r*'s = .08), but also with increased carotid intima-media thickness, a marker of atherosclerosis (*r* = .14) (Chida & Steptoe, 2010). Moreover, an older review by Chida and Hamer (2008) suggested that recovery from stress may reveal impairments in cardiovascular functioning even when reactivity to stress does not seem to yield similar deficiencies. It is possible then that studies examining reactivity exclusively may actually be underestimating the impact of stress responses on cardiovascular health.

The Allostatic Load Model

The allostatic load model expands upon the stress reactivity hypothesis and provides a more comprehensive framework to explain the long-term negative health consequences of stress, and specifically, its relationship with CVD. The concept of *allostasis,* which the allostatic load model is based on, means "*achieving stability through change*" (McEwen & Seeman, 1999). Through the process of allostasis, the organism achieves a state of healthy physiological stability by successfully adapting to constantly changing internal and environmental demands or stressors (McEwen & Seeman, 1999). For instance, blood flow is suddenly increased to the head when getting up in the morning, which makes standing possible without fainting (McEwen, 2005). Blood pressure then continually rises and falls throughout the day depending on constantly varying physical and emotional contexts. Similarly, glucocorticoids regulate energy input and expenditure and will trigger appetite after a burst of physical activity and/or when replenishment is required (McEwen, 2005).

There are four key components to the allostatic load model. First, when an event is interpreted as stressful by an individual, there are physiological and behavioral changes that ensue in response to the challenge (McEwen & Seeman, 1999). These physiological changes include, but are not limited to, those already described by Cannon (1932) and Selye (1936). Possible behavioral reactions include the "fight or flight" response (explained on page 3) or "freeze response", which occurs in situations in which chances of escaping or winning a fight against a predator are low (Barlow, 2002). In these cases, "freezing," or in other words, "playing dead" is the most adaptive response to the threat, as it may help to avoid capturing the predator's attention and inviting further attacks, or may increase chances of escape if the predator believes its prey to be dead (Korte, Koolhaas, Wingfield, & McEwen, 2005). Another possible reaction to stressful situations is the "tend and befriend" response, generally thought to be more common in females (Taylor et al., 2000). Although women will employ "fight or flight" or "freeze" when their lives are in danger, some research suggests that they will tend to favor protection of offspring (tending) and utilizing their social group (befriending) when faced with other non-life threatening stressful events (Taylor et al., 2000). Indeed, the second principle of the allostatic load model states that there are **individual differences** with regard to these stress responses. Differences attributed to sex, genetics, environmental factors, and health behaviors may also all predispose an individual to react in either adaptive or maladaptive ways to a stressor (McEwen & Seeman, 1999).

The third component of this model is that of **allostasis**. Once faced with a stressful event, the body must adapt to these rapidly occurring changes, achieved through allostasis, as was previously described (McEwen & Seeman, 1999). At the start of a stressful event, allostatic systems are initiated (e.g. circulating catecholamines and/or glucocorticoids are increased, blood pressure is altered, etc). This allostatic and adaptive response is sustained for the duration of the stressor and is expected to decrease once the stressor has subsided.

However, these continuous efforts to adapt to various challenges may incur physiological costs in the long term (McEwen, 1998).

Indeed, **allostatic load**, the fourth component, reflects the detrimental effect of prolonged, continuous, or sporadic disturbances of homeostasis, and repeated activations of mechanisms involved in allostasis (McEwen & Stellar, 1993). Although stress responses initiated by allostasis are adaptive in the short term, the long-term effects of repeated stress exposure (allostatic load) may be adverse. For example, blood pressure and heart rate are increased during daily challenges such as waking up in the morning and engaging in physical activity thanks to allostatic mechanisms. However, chronic job stress resulting in repeated increases in blood pressure and heart rate may eventually lead to failure of the system in shutting down the stress response. Research suggests that frequent changes in blood pressure and heart rate and/or failure to return to pre-stress levels may accelerate atherosclerosis and disturb metabolic functioning (McEwen, 1998). Thus, individuals who are more physiologically reactive to stressors and who also experience regular, repeated stress would be at increased risk of experiencing allostatic load. In sum, repeated stress leads to allostatic load, or "wear and tear" in the organism over time, increasing vulnerability to illness.

Stress and Metabolic Syndrome

Allostatic load processes related to stress (responses) may contribute to CVD through its impact on intermediary risk factors for CVD, such as metabolic syndrome (Steptoe & Kivimaki, 2013). The role of stress responses in metabolic syndrome will be the focus of this thesis.

Metabolic syndrome incurs significant risk for coronary artery disease, atherosclerosis, and increased mortality from cardiovascular diseases; increasing risk of these outcomes twofold (Dekker et al., 2005; Lakka et al., 2002; Malik et al., 2004; McNeill et al., 2005). While different nomenclatures have been proposed to describe metabolic syndrome internationally, in North America, metabolic syndrome typically refers to the presence of at least three of the following interconnected factors: central adiposity, high blood pressure, elevated triglycerides, increased fasting blood glucose, and low levels of high-density lipoprotein (HDL) cholesterol (Alberti et al., 2009; Alberti, Zimmet, & Shaw, 2006; Grundy et al., 2002; see Table 1 below for specific criteria). One in every five Canadians is diagnosed with metabolic syndrome over the lifespan, with prevalence increasing to approximately 40 percent at 60 years of age (Jorgensen, Nash, Lasser, Hymowitz, & Langer, 1988; Riediger & Clara, 2011).

Table 1

Metabolic Syndrome Criteria According to the National Cholesterol Education Program Adult Treatment Panel III

Must possess three or more of the following five factors:		
Fasting blood glucose	≥ 5.6 mmol/L	
Blood pressure	≥ 130/85 mm Hg	
Triglycerides	≥ 1.7 mmol/L	
HDL cholesterol	*Men*: < 1.04 mmol/L	*Women*: < 1.29 mmol/L
Waist circumference	*Men*: > 102 cm	*Women*: > 88 cm

Note . Table adapted from Alberti et al. (2009)

Stress Responses and Metabolic Changes

Although studies have shown a relation between stress exposure and the metabolic syndrome, whether physiological responses to stress are associated with a diagnosis of metabolic syndrome has yet to be investigated in adults (Chandola, Brunner, & Marmot, 2006; Whisman, 2010; Whisman, Uebelacker, & Settles, 2010). One recent cross-sectional study of 144 adolescents aged 15 to 17 did however examine the relation between stress reactivity and several individual parameters of metabolic syndrome. More specifically, greater DBP reactivity to a mirror tracing task in this sample was associated with greater a) SBP (accounting for 1.3 percent of the variance), b) waist circumference (accounting for 3.8 percent of the variance) and c) triglycerides (accounting for 5.1% of the variance) (Countryman, Saab, Schneiderman, McCalla, & Llabre, 2014). These results were independent of relevant covariates such as age, sex, race, and mother's education level. Additionally, absence of metabolic syndrome was associated with less DBP reactivity to the mirror tracing and cold pressor tasks. The odds of not meeting any metabolic syndrome criteria compared to meeting at least three (specified according to the American Heart Association adult criterion guidelines) decreased by 13.5 to 15.8 percent for every 1 mm Hg increase in DBP reactivity (Countryman et al., 2014). In other words, greater DBP reactivity was associated with a higher likelihood of meeting metabolic syndrome criteria. On the other hand, less HR reactivity to the cold pressor was related to greater metabolic syndrome risk. Specifically, the odds of not meeting any metabolic syndrome criteria increased by 10.7 % for every 1 mm Hg increase in HR reactivity. This is not surprising as the cardiovascular response to the cold pressor task is thought to be driven mostly by vasoconstriction, i.e. narrowing of arterial walls, in order to reduce heat loss (Frank, & Raja, 1994; Greaney, Alexander, & Kenney, 2015). Increases in DBP in this case lead to engagement of baroreceptors which lead to decreases (or only small increases) in HR in order to compensate for heat loss. Therefore, less HR reactivity to the cold pressor, in combination with heightened DBP reactivity, still suggests that heightened reactivity was associated with metabolic syndrome in this study.

A greater body of research is available examining the relation of stress responses with individual components of metabolic syndrome, the results of which are discussed below.

High blood pressure/hypertension. High blood pressure and hypertension diagnoses are the parameters that have been the most examined in relation to stress responses. As was mentioned, a meta-analysis of 41 independent studies found hypertension to be consistently predicted by increased cardiovascular reactivity to stress in both cross-sectional and prospective research ($r_{equivalent} = .10$) (Chida & Steptoe, 2010). This association between reactivity and negative cardiovascular outcomes was most pronounced in men ($r = .12$) and tended to be particularly true for cognitive-type stressors ($r = .09$) and in longitudinal studies with follow-ups longer than 3 years ($r = .12$). Poor BP and HR recovery from stress was also independently associated with higher resting SBP and DBP (both *r*'s = .08). Although effect sizes appear small, they are comparable to those of other biological indicators of disease observed in prospective research (Chida & Steoptoe, 2010). These findings have received further support in other more recent studies. For instance, a large-scale investigation involving 1196 healthy men and women aged 24, 44, and 63 at study onset reported that elevated SBP reactivity to the Paced Auditory Serial Addition Test (PASAT) predicted risk of hypertension 12 years later (OR = 1.03, 95% CI = 1.01-1.04, $p < .001$) independent of age, sex, socioeconomic status, physical activity, resting BP, BP medication at baseline, and BMI at baseline (Carroll, Phillips, Der, Hunt, & Benzeval, 2011). These results remained virtually identical after the authors removed those participants who were hypertensive at baseline. Increased SBP (but not DBP) reactivity was also significantly associated with future elevations in resting SBP in both men ($\beta = .10$, $p = .01$, $R^2 = .01$) and women ($\beta = .12$, $p = 0.002$, $R^2 = .01$) (Carroll et al., 2011). In addition, systolic blood pressure reactivity to a Stroop and speech task was predictive of future hypertension independent of possible confounds in a 5 year follow-up study featuring a large community sample (OR = 1.02, CI 1.00–1.04, $p = .02$) (Carroll et al., 2012).

Central adiposity. A smaller body of research examining the relation between stress responses and central adiposity has revealed mixed results. In earlier studies, reactivity was typically investigated as an outcome of central adiposity rather than as its predictor. For instance, in a small sample of middle-aged Black men and women, participants with larger waist circumferences (>100 cm) demonstrated greater SBP, DBP, and HR reactivity to a speech, mental arithmetic, and Stroop task than those with smaller waist circumferences (<100 cm) (Waldstein, Burns, Toth, Poehlman, 1999). Similarly, greater central adiposity was associated with increased DBP reactivity to a cold pressor and public speaking task in a small sample of pre-menopausal women (Davis, Twamley, Hamilton, & Swan, 1999). For their part, Steptoe and Wardle (2005) examined whether reactivity and recovery predicted central adiposity (indicated by waist to hip ratio) in healthy middle-aged (45-59 years) men and women in both cross-sectional and prospective analyses. Delayed SBP and DBP recovery (but not reactivity) from a color word inference task and mirror tracing task was associated with greater concurrent waist to hip ratio independently of age, sex, socioeconomic status, alcohol consumption, baseline BP, and subjective stress reported during the tasks.

Delayed SBP recovery also predicted increases in waist to hip ratio after a three year follow-up period in men ($\beta = .001$, $p = 0.03$) but not in women (Steptoe & Wardle, 2005). The authors hypothesized that the hormonal status of the women in this age group may have accounted for these sex differences as reactivity may be altered from perimenopause to post-menopause.

Interestingly, recent research involving HR reactivity and waist-to-hip ratio and/or BMI is more consistent but in a direction opposite to that just presented; greater HR reactivity appears to decrease risk of elevation in these parameters. For instance, while heightened SBP and DBP reactivity to the PASAT was associated with higher concurrent central adiposity (waist to hip ratio) in a sample of 1647 participants aged 15, 35, or 55 at study onset, greater HR reactivity to the task was associated with less central adiposity (Carroll, Phillips, & Der, 2008). Once analyses were adjusted for age, sex, occupation, medication, smoking status, and baseline BP and HR, relations involving SBP and DBP reactivity were no longer significant. However, the negative association between HR reactivity and central obesity remained ($\beta = -.09$, $p < 0.001$). Although cardiovascular responses to stress did not predict waist to hip ratio prospectively, greater HR reactivity was related to a significantly reduced likelihood of becoming obese (BMI ≥ 30 kg/m^2) over a five year follow-up (OR = .97, $p = .02$) (Carroll et al., 2008). Comparable results were obtained in another independent sample of 725 middle-aged individuals: less HR (but not BP) reactivity to a stress protocol including a Stroop, mirror tracing, and public speaking task predicted an increased likelihood of becoming or remaining obese after a follow-up of 4 to 7 years (OR = 1.03, $p = .01$) (Phillips, Roseboom, Carroll, & de Rooij, 2012). This association was independent of possible confounds including sex, socioeconomic status, age, alcohol consumption, smoking status, use of antihypertensive, antidepressant, or anxiolytic medication, and baseline HR. Consistent with these results, Singh and Shen (2013) recently reported that less SBP reactivity to a public speaking and mental arithmetic task was associated with higher waist circumference in a sample of 122 undergraduate students ($\beta = -.63$, $p < .001$).

The discrepancy in direction of results between older and newer studies may reflect differences in methodology. Earlier studies employed very small sample sizes (22-24 participants) and used strictly cross-sectional designs (Davis et al., 1991; Waldstein et al., 1999). Central adiposity was also used as the predictor of cardiovascular reactivity rather than the reverse. More recently, authors conducted large-scale prospective studies with the power to include numerous demographic, behavioral, and medical covariates (including medication use) (Carroll et al., 2008; Phillips et al., 2012), which increases confidence that can be had in results obtained.

Cholesterol, Triglycerides, and Glucose. Reactivity and recovery from stress have been nearly exclusively examined as outcomes of cholesterol, triglycerides, and glucose rather than their predictors. This approach does not permit us to elucidate whether maladaptive stress responses contribute to these metabolic abnormalities in otherwise healthy individuals or rather develop as a result of these abnormalities. Authors tend to report positive associations between reactivity and elevations in these parameters, although research is sparse and some conflicting evidence has emerged. For instance, in a study of 59 middle-aged men with mild hypertension, those above the median of HR reactivity to a video game and Stroop task had significantly higher levels of overall cholesterol and triglycerides than those below the median of HR reactivity (Jorgensen et al., 1988). Burker and colleagues (1994) reported that those with elevated SBP and DBP reactivity to a stress protocol including mental arithmetic, public speaking, the cold pressor test, and a videogame, had significantly higher levels of low-density lipoprotein (LDL) cholesterol in sample of 97 hypertensive men and women. High DBP reactors also had significantly lower HDL cholesterol in the latter study. For their part, Owens, Stoney, and Matthews (1993) reported significant positive correlations between cholesterol and SBP (r = .28) and DBP (r = .28) reactivity to a public speaking task in a sample of of 49 healthy individuals. Similar associations were observed by other authors (Clark, Moore, & Adams, 1998; Fredrikson, Lundberg, & Tuomisto, 1991; McKinney et al., 1987). However, another study reported a significant *negative* correlation between overall cholesterol and DBP response to a mental arithmetic task (r = -.40) in a sample of 24 middle-aged men (Suarez, Williams, Kuhn, Zimmerman, & Schanberg, 1991). Other authors reported no significant associations between cardiovascular reactivity and cholesterol levels (Fredrikson & Blumenthal, 1992).

There are some noteworthy limitations of these various investigations. First, nearly half of the studies reporting associations between reactivity and cholesterol neglected to include women in their samples (i.e. Fredrikson & Blumenthal, 1992; Jorgensen et al., 1988; McKinney et al., 1987; Suarez et al., 1991). Authors did not always control for use of medications such as β-blockers, which may independently influence reactivity to stress (Fredrikson et al., 1988; McKinney et al., 1987). Several of these studies were cross-sectional, limiting our understanding of whether non-normative stress responses lead to changes in cholesterol and triglycerides (McKinney et al., 1987; Owens et al., 1993; Suarez et al., 1991). With the exception of one study described in detail below, research examining these parameters has been stagnant for the last 15 years.

The only study investigating the relation between fasting blood glucose and cardiovascular reactivity to stress was conducted recently by Clark, Perkins, Carson, Boyd, and Jefferson, (2015). Fasting blood glucose predicted mean arterial pressure during the recovery period of a video stressor depicting African slavery in a sample of 48 African-American college students. Specifically, those with higher levels of blood glucose recovered more rapidly from stress than their counterparts ($\beta = -.32$, $p = .04$). It should be noted that the authors did not characterize recovery by means of a change score; rather, the absolute value of mean arterial pressure during the recovery period was used as the dependent variable. However, the authors did not include the means of the cardiovascular parameters during the baseline, stress, or recovery periods, making it impossible to estimate magnitudes of response. It may simply be that the significant associations were actually a result of individual differences in basal activity rather than ability to recover from stress.

In sum, while the relation between physiological stress responses and BP has been well established, the picture remains unclear for central adiposity and research on the remaining metabolic parameters is sparse. The literature as of now does not clearly address whether stress responses are predictive of metabolic syndrome.

Limitations and methodological shortcomings of the existing literature

Individual differences in risk. Methodological differences relating to sample characteristics may explain some of the inconsistencies observed in the studies reported. Although several sample characteristics may influence the association between stress responses and metabolic activity (e.g. race, health status of participants, family history of cardiovascular disease), sex and age of participants will be the focus of this thesis.

Sex differences exist in the prevalence of metabolic syndrome in Canada. In adults over age 60, approximately 46 percent of men are diagnosed with metabolic syndrome, as compared to 37 percent of women (Statistics Canada, 2013). Men and women also differ in both their physiological responses to and psychological perceptions of stress. For instance, men tend to be more physiologically reactive to stress than women, especially in response to cognitive and performance oriented tasks (Allen, Stoney, Owens, & Matthews, 1993; Carroll et al., 2008; Lassner, Matthews, & Stoney, 1994; Matthews, Davis, Stoney, Owens, & Caggiula, 1991). Yet, women tend to report higher levels of perceived stress than men (Allen, Bocek, & Burch, 2011; Brougham, Zail, Mendoza, & Miller, 2009) and view family relationships, social interactions, finances, and daily hassles as more stressful than men do (Brougham et al., 2009).

Research also supports that women and men cope with stressors in a different manner. Women tend to seek social support when faced with acute stressors more frequently than men and tend to use emotion-focused coping strategies such as self-help and self-punishment more often (Brougham et al., 2009; Ptacek, Smith, & Dodge, 1994). Other authors suggest that men tend to employ more maladaptive coping strategies when stressed than women, such as engaging more frequently in consumption behaviors (cigarettes, alcohol, and unhealthy foods), or avoiding and denying the presence of stress altogether (Kieffer, Cronin, & Gawet, 2006; Lindquist, Beilin, & Knuiman 1997). It seems conceivable then that sex differences in the experience and response to stress may yield distinct impacts on health outcomes. Indeed, Lindquist et al. (1997) reported that "consumption behavior-based coping" was related to higher resting BP in men in their study. Yet, few investigations have specifically examined the moderating effect of sex on results obtained. Some limited data suggests that this may be of importance. For instance, Steptoe and Wardle (2005) observed that delayed SBP recovery following stress predicted increases in central adiposity three years later in men but not women. Similarly, in their meta-analysis, Chida and Steptoe (2010) found exaggerated cardiovascular reactivity and delayed recovery to predict poorer cardiovascular outcomes, such as hypertension, in men. These associations were less consistent in women. Taken together, it would appear important to examine sex as a potential moderator of the relation between stress responses and metabolic outcomes.

Age is another possible moderator of the association between stress responses and metabolic syndrome. Older adults suffer disproportionately from metabolic syndrome in Canada. Although the overall prevalence of metabolic syndrome is approximately 22 percent, the risk increases to over 40 percent in Canadians over 60 years of age (Statistics Canada 2013). Moreover, the number of metabolic syndrome criteria present in the population increases sharply with age. Roughly 50 percent of adults aged 18 to 39 meet criteria for at least one component of metabolic syndrome, compared to 80 percent of adults aged 60 to 79.

Older adults have also been shown to exhibit heightened cardiovascular reactivity to stress in comparison to younger individuals (Uchino, Holt-Lunstad, Bloor, & Campo, 2005; Uchino, Uno, Holt-Lunstad, & Flinders, 1999; Villegas, Perry, Creagh, Hinchion, & O'Halloran, 2003) although some conflicting research suggests that HR reactivity declines with age (Carroll et al., 2008). Interestingly, Stawski, Sliwinski, Almeida, & Smyth (2008) reported that older adults (M_{age}=80) reported less exposure to everyday stressors compared to young adults (M_{age}=20) in their study in which 183 individuals kept a detailed stress diary. Moreover, the type of stress experienced tends to change with age. While younger and middle-aged adults tend to face episodic stressors related to work and childrearing, older adults are more frequently exposed to chronic stressors such as ongoing health issues (Aldwin, Sutton, Chiara, & Spiro, 1996).

Although it would appear that younger and older individuals differ in their physiological responses to stress and the types of stressors they are exposed to, very few studies have specifically examined the moderating effect of age on the relation between stress responses and cardiovascular outcomes, let alone metabolic syndrome. Limited data suggests that this could nevertheless be of interest. In a four-year longitudinal study, Kamarck et al., (1997) examined the relation between cardiovascular reactivity and carotid artery wall thickness, a measure of arthrosclerosis. A total of 1038 Finnish men aged 42, 48, 54, and 60 at baseline were tested. Results showed that SBP and DBP reactivity to four cognitive and performance-based stressors were associated with carotid artery thickness in the youngest half of the sample (aged 46 and 52 years) but not the older half (aged 58 and 64 years). The authors suggested that this may be due to a "survivor effect" in that these older adults may be particularly resilient to cardiovascular disease risk factors. It was also posited that the importance of reactivity in the development of negative cardiovascular endpoints may decrease over time (Kamarck et al., 1997). Given these findings, it appears possible that age may moderate the relation between stress responses and metabolic syndrome.

The stress protocols. The stress protocols used in the literature may have contributed to some of the observed inconsistencies. For instance, nearly all the studies presented thus far have utilized physical or cognitive tasks to induce stress in the laboratory. Examples of these tasks include the cold pressor (*immersion of the hand in ice cold water for several minutes*), mental arithmetic (*subtracting seven from a three digit number out loud at timed-intervals, or similar variations*), mirror tracing (*tracing of an star with a metal stylus, which could only be* *seen in a mirror image, that is, a seemingly identical image but reversed*), and different variations of the Stroop task (e.g. *naming the written color name that is spelled out in a different colored ink and then naming the ink color of a word, but the letters of that word spell out another color*). Participants may be told that their performance on these tasks is being evaluated.

Although these tasks are effective in eliciting physiological changes, they have limited ecological validity. That is, they do not necessarily reflect the types of stressors individuals typically encounter in their daily lives (Linden, Earle, Gerin, & Christenfeld, 1997), nor do they resemble the most distressing situations people tend to experience. It has been reported that interpersonal conflicts are among the most upsetting of stressors, even compared to overload at work, family demands (such as a sick child or spouse), or financial issues (Bolger, Delongis, Kessler, & Schilling, 1989). Conflicts and tensions in continuous relationships with non-family members (i.e. friends, coworkers) were reported as the most distressing (Bolger et al., 1989). Moreover, it has been argued that stress responses to interpersonal laboratory challenges may generalize to natural settings more effectively than responses to cognitive stressors. In support of this, Linden, Rutledge, and Con (1998) demonstrated that social laboratory stress tasks were superior to cognitive tasks in the prediction of mean ambulatory blood pressure levels. Although the use of interpersonal stressors in stress reactivity protocols has been highly recommended, they are still rarely included representing a major shortcoming of the literature (Kamarck & Lovallo, 2003).

Recovery from stress. As was mentioned earlier, recovery from stress is largely ignored in the literature investigating stress responses and disease outcomes. Yet, not only does delayed or prolonged recovery contribute to allostatic load, recovery indices may provide additional data that are not captured by reactivity measures (Brame & Singer, 2010; Linden et al., 1997; Logan & Barksdale, 2008). Indeed, Brosschot, Gerin, and Thayer (2006) suggest that prolonged activation once a stressor has subsided is more important in predicting adverse health consequences than heightened reactivity as prolonged activation is necessary for the development of chronic pathogenic processes. Maintenance of physiological arousal after an acute stressful circumstance may be due to rumination, worry, and/or anger inhibition elicited by the stressor (Brosschot et al., 2006; Brosschot & Thayer, 1998).

The physiological measures of stress. Another major shortcoming of the literature is that most studies tend to use cardiovascular measures of reactivity *exclusively* (e.g. BP), and fail to include any autonomic indices. The autonomic nervous system (ANS) is a branch of the peripheral nervous system that manages bodily functions including heart rate, blood pressure, respiration, digestion, as well as metabolism. It can be further divided into two branches: the parasympathetic and sympathetic nervous systems. These two systems generally function simultaneously in a dynamic balance when faced with a stressful event. That is, the parasympathetic system tends to dominate at rest and typically decreases its activity immediately in response to a stressor. The sympathetic nervous system, which is slightly slower acting than the parasympathetic response, dominates during stress, as it mobilizes resources in order to prepare the body to fight or flee from threat. Once the threat has subsided, the parasympathetic system counteracts the sympathetic nervous system by restoring bodily functions to their homeostatic states. The ANS is one of the major systems involved in the regulation of metabolism (Kalsbeek et al., 2010). Indeed, the key organs that control metabolism (e.g. brain, liver, pancreas) are all innervated, in part, by sympathetic and parasympathetic nerve fibres (Carnethon & Craft, 2008).

Disruptions of the autonomic nervous system have been associated with the development of individual or combined parameters of metabolic syndrome (Brunner et al., 2002; Liao et al., 1996; Liao et al., 1998; Reaven, Lithell, & Landsberg, 1996; Tentolouris, Argyrakopoulou, & Katsilambros, 2008; Thayer, Yamamoto, & Brosschot, 2010; Tsuji et al., 1996). For instance, Liao et al., (1996) reported that indices of autonomic dysfunction (i.e. reduced vagal function at rest) predicted the development of hypertension after a three-year follow-up in middle-aged men and women. Additionally, excessive or prolonged activation of the sympathetic nervous system tends to be typical of patients with metabolic syndrome (Brunner et al., 2002; Tentolouris et al., 2008). Yet, no research has specifically examined the relations between autonomic responses to psychological stressors and metabolic syndrome parameters.

Indices of ANS activity and reactivity can be obtained non-invasively via the analysis of heart rate variability (HRV) (Rajendra Acharya, Paul Joseph, Kannathal, Lim, & Suri, 2006). HRV refers to the natural discrepancies in time interval that occur between successive heartbeats (Rajendra Acharya et al., 2006). The heart rate of healthy individuals fluctuates naturally from beat to beat as a result of ANS control; that is, a balance of sympathetic and parasympathetic nervous system activation (Hayano, Sakakibara, et al., 1991; Rajendra Acharya et al., 2006). More specifically, increased sympathetic and decreased parasympathetic activity results in accelerated HR, whereas dominance of parasympathetic activity over sympathetic leads to slowed HR (Rajendra Acharya et al., 2006). Given that the parasympathetic nervous system's response time is faster than that of the sympathetic nervous system, high to mid frequency fluctuations in HR are mediated exclusively by the parasympathetic system, whereas both systems mediate fluctuations of the low frequency peak (Akselrod et al., 1981). One way of characterizing HRV is through frequency domain analyses, which involves specifically analyzing high frequency (HF-HRV; 0.15–0.40 Hz) and low frequency (LF-HRV; 0.04– 0.15 Hz) signals of the electrocardiogram, as recommended by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (Task Force of the European Society of Cardiology, 1996). HF-HRV reflects parasympathetic activity. Given that the parasympathetic nervous system has traditionally been thought to withdraw in response to stress, HF-HRV is expected to decrease during an acute stressor (Task Force of the European Society of Cardiology, 1996). The LF/HF ratio tends to be used as a measure of sympathovagal balance or sympathetic activity (Task Force of the European Society of Cardiology, 1996). Traditionally, it is expected that LF/HF increases as stress increases.

In general, greater variability in HR suggests greater ANS control of the heart. High overall HRV is also indicative of the capacity of the heart to adapt adequately to fluctuating situations in everyday life (Omerbegovic, 2009). Indeed, lower HRV has been associated with atherosclerosis, myocardial infarction, sudden cardiac death, and mortality (Bigger, Fleiss, Rolnitzky, & Steinman, 1993; Hayano, Yamada, et al., 1991; Kataoka, Ito, Sasaki, Yamane, & Kohno, 2004; Thayer & Lane, 2007; Tsuji et al., 1994). Pre-menopausal women are reported to have higher HRV than men, and this has been suggested as a possible explanation for why they seem to be protected from cardiovascular disease earlier in life (Dekker et al., 2000). Traditionally, overall HRV is expected to decrease during stressful situations and to increase with rest (Dekker et al., 2000).

Stress Management through Mindfulness

Given the association of stress with metabolic parameters, it is possible that stress management may decrease metabolic disturbances. Stress management approaches targeting both body and mind are of particular interest to this dissertation. The most commonly used of these approaches include relaxation techniques, biofeedback, yoga, various forms of meditation, and mindfulness. These practices are particularly pertinent because a) they incur very little emotional and physical side-effects, b) are fairly low in cost for the patient, c) are relatively easy to learn and allow patients to actively participate in treatment, and d) are convenient for the patient as many of the techniques can be done at home or elsewhere once learned (Younge et al., 2014).

Mindfulness for stress reduction was chosen as the intervention for the third study of this thesis as it has recently garnered increased attention from medical professionals, researchers, and the public. Mindfulness refers to paying attention in a nonjudgmental, open, and welcoming manner to individual experiences as they occur in the present moment (Kabat-Zinn, 1990). This awareness is approached with a curious and non-reactive mind and aims to help those who live primarily on "auto-pilot" to accept and be fully present in their moment to moment reality (Kabat-Zinn, 1990; Kabat-Zinn, 2003).

There are several fundamental tenets of mindfulness practise (Kabat-Zinn, 1990), which will be described briefly below. First, the stance of *non-judgement* refers to taking the position of an impartial witness to one's individual experience. That is, becoming aware of the tone of one's judging mind (good, bad, neutral), without trying to alter it. The tenet of *trust* refers to having faith in one's intuition, trusting oneself and one's feelings. *Patience* signifies letting things unfold in their own time and allowing oneself to live fully through every moment, without rushing to experience something better or different. Approaching situations with a *beginner's mind* is another central tenet of mindfulness. That is, developing one's mind to perceive experiences as if it was the first time without the bias of our prior experiences influencing our perception. It is being receptive to new possibilities, treating each experience as unique, and not allowing past experiences and knowledge to prevent us from viewing a situation clearly. The principle of *non-striving* in mindfulness refers to accepting that meditation has no objective other than paying attention to oneself in the present and being true to oneself. Rather than constantly striving to meet goals, *non-striving* emphasizes focusing on seeing things as they are and accepting them from moment to moment, which in turn allows a natural progression towards achievement of goals. *Acceptance* signifies accepting what is occurring in the present and accepting oneself without abandoning principles and values. According to mindfulness principles, it is essential that one accepts who he or she is before inner change becomes possible. Finally, *letting go* refers to letting things be as they are, rather than allowing something to gain a strong hold in our minds, occupying unnecessary attention and energy. Although mindfulness practices have been cultivated for thousands of years, they were introduced to Western medicine in 1979 by Jon Kabat-Zinn Ph.D., professor of medicine at the University of Massachusetts Medical School, in the form of Mindfulness-Based Stress Reduction (MBSR). MBSR is an established, standardized eight-week stress reduction program that embodies these fundamental concepts.

Stress reduction through mindfulness has been associated with some positive health outcomes. For instance, in a recent review of seven randomized-controlled trials (RCT's) examining the impact of mindfulness-based interventions for functional gastrointestinal disorders, Aucoin, Lalonde-Parsi, and Cooley, (2014) reported that participation in mindfulness interventions resulted in decreased irritable bowel symptom severity (pooled ES =.59) and increased overall quality of life, (pooled ES =.56), with medium effect sizes. MBSR has also shown promise in individuals with chronic pain within primary care settings. La Cour and Petersen (2015) conducted an RCT (n=109) comparing the standardized MBSR program against waitlist controls in individuals with various types of chronic pain. Participation in MBSR resulted in significant improvements in perceived control over pain (Cohen's d =.55) and pain acceptance/engagement in activities despite pain (Cohen's d =.71), with medium to large effect sizes. MBSR may additionally result in decreased overall pain severity ratings for individuals with chronic headaches compared to treatment-as-usual controls (Omidi & Zargar, 2014) and improvements in degree of pain disability as per a small uncontrolled pilot study (Beaulac & Bailly, 2015).

Research also largely supports the use of mindfulness-based approaches for improvement of mental health. A large-scale meta-analysis of 209 studies investigating the effect of mindfulness-based therapies in men and women of various ages with diverse clinical profiles revealed moderate effectiveness for within-group analyses (Hedges' g =.55), particularly for stress, anxiety, and depression (Khoury et al., 2013). Mindfulness-based therapies were also moderately effective when compared to waitlist controls (Hedges' g = .53) and active treatment conditions (Hedges' g = .33) including other psychological therapies (Hedges' g = .35) (Khoury et al., 2013). Additionally, Hoffman and colleagues (2010) conducted a meta-analysis of 39 studies (16 controlled) examining the influence of mindfulness-based interventions on anxiety and depression in individuals with an existing psychiatric or medical condition (e.g. cancer, diabetes, cardiovascular disease, major depressive disorder, generalized anxiety disorder, fibromyalgia, etc). Participation in these interventions was associated with moderate improvements in anxiety (Hedges' g = .63) and depressive symptoms (Hedges' g = .59) in the overall sample, as well as robust improvements for those with a diagnosed anxiety disorder (Hedges' g = .97) and major depression at baseline (Hedges' g = .95) (Hofmann, Sawyer, Witt, & Oh, 2010). A meta-analysis of 29 studies examining the impact of MBSR on stress and anxiety in otherwise healthy participants also demonstrated moderate effectiveness in within-group (Hedges' g = .55) as well as in between-group comparisons (Hedges' g = .53) (Khoury, Sharma, Rush & Fournier, 2015). Effects of MBSR were maintained for an average of 19 weeks post-intervention (Khoury et al., 2015).

Of note, some of the health issues for which MBSR has yielded positive impacts tend to be either triggered by or at least aggravated by the experience of stress (e.g. gastrointestinal problems, chronic pain, depression, anxiety) (Cohen, Janicki-Deverts, Miller, 2007; Creswell, Pacilio, Lindsay, & Brown, 2014). One pathway by which MBSR may influence health outcomes is through its impact on physiological stress responses. Indeed, Creswell et al. (2014) propose that mindfulness training may protect against stress-related illnesses or reduce stress-related exacerbation of symptoms by reducing physiological reactivity to stress (Creswell at al., 2014). Mindfulness aims to help individuals become more aware and accepting of internal experiences and teaches participants to "let go" of stressors that occupy mental or emotional energy (Grant, Hobkirk, Persons, Hwang, & Danoff-Burg, 2013; Kabat-Zinn, 1990). The regular practise of mindfulness may thus limit the emotional impact of stressors, which in turn may reduce physiological reactivity. Indeed, some mindfulness meditations focus on stressors themselves, allowing them to be experienced in controlled repeated ways, akin to exposure therapy (Tang, Hölzel, & Posner, 2015). This may in turn reduce reactivity as well as enable the individual to practise adaptive stress responding in preparation for future challenges (Tang et al., 2015). Through its emphasis on bringing awareness to changing internal states, mindfulness helps create space between the stressor and the individual's response, potentially allowing for a more moderate response rather than an automatic heightened reaction (Loucks et al., 2015; Segal, Williams, & Teasdale, 2012). Others suggest that mindfulness may buffer prolonged stress responses by targeting persistent negative thoughts that occur once the stressor has subsided (Gu, Strauss, Bond, & Cavanagh, 2015). Indeed, several studies have reported associations between persistent angry cognitions and sustained BP following completion of an anger recall task (Gerin, Davidson, Christenfeld, Goyal, & Schwartz, 2006; Schwartz, Gerin, Davidson, & Christenfeld, 2000; Suchday, Carter, Ewart, Larkin, & Desiderato, 2004). The ability to apply the tenets of *letting go* and *acceptance* in mindfulness practise, rather than thinking excessively about the stressful event, may facilitate physiological recovery from the stressor. Despite literature examining the mechanisms by which mindfulness may impact reactivity and/or recovery, very little research has been conducted on the influence of MBSR on phasic stress responses.

Mindfulness-Based Stress Reduction and Stress Responses

Only one study has examined the impact of MBSR in its standardized eight-week format on stress responses specifically. In their randomized-controlled trial of 88 healthy individuals reporting high levels of perceived stress, Nyklicek and colleagues (2013) found that participants assigned to the MBSR training group had significantly decreased SBP and DBP post-intervention across baseline, stress, and recovery periods compared to waitlist controls, with a rather large effect size, ($\eta^2 = .16$). Additionally, those in the MBSR group demonstrated significantly less SBP and DBP reactivity to a 12 minute stress period including a mental arithmetic and speech task than those on the waitlist, with moderate effect sizes (SBP, $\eta^2 = .08$, DBP $\eta^2 = .10$). No differences were observed between the MBSR group and waitlist group in LF, HF, or LF/HF from pre- to post- intervention.

A few other studies have examined whether components of MBSR buffer heightened stress reactivity, with mixed results. For instance, Creswell, and colleagues (2014) examined whether brief mindfulness meditation training impacts cardiovascular reactivity to the Trier Social Stress Test (TSST). This brief training consisted of three sessions of 25 minute audio-guided meditation exercises, taking place once a day across three days in the laboratory. Questionnaire periods both preceded and followed the guided meditation on each day. On day three, participants also engaged in the TSST upon completion of the final meditation. The first meditation session focused on breath awareness, the second session emphasized full body awareness and the body scan, and the third session focused on awareness of emotions and thoughts in relation to breath and body awareness. This study of 66 undergraduate students included an active control group who analyzed poetry passages as a critical thinking exercise across a three day period. Results showed that those in the mindfulness group did not differ in their SBP or DBP responses to the stressor when compared to the cognitive training group (Creswell et al., 2014).

For their part, Steffen and Larson (2015) investigated whether 62 undergraduate students engaging in a brief mindfulness breathing exercise (guided by a CD, lasting approximately 15 minutes) would exhibit less cardiovascular reactivity during the PASAT compared to control participants who engaged in a passive listening task. In this study, participants completed the PASAT immediately following their guided breathing exercise or listening task. Results were such that those in the brief mindfulness training group demonstrated less SBP ($\eta^2 = .23$) and DBP ($\eta^2 = .08$) reactivity to the stressor compared to controls, with large and moderate effect sizes, respectively. HR reactions to the stressor and overall recovery responses did not differ between the mindfulness group and controls. In another recent study of undergraduate students, 97 participants were assigned either to a mindfulness condition in which they practiced a guided meditation breathing exercise or to a control condition in which they listened to an audio-book. Cardiovascular reactivity and recovery responses to a cold pressor and mirror tracing task were then immediately measured and compared (Grant et al., 2013). Although no differences in reactivity emerged between the two groups, participants in the focused-breathing condition actually exhibited slower SBP recovery following the cold pressor task than controls (Grant et al., 2013).

Ditto and colleagues (2006) investigated the immediate effects of mindfulness meditation on general autonomic functioning (Ditto, Eclache, & Goldman, 2006). In a study of 32 healthy meditation-naive adults, participants were randomly assigned to a body-scan meditation, progressive muscle relaxation, or control condition (Ditto et al., 2006). Participants practised their assigned technique with help from an audio tape (or sat quietly, in the case of controls) for 20 minutes during two testing sessions in the laboratory (Ditto et al., 2006). Participants engaging in body-scan meditation showed significantly greater increases in respiratory sinus arrhythmia (an indicator of enhanced parasympathetic activity) than those engaging in progressive muscle relaxation or controls (Ditto et al., 2006). Respiratory sinus arrhythmia refers to the natural occurring fluctuations in HR that happen within a breathing cycle and is used as an index of vagal function (Yasuma & Hayano, 2004). Other authors have demonstrated that tonic HRV levels tend to increase during the practice of mindfulness meditation (Krygier et al., 2013; Peressutti, Martín-González, García-Manso & Mesa, 2010). However, it is not possible to assert whether these improvements generalize to phasic HRV stress responses.

In sum, although recent studies have emerged examining the impact of MBSR and its components on stress responses, research in this domain remains scarce. Only one study has examined whether the standardized eight-week MBSR program buffers exaggerated reactivity to stress, while a few other studies have investigated the impact of brief mindfulness exercises on stress responses. It remains unclear whether MBSR influences stress response parameters.

Mindfulness-Based Stress Reduction: Metabolic Outcomes

Although MBSR seems promising for some diseases that are exacerbated by stress, its impact on a diagnosis of metabolic syndrome has never been investigated. Another objective of this dissertation is to determine whether alterations in stress responses through stress management contribute to changes in metabolic syndrome parameters. If so, this would provide additional evidence for the pathogenic role of stress responses in metabolic syndrome as well as the reversibility of such effects through self-management approaches. Indeed, interventions targeting reactivity to stress may be a useful adjunct in secondary prevention efforts to reduce metabolic syndrome and in turn, cardiovascular morbidity.

While MBSR has not been investigated with respect to metabolic syndrome, there is some literature on its impact on individual metabolic parameters.

MBSR and blood pressure. Blood pressure is the parameter that has been the most examined in relation to MBSR and conflicting results have emerged (Campbell, Labelle, Bacon, Faris, & Carlson, 2012; de la Fuente, Franco, Salvador, 2010; Hartmann et al., 2012; Hughes et al., 2013; Joo, Lee, Chung, & Shin, 2010; Palta et al., 2012; Parswani, Sharma, &

Iyenger, 2013; Nyklicek et al., 2013). For example, in a sample of 56 middle-aged adults with un-medicated pre-hypertension, participation in an MBSR program was associated with significant reductions in SBP (-4.8 mm Hg) and DBP (-1.9 mm Hg) as compared to participation in a progressive muscle relaxation control condition (Hughes et al., 2013). Control participants also showed reductions in SBP and DBP but these were of lesser magnitude, (-0.07 mm Hg and – 1.7 mm Hg, respectively). As was previously mentioned, Nyklicek and colleagues (2013) similarly found that participants randomly assigned to receive MBSR exhibited significant decreases in resting SBP (-3 mm Hg) and DBP (-8.1 mm Hg) compared to waitlist controls, who exhibited increases in SBP (+1.5 mm Hg) and DBP (+0.8 mm Hg) over the 8 week waiting period. This was one of the few studies to provide an effect size, $\eta^2 = .16$ (deemed large). MBSR was also associated with reductions in BP in three other investigations (de la Fuente et al., 2010; Palta et al., 2012; Parswani et al., 2013). In contrast, Hartmann et al. (2012) reported no significant differences in SBP or DBP in patients with Type 2 Diabetes post-MBSR (n=53), compared to treatment-as-usual controls (n=57). Additionally, participation in MBSR did not have an impact on casual BP in another study of 70 women with breast cancer compared to waitlist controls (Campbell et al., 2012). Participants in this study were provided with monitors to self-assess their BP either at home immediately before and after their participation in MBSR or at the start and end of the 8 week wait period depending on which group they belonged to (Campbell et al., 2012). Given that a casual self-assessed measure of BP was used, comparison with studies including BP obtained by research personnel in the laboratory may be limited.

Indeed, methodological differences may account for discrepancies in results of this domain; close examination of these studies is warranted before drawing conclusions. For instance, Parswani et al. (2013) assert that MBSR was effective in reducing SBP in 30 men with cardiovascular disease (-11.20 mm Hg) compared to treatment-as-usual controls, who exhibited increases in SBP immediately post-intervention (+10.14 mm Hg). However, it is unknown whether the two groups differed significantly in socio-demographic or physiological variables at baseline. Upon consultation of their results table, it is evident that the MBSR group had a higher SBP (135.67 mm Hg) at rest than the control group (125.33 mm Hg). Group differences in SBP post-intervention could thus possibly be attributed to group differences at baseline or a regression to the mean effect, rather than the intervention. Moreover, variations to the standardized MBSR program (number of sessions, duration of sessions, individual versus group contexts) are often made, making it difficult to draw comparisons across MBSR studies (Campbell et al., 2012; de la Fuente et al., 2010; Parswani et al., 2013). For example, in Parswani et al. (2013), the sessions were 1 to 1.5 hours long and the credentials of the individual providing these interventions were not described. These sessions were also offered individually to participants (rather than in a group format) and whether the meditation retreat was included was not detailed. The authors nevertheless concluded that MBSR is effective in reducing BP; the fact that it had no impact on DBP was not specified in the abstract, nor addressed in writing in the results section. Given that some of these studies lack methodological diligence in their study design and/or reporting style, the relation between MBSR and BP remains unclear and in need of further investigation.

MBSR and other metabolic syndrome parameters. Research on the effects of MBSR on the remaining parameters of metabolic syndrome is mixed and scarce. Given that mindfulness-based interventions are increasingly studied in the context of weight loss, metabolic parameters and BMI (which can be used as a proxy for waist circumference) are sometimes included as outcome variables. For instance, Daubenmier et al., (2012) tested the impact of a combination of traditional MBSR with a mindfulness-based eating awareness program (MB-EAT) on 47 overweight women (BMI between 25 and 40) in a randomized controlled pilot study. Participants were pre-menopausal and had no history of diabetes or cardiovascular disease. The 4-month program consisted of nine 2.5 hour MBSR sessions and a 7 hour meditation retreat, while the control group consisted of a waitlist. Participation in the intervention *did not* lead to any significant differences between the intervention group and control group in weight loss, BMI, or glucose. In fact, both groups exhibited increases in glucose (but no change in BMI or weight) post-intervention (Daubenmier et al., 2012). Groups also did not differ significantly over time in abdominal fat (as measured by dual-energy X-ray absorptiometry) (Daubenmier et al., 2011). In contrast, Parswani et al. (2013) reported that participation in MBSR was related to a significant decrease in BMI (-0.59 kg/m^2) compared to treatment-as-usual controls (-0.35 kg/m^2) in a sample of 30 men with cardiovascular disease. However, as was stated in the previous section, results of this article should be interpreted with caution given methodological shortcomings.

The impact of mindfulness on glucose levels has only been examined by three studies, and findings have been mixed. While Daubenmier and colleagues (2011) reported increases in glucose in both the mindful eating group and waitlist control group post-intervention, MBSR was shown to improve glycemic regulation (decreased levels of glycosylated hemoglobin) in a pilot study of 11 patients with diabetes (Rosenzweig et al., 2007). Youngwanichsetha and colleagues (2014) also reported that participation in a mindfulness-based eating program coupled with yoga exercise resulted in significant decreases in fasting blood glucose in pregnant women with gestational diabetes compared to controls. It is important to note, however, that mindfulness-based eating programs typically use mindful eating as the intervention focus and not stress reduction through mindfulness, reflecting important differences in content (Youngwanichsetha, Phumdoung, & Ingkathawornwong, 2014). They may differ in structure and length as well, making it difficult to compare these interventions with standard versions of MBSR.

Limitations of Existing Mindfulness Literature

There are some noteworthy limitations to the literature examining the relation of MBSR with stress responses or metabolic syndrome parameters. First, only one study has examined the impact of MBSR in its full form on stress responses and details regarding the study's procedure and results are limited as it was published as a five-page brief report (Nyklicek et al., 2013). It is also the only investigation which examined ANS responses to stress. Similarly, research examining the impact of MBSR on individual metabolic syndrome parameters is both scarce and mixed. In general, it is difficult to compare results from these few studies as alterations are often made to the standardized MBSR program and/or different components of the program are used.

Additionally, drawing comparisons across these few studies is further complicated by the fact that various types of control groups including active controls and waitlists have been used. Progressive muscle relaxation (Hughes et al., 2010), cognitive training through the analysis of poetry passages (Creswell et al., 2014), listening to a fictional audio-book (Grant et al., 2013), and participating in a social support group (Palta et al., 2012) are just some examples of the control conditions that have been used against MBSR. Not only are these conditions fundamentally different, but few authors explain or empirically justify why they are chosen as controls.

A number of authors have emphasized the need for higher quality studies in this field (Abbott et al., 2014; Aucoin, 2014; Younge et al.) For instance, in a review examining the effectiveness of mind-body interventions such as MBSR for patients with cardiovascular disease, Younge et al., (2014) reported that most studies failed to include details of their randomization procedure, lacked statistical power, and did not provide enough information about their study design. Indeed, structural organization of some of these articles is rather poor and it is often difficult to locate essential information such as sample size, type of control group used, and results tables. The authors conclude that methodology in this field is overall inconsistent; future studies should aim to implement more robust methodological procedures and describe them in detail.

Conclusion

Nearly one in four Canadians reports feeling highly stressed on a daily basis. The experience of stress has been associated with the onset and progression of CVD, the leading cause of death in men and women worldwide. A pathway by which stress may contribute to CVD is through its impact on intermediary risk factors of CVD, i.e. metabolic syndrome. This thesis will extend current knowledge by examining the contribution of stress responses to metabolic syndrome in order to better understand how stress influences CVD. To date, no research has examined the impact of stress responses on a global index of metabolic syndrome in adults, and studies examining the relation between stress responses and individual parameters of metabolic syndrome have yielded mixed findings. Discrepancies in earlier studies may reflect individual differences in the extent to which stress responses and metabolic syndrome are related. Indeed, it appears likely that the relation between stress and metabolic syndrome may be influenced by sex and/or age, though few studies have investigated their potential moderating effects.

This thesis has important research implications, as it will also attempt to compensate for methodological shortcomings in existing stress reactivity research. For example, physiological recovery from stress has largely been ignored in the literature regardless of its hypothesized contribution to allostatic load. In addition, most of the previous investigations omitted autonomic indices of reactivity and focused solely on cardiovascular indices, despite the ANS' critical role in metabolism. This thesis will contain some of the first work to include autonomic indicators of stress response. The inclusion of a prospective study also permitted the evaluation of the predictive value of stress responses to future metabolic dysfunction.

Finally, obtaining an enhanced understanding of stress' contribution to metabolic syndrome, while considering the potential impact of sex and age, may shed light as to how to most effectively intervene in order to diminish the impact of stress on metabolic syndrome, and in turn, CVD. Thus, this dissertation includes a pilot proof-of-concept intervention study examining the feasibility and acceptability of mindfulness-based stress reduction for older adults with current or past metabolic syndrome as an adjunct to usual treatment. It will also investigate whether elevations in metabolic parameters can be reversed through mindfulness-based stress reduction and will provide initial evidence as to whether MBSR influences the magnitude of stress reactivity responses. This will further elucidate the role of stress responses in the pathogenesis of metabolic syndrome.

Thesis Breakdown

The current thesis consists of three investigations, two of which are presented in article format. A principal goal of this research program is to improve understanding of the contribution of cardiovascular and autonomic responses to stress in metabolic syndrome in men and women of differing ages. Two observational studies (**Articles 1 and 2**) with an experimental stress protocol and longitudinal design (Study 1) will be used to address these goals. A third small pilot randomized study will investigate the feasibility and acceptability of mindfulness-based stress reduction in a small sample of older adults with metabolic syndrome (**Study 3**). All of these investigations will include measures of physiological reactivity to and recovery from stress as well as both cardiovascular and autonomic indices of stress response.

Objectives

Study 1. The objective of the first prospective study was to examine whether physiological (blood pressure, heart rate, and HRV) responses to a laboratory stress protocol predicted increased disturbances in a global index of metabolic dysfunction, herein referred to as metabolic burden (MB), over a three year follow-up in a healthy adult sample of working men and women. The moderating effect of sex and age on these associations was also examined.

Study 2. The objective of the second cross-sectional study was to determine whether findings obtained in Study 1 replicated in a larger, older, and less healthy sample of men and women with and without cardiovascular disease. In this more compromised population, the clinical definition of metabolic syndrome was employed as a dependent variable. Whether sex and age moderated the associations observed was again examined.

Study 3. The primary objective of this pilot study was to examine the feasibility (based on response rate, recruitment rate, refusal rate) and acceptability (based on program completion rate and attendance, practise time, participants' written and verbal feedback) of MBSR for older adults with current or past metabolic syndrome, recruited from Study 2. Secondary objectives included investigating whether MBSR improves individual parameters of metabolic syndrome. We also aimed to examine if MBSR training "normalized" physiological stress reactivity and recovery. Finally, we were interested in whether changes in stress responses were associated with changes in metabolic syndrome. Direction of effects and effect sizes were of primary interest for the secondary objectives.

Hypotheses

Study 1. We hypothesized that heightened reactivity to and delayed recovery from stress would predict greater metabolic burden, especially in older men, given that these individuals tend to be disproportionately diagnosed with metabolic syndrome compared to younger adults and women. Consistent with the reactivity hypothesis and the allostatic load model, we hypothesized that heightened and/or delayed responses to stress may be a mechanism by which older men are at greater risk for metabolic dysfunction.

Study 2. Based on these results from Study 1 (see Article 1 presented in the next section), we hypothesized that both heightened/delayed and/or blunted responses to stress would be associated with concurrent metabolic syndrome, particularly in women.

Study 3. We expected this study to be feasible and acceptable for older adults with current or past metabolic syndrome, as reported retention rates for MBSR tend to be between 80 and 90 percent in populations with health issues (Campbell et al., 2012; la Cour & Peterson, 2015; Lengacher et al., 2012). Recruitment rates in the literature typically range between approximately 40 and 60 percent (Campbell et al., 2012; Lengacher et al., 2012), which is what we expected for our study. As for secondary hypotheses, we believed that MBSR would result in clinically significant changes in metabolic profile, particularly BP, which is the parameter that has been the most examined to date.

ARTICLE 1

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Sex Differences in the Prediction of Metabolic Burden from Physiological Responses to Stress

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Abstract

Background: Heightened or prolonged physiological responses to stress may contribute to the development or progression of metabolic abnormalities.

Purpose: Examine the prospective relations between stress responses and metabolic burden, and determine whether age and/or sex moderate these relations.

Methods: 199 healthy men and women (M_{age} =41±11.5) were exposed to four stressors while blood pressure, heart rate, and heart rate variability (HRV) were obtained. Residual change scores for reactivity (stress - baseline) and recovery (post-stress - baseline) scores were computed. Metabolic burden refers to the number of metabolic parameters for which participants were in the highest quartile (lowest for HDL) for their sex. Metabolic burden was reassessed in 136 participants three years later.

Results: Greater parasympathetic withdrawal in response to stress was associated with increased metabolic burden, though this was evident mostly in men. In women, dampened autonomic responses to stress were associated with higher metabolic burden.

Conclusions: Cardiac autonomic responses to stress predict future metabolic abnormalities, though the direction of effect differs according to sex.

Key words: stress, physiological reactivity/recovery, metabolic burden, individual differences, prospective

One of every five Canadians is diagnosed with the metabolic syndrome, with prevalence rates reaching 40 percent at 60 years of age (1, 2). Metabolic syndrome refers to a cluster of interconnected factors that incur significant risk for atherosclerosis, Type II diabetes, and increased mortality from cardiovascular diseases (3-6). It typically refers to the presence of at least three of the following: central adiposity, high blood pressure, elevated triglycerides and/or fasting blood glucose, and low levels of high-density lipoprotein (HDL) cholesterol (3, 7). Psychological variables, such as hostility, appear to contribute to individual and combined parameters of metabolic syndrome (8-11). This may occur, in part, as a result of heightened physiological responses to stress associated with these psychological variables (12).

The relationship between physiological responses to psychological stress and a global representation of metabolic syndrome has yet to be investigated. Some research exists, however, examining stress responses and the individual components of metabolic syndrome. For instance, a recent meta-analysis found hypertension to be consistently predicted by increased cardiovascular reactivity (CVR) to stress and poorer recovery from stress (13). To our knowledge, the relation between fasting blood glucose level and CVR and/or recovery from stress has not been examined, and the sparse research on other parameters of metabolic syndrome has yielded mixed findings. While some studies have reported heightened reactivity to laboratory stress in individuals with elevated total cholesterol and/or triglyceride levels (2, 14-17), others have reported no or opposite associations depending on the age and sex of the participants (18, 19). Confusing the situation further, in these studies, stress responses have often been examined as outcomes of metabolic abnormalities rather than their predictors. The relation between cardiovascular responses to stress and central adiposity has also yielded mixed results (20-23). For example, in a cross-sectional study of middle-aged men and women, body mass index (BMI) and waist-to-hip ratio were both associated with delayed systolic (SBP) and diastolic (DBP) blood pressure recovery from stress but not with heightened CVR (24). Delayed SBP recovery also predicted increases in waist-hip ratio after a three year follow-up in men but not women (24). In contrast, Carroll, Phillips and Der (25) found that greater heart rate (HR) reactivity to a cognitive task was associated with **less** central adiposity in a large community sample of men and women. These associations were maintained prospectively, with high HR reactivity predicting a reduced likelihood of becoming obese over a five year follow-up (25). Similar results were obtained in another independent sample (26).

Methodological differences relating to sample characteristics may explain some of the inconsistencies in the literature. While few investigations have specifically examined the moderating effects of sex and/or age on results obtained, there is some limited data to suggest that these may be of import (19, 24). Given that older adults and men suffer disproportionately from metabolic syndrome in Canada (27) and exhibit heightened CVR to stress in comparison to younger individuals or women (especially to cognitive and performance oriented tasks) (25, 28-30), it is possible that age and/or sex may similarly moderate the relation between stress responses and metabolic syndrome.

It has been proposed that prolonged physiological arousal following exposure to stress may more greatly contribute to allostatic load and resulting disease outcomes than CVR (31, 32). In support of this, Steptoe and Marmot (33) reported that delayed SBP and DBP recovery from stress predicted increases in blood pressure after a three year follow-up more consistently than heightened CVR during stress. However, few studies have examined the relations between recovery responses and metabolic syndrome parameters (13, 24, 33).

Finally, no research has specifically examined the relations between autonomic responses to psychological stress and metabolic syndrome parameters. Yet, the autonomic nervous system (ANS) plays a key role in the regulation of metabolism, with major organs involved in metabolism (e.g. heart, brain, liver, pancreas) innervated by the sympathetic and parasympathetic nervous systems (34). Importantly, disruptions of the ANS have been associated with the development of individual or combined parameters of metabolic syndrome (35-38).

In sum, physiological responses to stress may contribute to metabolic abnormalities, although conflicting findings have been reported, depending on sample characteristics and metabolic measure. To date, no investigations have examined the relations between stress responses and metabolic syndrome. Yet, the importance of metabolic syndrome to cardiovascular and related outcomes, and its independence of its individual components have repeatedly been shown (39-43). The objective of the current study was to examine the prospective relations between stress responses to a laboratory protocol and a global index of metabolic dysfunction, herein referred to as metabolic burden, in a healthy adult sample of men and women. Healthy participants were sought to minimize the impact of disease processes or medications on stress responses and their relation with metabolic dysfunction. However, this rendered assessing metabolic syndrome unfeasible, as its prevalence in the sample was low. Metabolic burden was therefore defined as the number of metabolic syndrome parameters for which participants were in the highest quartile (lowest for HDL) for their sex. Such count-based summary measures have been shown to be predictive of a larger spectrum of health outcomes than individual parameters (44). Reactivity and recovery were examined for HR, BP, and for indices of ANS responses to stress obtained via the analysis of heart rate variability (HRV) (45). Finally, the moderating effect of age and sex on the associations between stress responses and metabolic burden was evaluated. It was hypothesized that heightened reactivity to and delayed recovery from stress would contribute to increased metabolic burden prospectively, particularly in men and older adults.

Methods

This prospective study was part of a larger project that sought to examine the association of psychological and psychophysiological variables with intermediary coronary artery disease risk factors (for examples of data published from this project, see (11, 46-50).

Time 1

Participants. One hundred and ninety-nine healthy adult men (n = 81) and women (n = 118) were recruited through advertisements in newspapers and community centers within the greater Montreal area. Individuals were excluded from the study if they: (a) used any mental health services within the past year; (b) had any current/diagnosed health problems (for example, asthma, hypertension, diabetes, hypercholesterolemia, heart disease, cancer, auto-immune disorders, disorders of the adrenal gland) or taking medication (for example, statins, beta-blockers, anti-inflammatory) capable of affecting cardiovascular, immune, or neuroendocrine functions; (c) had any cognitive disabilities rendering them unable to complete questionnaires or understand instructions, and (d) were undergoing any form of hormone replacement therapy. Individuals were interviewed by phone to ensure that they met the criteria before they were invited to participate. Similar numbers of participants were selected from three age groups (18–34 years, 35–44 years, and 45–65 years) to ensure a broad age range. Women were over-sampled to include a substantial number of post-menopausal women (*n*=34) for a separate component of the study not discussed here. Complete data were obtained for 193 participants (78 men, 115 women) at Time 1.

Procedure

Participants were scheduled for a laboratory appointment at 8:00 a.m. on a weekday to control for circadian rhythms. They were asked to abstain from drinking (with the exception of water), smoking, and strenuous exercise for 12 hours prior to testing. They were also asked to refrain from the use of drugs or alcohol for the 24 hours preceding their appointment. Participants were sent home and their appointment rescheduled if they did not adhere to these instructions or if they exhibited physical symptoms such as a cough, cold, or headache. Research assistants were trained to maintain a neutral tone and expression during testing and were paired with participants of the same sex. Once participants provided written consent, anthropomorphic data (weight, height, and waist circumference) were obtained. The electrodes for electrocardiographic (ECG) monitoring were then attached in a bipolar configuration to the lower side of the rib cage and a ground electrode was placed on the left hip. Participants completed sociodemographic, medical, and psychological questionnaires, after which they rested quietly during a 10-min baseline period. Blood samples were taken following the baseline period as well as after the final recovery session. Participants engaged in four psychological challenges of 5 minutes each (a neutral reading task, two role-plays, and a nonscripted debate). Each stressor was preceded by a 5-min taped autogenic relaxation procedure and a 2-min preparation phase, and followed by a 5-min recovery period. The ECG was obtained continuously during laboratory testing. SBP and DBP were measured every 2 minutes in the laboratory through a standard inflatable cuff placed on the participant's non-dominant arm. After completing the stress protocol, participants were equipped with ambulatory BP and ECG equipment, and measures were obtained continuously over a 24-hour period. Participants were compensated $200 for their time and travel. This study was approved by the Research and Ethics Board of the Montreal Heart Institute.

Laboratory Tasks

In order to augment task stressfulness, participants were informed that their performance would be rated and that they would be videotaped during each task. The tasks led to significant affective and physiological reactivity in pilot testing or prior studies (e.g. (51-53)).

Public reading of a neutral text. Participants read an affectively neutral text on Antarctica's geography aloud in the presence of a same-sex confederate.

Role-plays. As with a prior study (51), participants engaged in two scripted role-play scenarios manipulating quarrelsome behavior. Participants were asked to play the role of a supervisor providing feedback to an employee whose performance had been mediocre. The script of the first role-play scenario contained agreeable assertions while the script of the second role-play contained an equal number of quarrelsome assertions. The participant was asked to enact the script as authentically as possible with a confederate acting as the employee. These role-plays were counterbalanced across participants.

Debate. In the final task, the participants engaged in a non-scripted debate regarding abortion. They argued from a partisan position and alternated speaking and listening for 1-min periods with a confederate who was debating the opposite position. The participant began the debate, which resulted in a total of 3 minutes of active debate for the participant, and 2 minutes of listening while the confederate spoke.

Measures

Sociodemographic variables: Data on sex, age in years, ethnicity, weight, height, marital status, income, and years of schooling were obtained. Behavioral risk factors, such as daily tobacco and alcohol consumption and hours of physical activity, were reported by the participant.

Metabolic burden was defined as the number of metabolic syndrome parameters for which participants were in the highest quartile (lowest for HDL) for their sex, for a total range of 0 to 5. For the sex-specific cutoff values for each of the metabolic parameters used to assess metabolic burden, please refer to Table 1 on page 72. Serum samples were analyzed for lipids and glucose at the Montreal Heart Institute. These determinations were made using respective reagent Flex on the multianalyzer Dimension RxL Max (Dade Behring Diagnostics, Marburg, Germany) with heparinized plasma, as simultaneously as possible following the blood draw. Waist circumference was measured using a standard measuring tape. Twenty-four hour ambulatory BP measures were obtained at 20 min intervals during the daytime and at one hour intervals from 22h00 to 6h00, using Spacelab Ambulatory Blood Pressure Units, which use an oscillometric method. The BP measures were based on values averaged over the 24 hours. Twenty-four-hour ambulatory BP measures were chosen as they are more predictive of cardiovascular endpoints than laboratory or clinic readings (54, 55), and have been recommended as the gold standard measurement of BP in the diagnosis of hypertension and metabolic syndrome (56). Usable ambulatory BP data were obtained for 98% of the sample.

Physiological responses during the stress protocol: The stress protocol began following a 20-minute adaptation period in the laboratory. BP during the stress protocol was assessed using an AccutorPlus automated BP monitor from Datascope. This model uses an oscillometric method and has been recommended by the European Society of Hypertension (57). A mean of two readings per period (baseline, stressor, recovery) was used for analysis. Baseline BP was based on the average of two readings obtained during the last 5 minutes of the 10-min rest period preceding the blood draw and exposure to the stress tasks.

The ECG was obtained using disposable electrodes and the Biopac acquisition system (Biopac Systems Canada, Inc., Montreal Canada) using Acq- Knowledge 3.7.3 software (Goleta, CA, USA). Signals were first filtered with a digital band-pass filter and a 1,000-Hz sampling rate. Interbeat intervals were generated using a peak detection algorithm, after which the series was screened by hand and corrected for artifacts. Spectral analysis of HRV was performed offline using fast Fourier transformations of the interbeat intervals (RR) in MATLAB using published algorithms (58) and was characterized by the high frequency (HF; 0.15–0.40 Hz) and the low frequency components (LF; 0.04– 0.15 Hz) as recommended by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (45). HF-HRV reflects parasympathetic control of the heart. LF-HRV was once used as an index of sympathetic activity, though recent evidence suggests that, under some circumstances, it may actually reflect vagal influences (59). Given debate on this issue, LF/HF ratio was used instead as a measure of sympathovagal balance in the main analyses. Traditionally, it is expected that as stress increases acutely (as per a stress protocol), sympathovagal balance increases, while parasympathetic control of the heart (as denoted by HF) decreases. HF-HRV was assessed in both absolute and normalized units (nu). The latter is a relative measure that accounts for changes in total spectral power (45), such as may occur during a stress protocol.

Affect and Arousal were assessed by means of the affect grid, a 1-item instrument measuring both valence and intensity of affect (60). The participant is asked to indicate the extent to which he is feeling pleasure-displeasure on the horizontal axis and arousal–sleepiness on the vertical axis of a 9 × 9 grid of squares. Elevated scores on both axes suggest high arousal and pleasant affect. Intensity of specific affects (e.g., anger, fear, happiness) was also measured using a 7-point rating scale from 1 (not at all) to 7 (very much).

Psychological Variables: Various psychological questionnaires were administered for a separate component of the overall investigation that were examined here in post-hoc analyses only. These include the Anxiety Sensitivity Index (61, 62), the Beck Depression Inventory-II (63, 64), and the Beck Anxiety Inventory (65-67).

Data reduction

SBP, DBP, HR, HF-HRV, HF_{nu}, LF-HRV, and LF/HF readings were averaged over each baseline, stress, and post-stress period. The four stress periods were averaged to create a stress composite score. A composite post-stress score was similarly created. Prior research has shown that such aggregate measures, when compiled from multiple stressors that induce similar physiological responses, are more reliable and reflective of a person's typical or trait-like reactivity and recovery compared to responses to individual tasks (68-70). Stress reactivity (stress-baseline) and recovery (recovery-baseline) change scores were then created as per established methods (71). Finally, in order to minimize the impact of individual differences in baseline values on the change scores, the latter were further regressed on baseline values. These residual change scores were utilized for the primary analyses.

Protocol: Time 2

Participants were contacted for a follow-up visit approximately three years later (*M* = 2.87, *SD* = 0.30 years). Of the 184 individuals who were successfully contacted, six participants were excluded for medical reasons including pregnancy (n =3), cancer (n=2), and sleep apnea (n=1), while 35 refused due to lack of interest (*n*=16), scheduling issues (*n*=15), or perception that the protocol was too demanding (*n*=4). Complete data for current analyses was obtained for 136 participants. Metabolic parameters were obtained as per Time 1.

Participants who returned at follow-up were significantly older (M = 42 vs. M = 39 years), had spent more years on the job market (24 vs. 20 years), smoked fewer cigarettes a week (M = 8 vs. M = 20), and had higher HR post-stress compared to baseline (M = 2.18 vs. M = 0.88) (all *p'*s < 0.05) compared to those who did not return at follow-up. No other significant differences emerged.

Analyses

All distributions were verified for normality; BMI, number of hours of exercise per week, and HF-HRV were log-transformed to increase the normality of their distributions. Bivariate correlations were employed to investigate the relation between metabolic burden and possible covariates, such as sociodemographic (sex, age, marital status, income, education), and behavioural variables (smoking, exercise, caffeine, alcohol consumption). Potential covariates were selected based on prior research suggesting an association with metabolic syndrome.

Various preliminary analyses were performed. To evaluate whether it was appropriate to create a composite score from the four stressors, we examined the internal consistency of each physiological measure across the four tasks and post-task periods. The extent to which metabolic burden serves as a proxy for metabolic syndrome was assessed using a one-way ANOVA. Sex differences in the reactivity and recovery change scores were also examined using one-way ANOVAs. Finally, partial correlations were performed between each residual reactivity or recovery change score obtained at Time 1 and metabolic burden at Time 2, while controlling for metabolic burden at Time 1, to evaluate the extent to which stress responses predicted change in metabolic burden in the overall sample.

The main analyses consisted of hierarchical linear regressions on the outcome measure of metabolic burden at Time 2. Covariates at Time 1 were chosen based on their univariate associations of $p< 0.250$ with metabolic burden at Time 2. Block 1 included age, sex, marital status, and metabolic burden at Time 1. BMI was not included given its statistical and theoretical overlap with waist circumference. A reactivity or recovery change score was entered in Block 2. The interactions of the reactivity or recovery change score with age and/or sex were entered Stepwise in Block 3. Analyses were repeated for each physiological measure of reactivity and recovery. Significance was set at $p < 0.05$. Significant interactions were evaluated using simple slopes analyses with lower and higher estimates for age based on values ±1 SD from the mean (72). No significant multicollinearity was observed.

Results

The women in our sample were slightly older than the men due to the oversampling of menopausal women for purposes not examined here. Men consumed significantly more alcoholic drinks per week than women but less caffeinated beverages, and engaged in more weekly exercise. Please refer to Table 2 on page 73 for a description of participant characteristics.

Examination of the composite scores

As the efficacy of the stress protocol has already been reported elsewhere (46, 48), we concentrate here on potential sex differences in reactivity and recovery. Men exhibited significantly greater DBP reactivity ($F(1, 135) = 6.37$, $p = 0.01$) and HF-HRV reactivity ($F(1,135) = 4.65$, $p = 0.03$) compared to women. Men also displayed significantly less HF-HRV recovery compared to women ($F(1, 135) = 8.20$, $p < 0.001$). No other differences emerged across the other parameters. Refer to Table 3 on page 74 for details.

The internal consistency of the composite stress and recovery scores was excellent, with Cronbach alpha reliability coefficients well above 0.90 across all measures of reactivity and recovery, except LF/HF, that nonetheless showed adequate internal consistency, substantiating the use of reactivity and recovery aggregate scores in the primary analyses.

Use of metabolic burden as a proxy for metabolic syndrome

Participants with metabolic syndrome in our sample showed significantly more metabolic burden at Time 2 (3.25 ± 1.18) than those without metabolic syndrome (1.14 ± 1.27; $p < 0.001$).

Metabolic burden and its univariate associations with stress responses. HF-HRV reactivity predicted increased metabolic burden at Time 2. Refer to Table 4 on page 75.

Metabolic burden as a function of stress responses, sex, and age.

Covariates (age, sex, marital status, and metabolic burden at Time 1) explained 33% of the variance.

Reactivity to stress.

A significant main effect emerged for HF-HRV (Beta = -0.14, $p = 0.047$), but not for any of the other reactivity change scores: SBP (Beta = -0.02, $p = 0.75$); DBP (Beta = - 0.07, $p = 0.37$); HR (Beta = 0.06, $p = 0.45$); HF_{nu} (Beta = 0.03, $p = 0.48$), and LF/HF (Beta = -0.06, $p = 0.38$).

However, significant interactions with sex emerged for HF_{nu} and LF/HF (see Table 5 on page 76 for details). Simple slope analyses indicated that women who did not show the expected decrease in HF_{nu} during stress compared to baseline tended to show an increase in metabolic burden over follow-up ($b = 0.26$, $p < 0.06$). In men, an opposite association was observed ($b = -0.23$, $p = 0.16$) (Figure 1a, page 79). Similarly, blunted LF/HF reactivity predicted increased metabolic burden at follow-up in women ($b = -0.35$, $p = 0.03$) but not in men ($b = 0.07$, $p = 0.60$) (Figure 2a, page 80). No significant interactions emerged with age.

Recovery from stress.

No main effects emerged for any of the recovery change scores: SBP (Beta = 0.08, $p = 0.23$); DBP (Beta = 0.10, $p = 0.18$); HR (Beta = 0.11, $p = 0.11$); HF-HRV (Beta = -0.02, $p = 0.77$), HF_{nu} (Beta = 0.10, $p = 0.15$), and LF/HF (Beta= -0.04, $p = 0.60$).

However, significant interactions with sex emerged for HF_{nu} and LF/HF (see Table 5 on page 76 for details). Women whose HF_{nu} values post-stress were closer to baseline values showed increased metabolic burden at Time 2 ($b = 0.41$, $p < 0.01$). In men, the opposite was true ($b = -0.11$, $p = 0.47$). (Figure 1b, page 79). For the LF/HF measure, greater LF/HF recovery predicted an increased risk of metabolic burden at Time 2 in women ($b = -0.34$, $p = 0.04$) but not in men ($b = 0.11$, $p = 0.36$) (Figure 2b, page 80). No significant interactions emerged with age.

Post-Hoc Analyses

Supplemental analyses were performed in order to better understand the results obtained. First, to increase our confidence in the findings regarding metabolic burden, we performed a series of logistic regression analyses using metabolic syndrome instead of metabolic burden as the outcome variable. Note that only 8 men and 9 women met metabolic syndrome criteria at follow-up, but results using metabolic syndrome are highly consistent with those obtained with metabolic burden. More specifically, a significant interaction between sex and HF_{nu} reactivity (O.R. = 17.30, $p = 0.03$, 95% C.I. = 1.30-229.43) and recovery (O.R. = 8.04, $p = 0.01$, 95% C.I. = 1.57-41.23) emerged. While non-significant, similar trends were nonetheless observed for the interaction terms between sex and LF/HF reactivity (O.R. = 0.29, $p = 0.10$, 95% C.I. = 0.06-1.27) and recovery (O.R. = 0.17, $p = 0.09$, 95% C.I. = 0.02-1.28). No associations or trends emerged with the cardiovascular measures.

The sample was then categorized into three equal groups (low, moderate, or high reactivity) according to their continuous HF_{nu} reactivity scores. HF_{nu} Reactivity Group (low, moderate, high reactivity) by Period (baseline, stress, post-stress) repeated measures ANOVAs were performed to determine whether the low HF_{nu} reactivity group was showing low stress responsiveness across all physiological parameters or whether these were limited to HRV parameters. In these analyses, LF-HRV was also examined to further comprehend the pattern of ANS activity contributing to the LF/HF ratio. The Period effects were all significant ($p < 0.002$) as expected. No Group or Group by Period interactions emerged for SBP, DBP, and HR, suggesting that the groups did not differ in their CVR to stress. However, a significant main effect of Group and a significant Group by Period interaction emerged for HF-HRV, LF-HRV, and LF/HF (all *p*'s < 0.002) The low HF_{nu} reactivity group showed higher overall HF-HRV **and** LF-HRV activity across the three periods (all *p*'s < 0.001), but showed less or no change in LF/HF and HF-HRV activity in response to stress (see Figure 3 on page 81).

A similar series of analyses was repeated on self-reported arousal, negative affect, and positive affect to verify that the protocol was ***experienced*** as equally stressful by all groups. No significant Group or Group by Period interactions emerged for any of these measures.

A Chi Squared analysis was performed to determine whether the sex differences reflected an insufficient number of men or women among extreme HF_{nu} responders. No significant sex difference was observed ($\chi^2 = 3.375$, $p = 0.185$). However, t-tests indicated a sex difference in self-reported arousal and negative affect during the stress period, with women reporting significantly more arousal, ($t(134) = 1.76$, $p < 0.01$)), and higher negative affect ($t(134) = 1.57$, $p < 0.01$)) compared to men.

To better understand what may be driving the relation between autonomic stress responses and metabolic burden, we conducted two-way ANOVAs with HF_{nu} grouping and sex entered as independent variables, and the difference in each of the individual metabolic burden parameters (Time 2 – Time 1) entered as dependent variable. A significant sex by HF_{nu} grouping interaction emerged for glucose, ($F(2,133) = 3.519$, $p = 0.003$). More specifically, in women, low responders exhibited an increase in glucose over time, whereas high responders showed a decrease. In men, the opposite was observed. A significant sex by HF_{nu} grouping interaction also emerged for waist circumference, ($F(2, 130) = 3.586$, $p = 0.031$). In women, low responders exhibited an increase in waist circumference, whereas high responders showed a decrease. Again, the opposite was observed in men.

Finally, Pearson correlations between the continuous HF_{nu} reactivity change score and various sociodemographic and psychological variables at Time 1 were performed to better characterize individuals with low HF_{nu} reactivity. Blunted HF_{nu} reactivity was associated with significantly higher scores on the Anxiety Sensitivity Index ($r = 0.20$, $p < 0.05$). No other significant associations emerged.

Discussion

The goal of the present research was to examine the prospective relations between physiological responses to stress and metabolic burden, and to verify whether these associations were moderated by sex and/or age. Blood pressure and heart rate responses to stress did not predict future metabolic dysfunction in either men or women. Greater parasympathetic withdrawal during stress, on the other hand, was associated with an increase in metabolic burden in the overall sample, though the overall pattern of results suggests that this was true mostly in men. In women, blunted autonomic responses to stress predicted increased metabolic burden over the three year follow-up period.

Cross-sectional studies have previously reported greater cardiovascular responses during or following exercise (73-75), as well greater catecholamine levels in urine (suggestive of increased sympathetic nervous system activity) (76) in those with metabolic syndrome or a mathematical representation of metabolic syndrome versus healthy controls. However, in cross-sectional investigations, especially those comparing individuals with metabolic dysfunction with healthy controls, it has not been possible to determine whether the heightened physiological responses to exercise represent an outcome of metabolic syndrome, whether it contributed to its pathogenesis, or whether both reflect another underlying process. The fact that heightened parasympathetic reactivity predicted increased metabolic burden three years later in the current study is consistent with the notion that autonomic responses to psychological stress may be implicated in the worsening of metabolic burden over time in otherwise healthy individuals.

Surprisingly, in the current study, it was blunted responsiveness of the parasympathetic system that predicted increased metabolic burden in women. These findings were rather robust and consistent with concurrent analyses at study onset (data not presented in text due to space limitations). In other cross-sectional work, women with metabolic syndrome were recently shown to display reduced LF/HF responsiveness to a resistance training exercise session (77). The reasons for these sex differences in the *relation* between autonomic responses and metabolic dysfunction are unclear. Sex differences in the meaning and experience of life situations may be involved. Indeed, some research suggests that women tend to report higher levels of perceived stress and psychological distress (78), and view life events as being more serious, disruptive, and stressful than men do (79). In the current study, there was limited evidence for this. Women reported slightly more depressive symptoms compared to men, and reported greater affect arousal and negative affect during stress compared to men. A positive association between blunted stress reactivity and higher levels of perceived stress or psychological distress has been reported, particularly in women (78). That sex differences may exist in the regulation of emotions and cardiac autonomic control has some basis in the literature. Indeed, individuals who show blunted BP reactivity to a stressor have been shown to exhibit blunted neural reactions of the limbic system to the same task (80, 81). However, this relation appears to differ in women (positive correlation) compared to men (no or negative associations) (82). It has also been suggested that men and women may differ in their hormonal response to stress (83). That is, the sympathetic nervous system "fight or flight" response may be inhibited in women as a result of their higher levels of oxytocin, favoring more affiliative "tend and befriend" behaviours (83). In the current investigation, however, the pattern of physiological responses to stress suggested sex differences in parasympathetic rather than sympathetic control of the heart, with greater and more prolonged parasympathetic withdrawal in men compared to women. The origin of such differences remains to be elucidated but their significance to the development of metabolic abnormalities is suggested by our results.

In contrast to the stress reactivity hypothesis, which posits that heightened and/or prolonged stress responses increase risk for disease outcomes, there is a small but growing body of literature in support of our findings in women; i.e., that blunted responsiveness of various stress systems, including the ANS, may have adverse health effects (25, 37, 84-89). For instance, reduced HR reactivity has been associated with an increased likelihood of becoming obese over periods of up to seven years (25, 85). Similarly, we recently reported that patients with a blunted parasympathetic response to an autonomic challenge (valsalva maneuver) had higher rates of complications during and after cardiac surgery compared to patients with "normal" autonomic responses (90). It has been hypothesized that blunted reactivity may reflect an overall deteriorating stress response (85) due to chronic exposure to stressful conditions. Phillips et al. (85) suggest that down regulation of beta-adrenergic stress receptors may be involved. However, blunted ANS responsiveness to psychological stress in the current study did not reflect overall low responsiveness of the stress systems in either men or women. Indeed, those with blunted parasympathetic reactivity were as reactive across the cardiovascular and LF-HRV measures as those who showed the expected decreases in parasympathetic activity in response to stress. Nonetheless, and consistent with the idea of chronic stress exposure, participants who showed blunted parasympathetic responses to stress also demonstrated significantly greater tonic or baseline levels of both sympathetic and parasympathetic activity. High tonic levels of parasympathetic activity may reflect the organism's attempt to limit the disruptions created by heightened sympathetic activity, the cost of which may be the inability of the parasympathetic system to adapt further as required by life circumstances. In a prior study in patients undergoing cardiac surgery, predictors of autonomic dysfunction had also included higher baseline parasympathetic activation and greater psychological distress (90). Dampened HR reactivity has similarly been reported in more depressed individuals (91-93), while dampened LF/HF reactivity to passive head-up tilt testing was found in more anxious individuals (94). The latter is consistent with reports of more anxiety sensitivity (fear of fear) in individuals with blunted autonomic responses to stress in the current study.

While there was some limited evidence for moderating effects of age on the associations between stress responses and concurrent metabolic burden at Time 1 (data not presented in text due to space limitations), these were not maintained prospectively. Whether this reflects lack of stability in the impact of age is unknown, though additional research may be warranted.

Certain limitations of the current investigation require consideration. The sample consisted primarily of francophone Caucasians, and results may not be generalizable to other cultural groups. Racial differences, particularly between African-Americans and Caucasians, have been reported with regard to cardiovascular reactivity to stress (95), and prevalence of metabolic syndrome (96). There were a few notable differences in the characteristics of those who returned for follow-up versus those who did not, which may also affect the generalizability of our results. For instance, our results may be less applicable to those who are heavier smokers. In addition, while the use of a healthy sample enabled us to examine the impact of stress responses on metabolic burden progression, unencumbered by other known disease processes, it may also have dampened our ability to observe significant associations. This may explain why cardiovascular measures did not emerge as significant predictors of metabolic burden. Relatedly, both the men and women in our sample had rather low BP values and tended more towards overweight. Given the substantial literature showing increased hypertension risk with greater cardiovascular reactivity, and the smaller literature suggesting greater obesity with blunted stress reactivity, our sample characteristics may have biased our results towards increased metabolic burden with blunted ANS responsiveness. Post-hoc analyses did indeed suggest that changes in waist circumference (and glucose) might be driving the metabolic burden findings in the current study.

Some have criticized the integrity of the metabolic syndrome construct, suggesting that it is the specific individual parameters that account for the increased risk of negative cardiovascular outcomes, rather than the syndrome itself (97-100). The use of metabolic burden rather than the individual parameters could in that viewpoint be construed a limitation. However, recent large-scale studies have supported that the metabolic syndrome construct is a genuine predictor of adverse cardiovascular outcomes, independently of its individual parameters (39-43). For example, in a 16 year longitudinal study (n = 2805), Simons, Simons, Friedlander and McCallum (41) showed that metabolic syndrome predicted negative cardiovascular outcomes and all-cause mortality, regardless of which individual components showed elevations. The use of metabolic burden as a proxy for metabolic syndrome in the main analyses may also be considered a limitation. However, we have shown that the two constructs are highly overlapping, and post-hoc analyses with metabolic syndrome as outcome variable produced results that were highly consistent with those obtained with metabolic burden.

Finally, it is noteworthy that significant group differences emerged on the HF_{nu} and LF/HF, but not the HF-HRV variable. Reyes del Paso, Langewitz, Mulder, van Roon and Duschek (59) recently reported concern regarding the interpretation of LF/HF, and showed that normalizing HRV indices may lead to artificially inflated correlations with variables. Replication of this study is therefore needed.

Nonetheless, the current study possesses several strengths that increase the confidence that can be had in the results obtained. This is the first investigation to examine the relation between stress responses and a global representation of metabolic syndrome. The design was prospective, and employed a rigorous methodology. Recruitment was performed such as to ensure a heterogeneous sample of healthy individuals (with respect to sex, age, sociodemographic, and work characteristics). Multiple stressors with an interpersonal component were chosen to be of relevance to women as well as men, and were aggregated to increase reliability and validity, compared to single tasks or purely physical or cognitive tasks. The blood pressure component of the metabolic burden construct was obtained from 24-hour ambulatory monitoring, which has been shown to be more predictive of cardiovascular outcomes compared to clinic or laboratory measures (54, 55). Autonomic measures of reactivity and recovery to psychological stress had been ignored to date in this literature. Yet, in the current study, these measures were of particular importance to the prediction of metabolic burden. The examination of sex differences was both novel and fortuitous, as results were significantly moderated by sex. Finally, analyses controlled for relevant characteristics of participants.

In conclusion, this study contributes to the small but growing body of evidence suggesting that both heightened *and* blunted stress responses may be detrimental for health. More specifically, blunted parasympathetic responses increased metabolic burden in women, while in men, greater and more prolonged parasympathetic responses to stress increased risk. While the reasons for these sex differences are unclear, they highlight the need to consider sex differences in such research. Future investigations may benefit from including more than one follow-up period to verify whether there are differences in the early versus later effects of stress responses on metabolic burden. Although stress management has been shown to be effective in reducing clinically significant metabolic abnormalities (101-103), their utility in preventing metabolic syndrome in healthy individuals is unknown. Moreover, these strategies have typically focused on reducing exaggerated physiological reactivity to stress (104-106). Our results suggest that developing interventions that also target *blunted* physiological responses to stress may be of importance.

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Table 1

Metabolic profile of participants and sex-specific cutoffs used to create the metabolic burden construct

	Metabolic Profile				**Sex-specific cutoffs for metabolic burden**			
	Time 1 - Mean (SD)		Time 2 - Mean (SD)		Time 1		Time 2	
	Men (n =78)	Women (n = 115)	Men (n = 55)	Women (n=81)	Men	Women	Men	Women
24-hour SBP (mm Hg)	116.4 (10.04)	106.9 (12.85)	116.9 (9.69)	108.0 (13.53)	123.0	115.0	120.0	117.0
24-hour DBP (mm Hg)	72.8 (8.22)	67.8 (9.26)	73.3 (8.50)	68.4 (9.68)	75.0	72.0	74.0	74.0
Glucose (mmol/L)	5.3 (0.50)	5.2 (0.51)	5.3 (0.47)	5.2 (0.53)	5.6	5.4	5.5	5.4
HDL (mmol/L)	1.2 (0.33)	1.5 (0.35)	1.2 (0.35)	1.5 (0.33)	1.0	1.2	1.0	1.2
Triglycerides (mmol/L)	1.4 (0.92)	0.9 (0.65)	1.4 (0.98)	0.9 (0.44)	1.7	1.2	1.7	1.2
WC (cm)	90.3 (11.64)	84.3 (13.01)	91.0 (11.50)	84.6 (12.75)	97.0	93.0	96.3	92.0
Metabolic burden (sum score)	1.39 (1.35)	1.44 (1.32)	1.42 (1.53)	1.37 (1.36)	-	-	-	-

Note . WC = waist circumference, SBP = systolic blood pressure, DBP = diastolic blood pressure, HDL = high density lipoprotein cholesterol.

Metabolic burden is the number of metabolic syndrome parameters for which participants were in the 75th percentile (25th percentile for HDL cholesterol) for their sex. Significant sex differences emerged for each metabolic burden parameter (except for glucose) at Time 1 and Time 2, all p's < 0.001.

There was no significant sex difference for metabolic burden sum scores.

Table 2

Participant characteristics (Mean ± SD) at initial recruitment (Time 1)

	Men (n = 78)	**Women** (n =115)
Age (years) *	39.1 (11.23)	42.8 (11.46)
Body Mass Index (kg/m^2)	24.9 (4.11)	25.3 (5.61)
Years of schooling	15.9 (3.39)	16.0 (3.43)
Marital Status *n* (%)		
Single	37 (47.4)	49 (42.6)
Married/living with someone	33 (42.3)	45 (39.2)
Separated/divorced/widowed	8 (10.3)	21 (18.3)
Annual family income *n* (%)		
≤ $29,999	26 (33%)	39 (34%)
$30 000-59 999	25 (32%)	47 (41%)
≥ $60 000	27 (35%)	29 (25%)
Smoker *n* (%)	13 (17%)	28 (24%)
Cups of coffee or tea/week*	11.6 (11.41)	15.0 (11.98)
Glasses of alcohol/week***	5.1 (6.10)	2.7 (4.18)
Hours of exercise/week***	4.7 (5.26)	2.6 (3.20)
Beck Depression Inventory-II Score*	7.2 (7.13)	9.4 (7.40)
Beck Anxiety Inventory Score	4.9 (6.07)	6.6 (6.48)
Anxiety Sensitivity Index Score	16.7 (10.61)	18.1 (10.31)
Baseline Cardiovascular & Autonomic Measures		
SBP (mm Hg) ***	114.4 (9.60)	106.5 (12.84)
DBP (mm Hg) **	71.7 (7.13)	67.6 (9.23)
HR (bpm)	64.0 (9.13)	66.2 (8.30)
HF-HRV (ms^2)	405.2 (824.2)	568.4 (950.0)
LF-HRV (ms^2)	612.5 (864.1)	537.5 (734.4)
LF/HF **	2.3 (2.18)	1.6 (1.54)
HF_{nu}	17.3 (19.39)	22.5 (26.60)
Medications (*Time 2*), n (%)		
Psychotropic Medication	2 (1%)	5 (4%)
Cardiovascular agents	1 (0.7%)	2 (1%)
Dyslipidemics	2 (1%)	0
Aspirin	0	1 (0.7%)

Note . *p< 0.05; **p< 0.01; ***p< 0.001; SBP = systolic blood pressure, DBP = diastolic blood pressure, HDL = high-density lipoprotein cholesterol, HR = heart rate, HF-HRV = high frequency heart rate variability, LF-HRV = low frequency heart rate variability, HF_{nu} = high frequency heart rate variability in normalized units. Both HF-HRV and LF-HRV were log transformed to increase normality. Medications refer to those taken by participants at follow-up. Psychotrophics included: selective serotonin reuptake inhibitors, benzodiazepines, atypical antipsychotics, and other antidepressants. Cardiovascular agents included: Angiotension II receptors antagonists, diuretic thiazide, and calcium channel blocking agents.

Table 3

Sex differences in reactivity and recovery change scores

	Reactivity			Recovery		
	Mean (SD)			Mean (SD)		
	men	women	*p*	men	women	*p*
SBP	11.5 (5.89)	12.3 (9.02)	0.57	3.2 (4.80)	3.8 (6.83)	0.52
DBP	10.2 (6.09)	7.6 (5.80)	0.01	2.8 (3.87)	1.8 (4.11)	0.15
HR	5.5 (4.25)	5.7 (4.73)	0.83	2.3 (2.70)	2.1 (2.94)	0.71
HF(log)	31.2 (7.21)	28.6 (6.58)	0.03	1.2 (0.01)	1.2 (0.03)	<0.001
LF/HF	1.7 (1.91)	1.2 (1.92)	0.15	1.7 (1.88)	1.1 (1.88)	0.09
HF_{nu}	-15.1 (16.22)	-17.9 (17.8)	0.35	-13.6 (17.78)	-15.3 (15.06)	0.52

Note . SBP = systolic blood pressure (mm Hg), DBP = diastolic blood pressure (mm Hg), HR = heart rate (beats per minute), HF = high frequency heart rate variability (ms^2) in log units, HF_{nu}= high frequency in normalized units, LF/HF = sympathovagal balance.

Table 4

Partial correlations between residualized reactivity and recovery change scores and metabolic burden obtained at Time 2

	Metabolic Burden Time 2
Reactivity Change Scores	
SBP	-0.008
DBP	-0.069
HR	-0.092
HF-HRV	**-0.170***
HF_{nu}	-0.079
LF/HF	0.027
Recovery Change Scores	
SBP	0.112
DBP	0.130
HR	0.154
HF-HRV	-0.025
HF_{nu}	-0.048
LF/HF	0.106

Note .Partial correlation analysis controls for Metabolic Burden at Time 1.
*$p < 0.05$. SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, HF-HRV = high frequency heart rate variability, HF_{nu}= high frequency in normalized units, LF/HF = sympathovagal balance.

Table 5

Summary of significant results

Block 1	β	t	*p*
Age	-0.019	-0.246	0.806
Sex	-0.026	-0.366	0.715
Marital status	0.110	1.485	0.140
Metabolic Burden at Time 1	0.573	7.697	0.000
F_{model} (4, 131) = 17.930, $p < 0.001$			
$R^2_{model} = 0.354$, $R^2_{adj} = 0.334$			
HF_{Log} Reactivity			
Block 2	β	t	*p*
HF_{Log}	-0.145	-2.002	0.047
F_{model} (1, 120) = 4.009, $p = 0.047$			
$R^2_{model} = 0.373$, $R^2_{adj} = 0.349$			
HF_{nu} Reactivity			
Block 2	β	t	*p*
HF_{nu}	0.035	0.484	0.629
F_{model} (1, 130) = 0.234, $p = 0.629$			
$R^2_{model} = 0.355$, $R^2_{adj} = 0.330$			
Block 3	β	t	*p*
HF_{nu} *Sex	0.159	2.224	0.028
F_{model} (1, 129) = 4.945, $p = 0.028$			
$R^2_{model} = 0.379$, $R^2_{adj} = 0.350$			
LF/HF Reactivity			
Block 2	β	t	*p*
LF/HF	-0.065	-0.872	0.385
F_{model} (1, 130) = 0.760, $p = 0.385$			
$R^2_{model} = 0.358$, $R^2_{adj} = 0.333$			
Block 3	β	t	*p*
LF/HF *Sex	-0.153	-2.085	0.039
F_{model} (1, 129) = 4.348, $p = 0.039$			
$R^2_{model} = 0.378$, $R^2_{adj} = 0.350$			
HFnu Recovery			
Block 2	β	t	*p*
HFnu	0.105	1.444	0.151
F_{model} (1, 130) = 2.084, $p = 0.151$			
$R^2_{model} = 0.364$, $R^2_{adj} = 0.340$			
Block 3	β	t	*p*

HF_{nu} *Sex	0.169	2.378	0.019
F_{model} (1, 129) = 5.653, p = 0.019			
R^2_{model} = 0.391, R^2_{adj} = 0.362			
LF/HF Recovery			
Block 2	β	t	p
LF/HF	-0.040	-0.527	0.599
F_{model} (1, 130) = 0.278, p = 0.599			
R^2_{model} = 0.355, R^2_{adj} = 0.330			
Block 3	β	t	p
LF/HF *Sex	-0.170	-2.263	0.025
F_{model} (1, 129) = 5.121, p = 0.025			
R^2_{model} = 0.380, R^2_{adj} = 0.351			

Note . HF-HRV = high frequency heart rate variability, HF_{nu}= high frequency heart rate variability in normalized units, LF/HF = sympathovagal balance. Reactivity = Stress – Baseline; Recovery = Recovery - Baseline

Figure Legend

Figure 1a. The prospective association between metabolic burden and HF_{nu} reactivity is moderated by sex. In women, there is a trend for low HF_{nu} reactivity to be associated with increased metabolic burden. An opposite association was observed in men.

Figure 1b. The prospective association between metabolic burden and HF_{nu} recovery is moderated by sex. ***$p < 0.001$. In women, faster HF_{nu} recovery was associated with increased metabolic burden. An opposite association was observed in men.

Figure 2a. The prospective association between metabolic burden and LF/HF reactivity is moderated by sex. *$p < 0.05$. In women, blunted LF/HF reactivity was associated with increased metabolic burden. An opposite association was observed in men.

Figure 2b. The prospective association between metabolic burden and LF/HF recovery is moderated by sex. Faster LF/HF recovery was associated with increased metabolic burden in women. An opposite association was observed in men.

Figure 3a. HF-HRV across Laboratory Period as a Function of HF_{nu} Stress Response Category.**$p < 0.01$, ***$p < 0.001$, referring to Period main effects. The low HF_{nu} responder group showed a slight significant increase in response to the stressor, whereas the medium and high responder groups showed significant decreases in response to stress.

Figure 3b. LF-HRV across Laboratory Period as a Function of Stress Response Category.***$p < 0.001$, referring to Period main effects. All groups showed a significant increase in response to stress.

Figure 3c. LF/HF Ratio across Laboratory Period as a Function of Stress Response Category**.** ***$p < 0.001$, referring to Period main effects. The high and medium responders exhibited significant increases in LF/HF in response to stress, whereas the low responder group showed no change in LF/HF across the protocol.

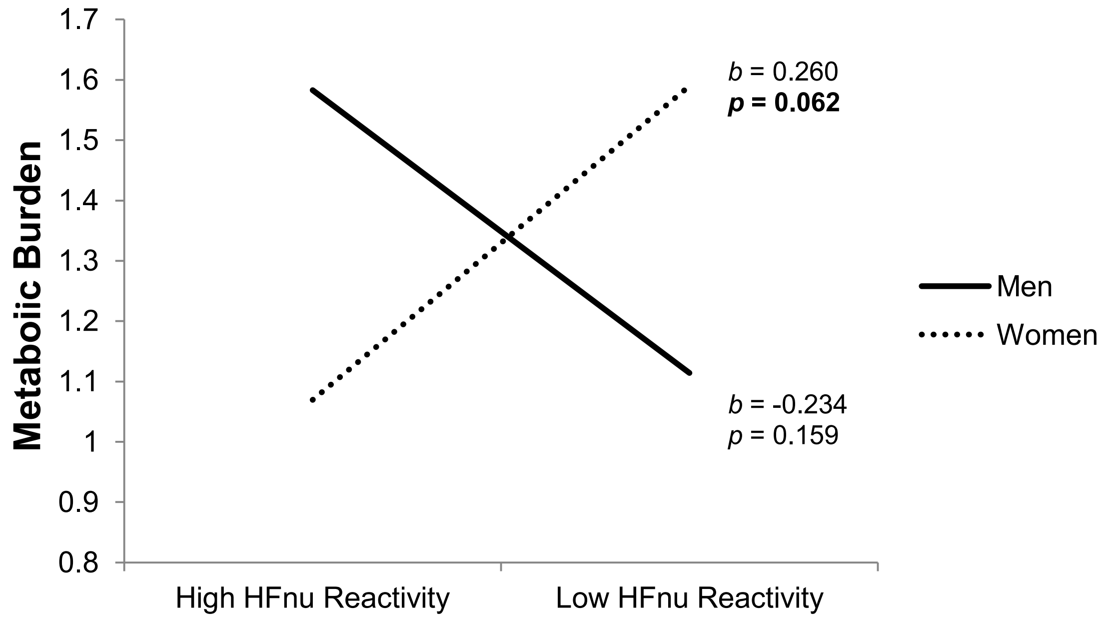

*Figure 1a.*The prospective association between metabolic burden and HF_{nu} reactivity is moderated by sex. In women, there was a trend for low HF_{nu} reactivity to be associated with increased metabolic burden. An opposite association was observed in men.

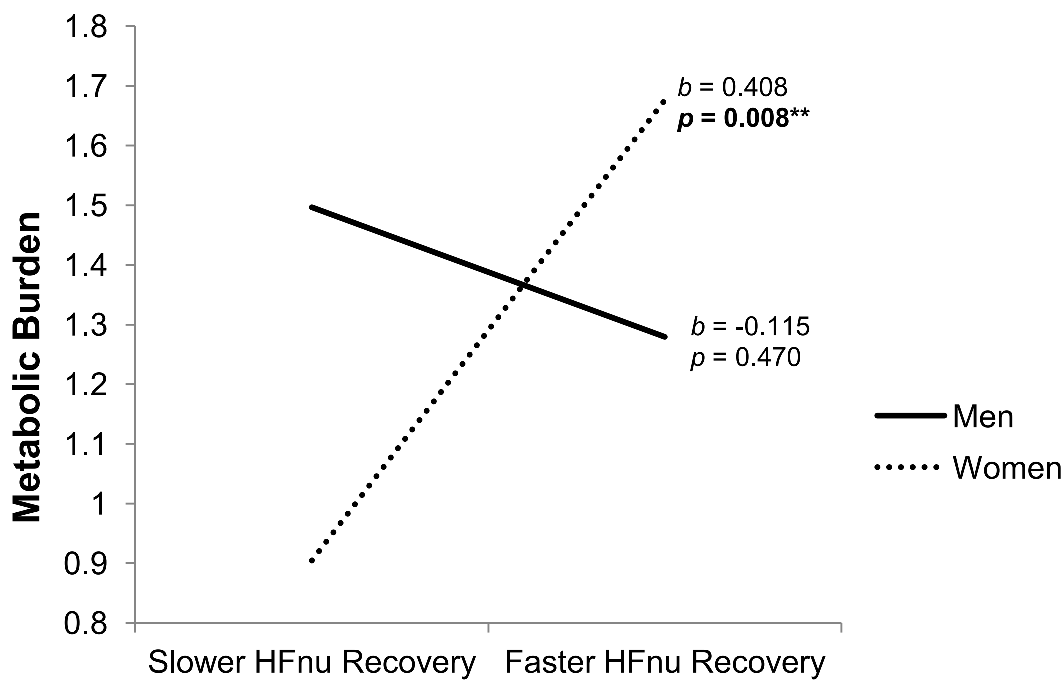

*Figure 1b.*The prospective association between metabolic burden and HF_{nu} recovery is moderated by sex ***p < 0.001. In women, faster HF_{nu} recovery was associated with increased metabolic burden. An opposite association was observed in men.

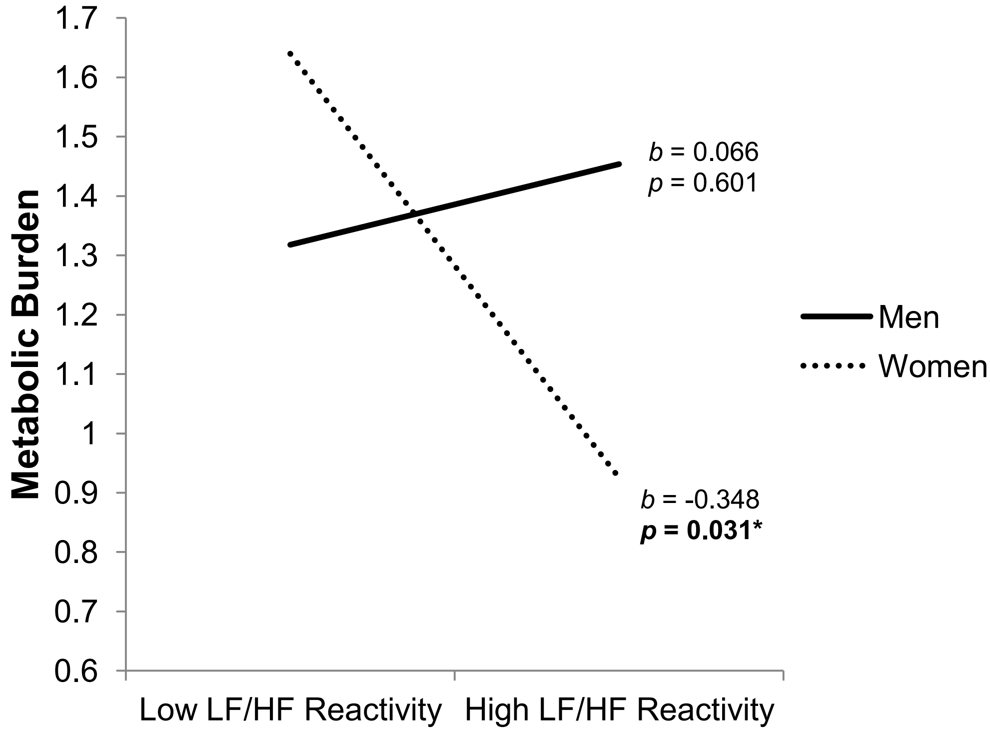

*Figure 2a.*The prospective association between metabolic burden and LF/HF reactivity is moderated by sex *$p < 0.05$. In women, blunted LF/HF reactivity was associated with increased metabolic burden. An opposite association was observed in men.

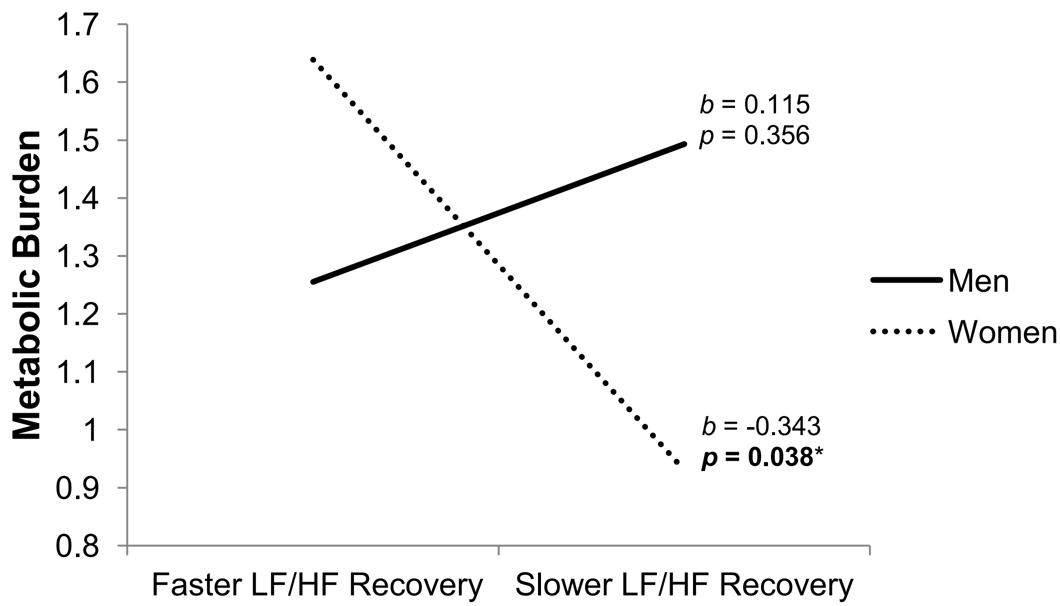

*Figure 2b.*The prospective association between metabolic burden and LF/HF recovery is moderated by sex. Faster LF/HF recovery was associated with increased metabolic burden in women. An opposite association was observed in men.

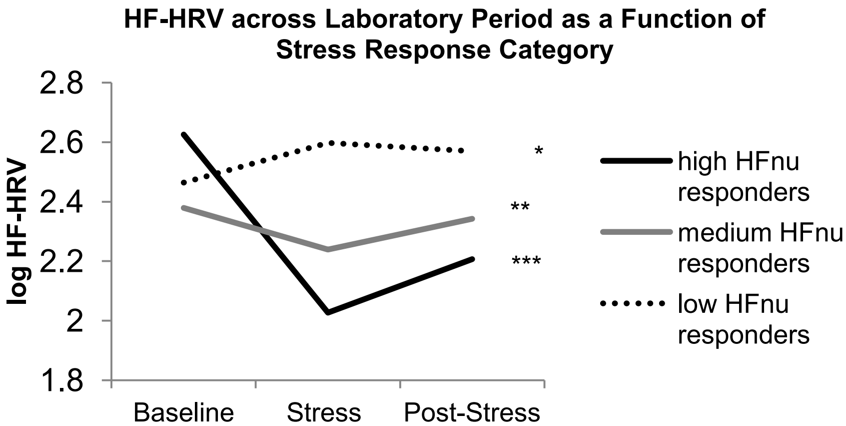

Figure 3a. HF-HRV across Laboratory Period as a Function of Stress Response Category.**$p < 0.01$, ***$p < 0.001$, referring to Period main effects. The low HF_{nu} responder group showed a slight significant increase in response to stress, whereas the medium and high responder groups showed significant decreases in response to stress.

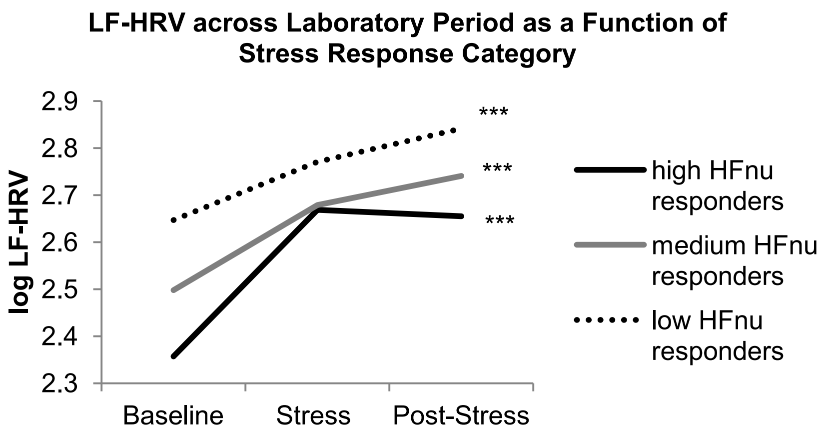

Figure 3b. LF-HRV across Laboratory Period as a Function of Stress Response Category**.*****$p < 0.001$, referring to Period main effects. All groups showed a significant increase in response to stress. In addition, the low responder group showed significantly higher values of LF-HRV across all periods.

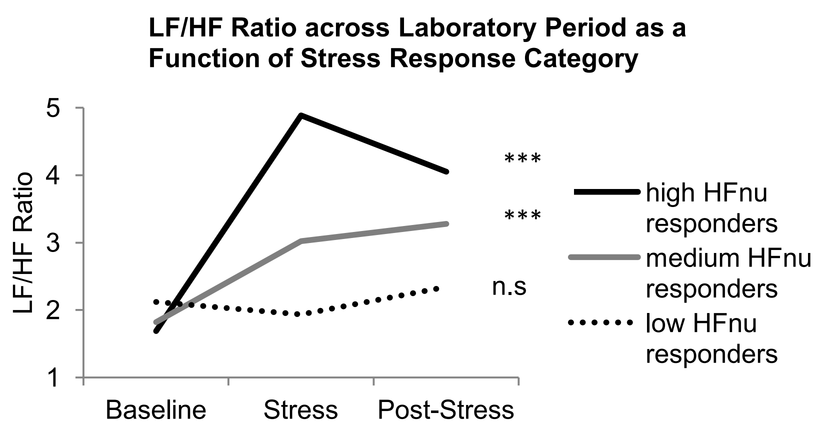

Figure 3c. LF/HF Ratio across Laboratory Period as a Function of Stress Response Category**.** ***$p < 0.001$, referring to Period main effects. The high and medium responders exhibited significant increases in LF/HF in response to stress, whereas the low responder groups.

Preface: Article 2

In Study 1, exaggerated autonomic responses to stress led to increased metabolic burden at follow-up among men, as expected. In contrast, blunted autonomic responses predicted future metabolic burden in women. The latter result was surprising but in line with emerging research associating blunted reactivity with negative metabolic endpoints (for more information, see Introduction, pages 15-16). This inspired the objectives and hypotheses for the second article of this thesis.

Given that blunted stress reactivity was a newer topic in the literature and that very few investigations included autonomic indices of stress responses, it appeared important to conduct an additional study in order to verify whether results were generalizable to a larger, older, more health-compromised sample of individuals. Furthermore, whether results would generalize using the clinically accepted definition of metabolic syndrome was unknown. In our previous study of healthy adults, few individuals met criteria of metabolic syndrome which is why a proxy (i.e. metabolic burden) was used. The second study with 1121 participants enabled us to use presence of metabolic syndrome as the major outcome variable and provided us with sufficient power to control for a variety of medical, behavioral, and socio-demographic covariates. Results of Study 1 also informed our hypotheses for Study 2: we expected that heightened and blunted parasympathetic stress responses would be associated with presence of metabolic syndrome and that this association would be moderated by sex.

In addition, this second study included the novel addition of clusters to characterize stress responses rather than examining reactivity and recovery change scores separately. As was reported in Study 1, those who exhibited “greater autonomic recovery” were more likely to show an increased metabolic risk over a period of three years. This was surprising given previous literature consistently indicating that greater recovery was an adaptive response to stress. Post-hoc analyses examining the pattern of both reactivity and recovery confirmed that “greater recovery” (or mean recovery scores approaching zero) was actually reflective of blunted autonomic reactivity. Thus, our initial recovery findings were grossly misleading in the absence of their associated reactivity data. We thus conducted the current study using stress response clusters, which encompassed both reactivity and recovery within one score. In addition, use of clusters was more parsimonious and allowed us to accommodate the possibility that relationships between stress responses and metabolic syndrome may not be linear. Indeed, our previous study illustrated that responses on the other end of the reactivity spectrum (i.e. blunted responses) are adverse for metabolic health.

ARTICLE 2

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Parasympathetic Response Patterns are Associated with Metabolic Syndrome among Older Women but Not Men

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Parasympathetic Response Patterns are Associated with Metabolic Syndrome Among Older Women but Not Men

Background: Little is known about the role of physiological stress responses in metabolic syndrome (MetS).

Purpose: To examine whether patterns of autonomic response to psychological stress are associated with MetS and whether this association is moderated by sex.

Methods: 1121 men and women (M_{age}=65.3± 6.77 years) with and without coronary artery disease (CAD) underwent an anger recall stressor task. Heart rate and heart rate variability (HRV; HF, LF/HF) were assessed. Clusters of participants showing similar patterns of response across baseline, stress, and recovery periods were created using ACECLUS and FASTCLUS in SAS. Logistic regressions included clusters and interaction between clusters and sex as independent variables, controlling for relevant covariates.

Results: Men and women showing greater tonic and phasic HR elevations were more likely to meet MetS criteria (OR = 1.45, [95% CI =1.02-2.07], p =0.037). HF-HRV cluster interacted significantly with sex (p<0.001) to predict MetS. In women, those with exaggerated parasympathetic withdrawal to stress and poor recovery were more likely to have MetS than women with a more moderate response (OR = 2.56, [95% CI =1.23-5.41], p =0.013). Women who displayed stress-related parasympathetic activation were also at greater risk of MetS (OR = 2.30, [95% CI =1.30-4.07], p = 0.004).

Conclusion: Among older participants with CAD or other non-cardiovascular disease, hyper-reactivity to stress was associated with greater prevalence of MetS, particularly in women. Consistent with emerging literature, women who showed blunting or activation of parasympathetic responses to stress were similarly more likely to have MetS.

Keywords: sex differences, metabolic syndrome, stress, autonomic, heart rate variability

MetS = metabolic syndrome

CAD = coronary artery disease

HF-HRV = high-frequency heart rate variability

LF/HF = ratio of low-frequency HRV to high-frequency HRV

Metabolic syndrome increases risk of atherosclerosis and mortality from cardiovascular disease (CVD) by approximately two-fold (1-4). The lifetime prevalence in Canadians is approximately 20 percent, although this increases to 40 percent in adults over 60 years of age (5). It is diagnosed when at least three of the following factors are present: elevated blood pressure, triglycerides, or fasting blood glucose, central adiposity, and low levels of high-density lipoprotein (HDL) cholesterol (1, 6). Metabolic syndrome predicts adverse cardiovascular outcomes over and above its individual components (7-9).

Psychological stress may increase risk of metabolic syndrome or its individual parameters through activation of heightened or prolonged physiological responses (10-13). A meta-analysis of 41 independent studies found hypertension to be consistently predicted by increased cardiovascular reactivity to and poorer recovery from stress, especially in men (14). The association of stress responses with other individual parameters of the metabolic syndrome has received less attention. For instance, while elevated total cholesterol and/or triglyceride levels have been associated with heightened cardiovascular reactivity to laboratory stressors (15-19), null and negative correlations between measures of cardiovascular reactivity and these parameters have also been reported (20-22). The one study examining fasting blood glucose reported that African-American students with higher glucose levels recovered more rapidly from a racially noxious stressor (DVD on African slavery) than their counterparts (23). In contrast to research on hypertension, *reduced* systolic blood pressure (SBP) and heart rate (HR) reactivity to stress have recently been associated with increased central obesity (24-26), although inconsistent results have also emerged (27-30).

Very few investigations have examined whether stress responses are associated with disturbances across combinations of metabolic syndrome parameters simultaneously (30-32). In a cross-sectional study of 144 adolescents, Countryman and colleagues (30) found that diastolic blood pressure (DBP) reactivity to a mirror tracing task was positively associated with the total number of metabolic syndrome criteria. Our laboratory examined concurrent and prospective associations between BP, HR, and autonomic responses to psychological stressors (assessed by high frequency heart rate variability, HF-HRV; and the ratio of low to high frequency heart rate variability (LF/HF)) and metabolic burden in a sample of 193 healthy adults aged 18 to 64 (28). Metabolic burden referred to the number of metabolic parameters for which participants were in the highest quartile (lowest for HDL cholesterol) for their sex. While BP and HR reactivity and/or recovery were not associated with metabolic burden, men with exaggerated stress-related decreases in HF-HRV displayed an increase in metabolic burden over time. However, the opposite response was observed in women. Women who had either increases or unusually small, blunted responses in HF-HRV displayed increased risk of metabolic burden. Recently, Hu and colleagues (32) also examined the concurrent and prospective relations between autonomic stress reactivity and components of metabolic syndrome in adults. While waist circumference and HDL cholesterol were negatively associated with HR reactivity to a cognitive task, results were generally in line with what was observed in our previous study in men; greater decreases in HF-HRV were associated with an increased number of metabolic syndrome components (32). This was particularly true in women, though the sex difference was not significant. These are the only two studies to our knowledge that specifically investigated the contribution of autonomic stress responses to metabolic syndrome risk, despite the autonomic nervous system's crucial role in metabolic processes (33-40).

The current investigation sought to confirm and extend research on the association between variable autonomic stress responses and metabolic syndrome. As an extension to our prior study among healthy adults (31), the current study aimed to examine whether the sex differences observed in the relations between autonomic stress responses and metabolic abnormalities generalize to an older sample of individuals whose health is more compromised as a result of coronary artery disease (CAD) or other health issues, in whom metabolic syndrome may further contribute to morbidity or mortality risk. Cluster analysis was utilized in order to empirically characterize stress response patterns and to capture how individuals react and recover from a stressor within a single measure. Given prior evidence, we expected that heightened and blunted (i.e. non-normative) parasympathetic stress responses would be associated with presence of metabolic syndrome, and that this association would differ according to sex.

Methods

This study is part of an ongoing project (BEL-AGE) that seeks to examine the role of psychological burden on pathological aging.

Participants. 1121 men and women with CAD or without CVD were recruited from the pool of individuals participating in the André and France Desmarais Hospital Cohort of the Montreal Heart Institute (MHI). The MHI cohort will recruit and follow 30 000 individuals with the goal of determining genetic and other markers of cardiovascular outcomes. CAD at the time of enrollment into BEL-AGE was documented by presence of coronary angiography (at least 50% stenosis) or prior myocardial infarct, coronary artery bypass grafting, or percutaneous coronary intervention. Absence of CVD was defined as no current or past history of coronary artery disease, angina, arrhythmia, congenital heart disease, heart failure, cardiomyopathy and stroke. Individuals were excluded from the study if they: (a) were diagnosed with bipolar disorder, schizophrenia, Alzheimer's disease, or irreversible dementia, as these may have influenced their ability to understand and engage in the protocol/questionnaires; (b) were diagnosed with a life-threatening degenerative disease such as cancer (except skin cancer), AIDS, Creutzfeldt-Jakob disease, and amyotrophic lateral sclerosis, (c) were pregnant or breastfeeding, or (d) if a family member (including spouses) participated in the study or was scheduled to participate. Medical history was obtained through self-report and corroborated by consultation of participants' medical file. Twenty-five participants were excluded from analyses because they did not meet eligibility criteria at the time of testing. Three additional participants did not complete the protocol as they found it too demanding, yielding a final sample of 1093 individuals.

Procedure

Participants were scheduled for a laboratory appointment between 8:00 a.m. and 10:00 am on a weekday to control for circadian rhythms. They were asked to abstain from eating, drinking (with the exception of water), smoking, and strenuous exercise for 12 hours prior to testing. They were also asked to refrain from using illicit drugs or alcohol 24 hours preceding their appointment, but could continue taking medications as prescribed. Testing was rescheduled if participants did not adhere to these instructions. Once participants provided written consent, a blood sample and anthropomorphic data (weight, height, and waist circumference) were obtained. A structured interview was then conducted to obtain additional demographic and medical information. The electrodes for electrocardiographic (ECG) monitoring were then attached in a bipolar configuration to the lower side of the participant's rib cage and a ground electrode was placed under the clavicle on the right side. A Finopres Finometer was placed on the participant's middle finger of the non-dominant hand in order to continuously measure BP. A brief stress protocol ensued, consisting of a 5 minute baseline period, a 2 minute preparation phase, a 5 minute anger recall task, and a 5 minute recovery period. Participants then completed several other questionnaires relating to psychological traits and states, as well as health behaviors. Participants were only compensated for travel/parking costs. This study was approved by the Research and Ethics Board of the Montreal Heart Institute.

Laboratory Task

Anger Recall: Participants were asked to recall and recount an event in which they experienced anger and which still made them angry when they thought about it. They were encouraged to remember the situation as accurately as possible and to relive their emotions. Participants were given 2 minutes to choose and think about the event and then were asked to speak about it for 5 minutes with a research assistant trained to maintain a neutral tone. This task has been widely-used to elicit psychological and physiological stress responses (41-44).

Measures

Sociodemographic variables: Data on sex, age, ethnicity, weight, height, marital status, income, and years of schooling were obtained.

Behavioral variables: Information regarding smoking habits and hours spent exercising per week was collected.

Medical Variables included information on personal and family medical history as well as a current list of medications taken by the participant.

Physiological responses during the stress protocol: The ECG was recorded using PowerLab and HRV was analyzed offline in LabChart (ADInstruments, Oxford, UK). HRV parameters of interest included high frequency (HF; 0.15–0.40 Hz) and low frequency components (LF; 0.04– 0.15 Hz) as recommended by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (45). HF-HRV reflects parasympathetic control of the heart. LF/HF ratio was used as a measure of sympathovagal balance (46). Traditionally, it is expected that as stress increases acutely (as per a stress protocol), parasympathetic control of the heart is dampened (denoted by HF decrease), while sympathetic control of heart dominates (denoted by LF/HF increase). HF-HRV was assessed in both absolute and normalized units (nu). The latter is a relative measure that accounts for changes in total spectral power (45), such as may occur during a stress protocol.

Metabolic Syndrome (MetS): was defined as per the National Cholesterol Education Program, ATP III (1). Plasma samples were analyzed for lipids and glucose at the Montreal Heart Institute. These determinations were made using respective reagent Flex on the multianalyzer Dimension RxL Max (Dade Behring Diagnostics, Marburg, Germany) with heparinized plasma. The samples were frozen (-80°C) and then assayed in batch. Waist circumference was measured using a standard measuring tape. BP was obtained during the baseline period of the stress protocol, and was assessed using a noninvasive instrument fastened to the participant's wrist as well as a sensor wrapped around the index finger of the non-dominant hand (Finapress Finometer, Amsterdam, the Netherlands).

Affect and Arousal was assessed during the baseline, stress, and recovery phases of the protocol using the Self-Assessment Manikin (SAM) (47).

Psychological Variables: The Perceived Stress Questionnaire (PSQ) (48), The Center of Epidemiological Studies Depression Scale (CES-D) (49), and The State-Trait Anxiety Inventory (STAI) (50) were administered during the protocol for purposes not covered in the current manuscript.

Data Analysis

Data Reduction

Mean values of HR, HF-HRV, LF/HF, and HF_{nu} were obtained for the baseline, stress, and recovery periods. Given that the metabolic syndrome categorization relied partly on systolic and diastolic blood pressure obtained at baseline, BP response patterns were excluded from analyses.

Preliminary analyses

Covariates were selected based on prior research indicating an association with metabolic syndrome and the results of bivariate correlations between metabolic syndrome and other variables in the dataset. Specifically, those variables that were significantly associated with metabolic syndrome ($p < 0.05$) were retained for analyses.

Rather than using individual stress reactivity and recovery change scores, response patterns (as determined using cluster analyses) across the stress protocol (baseline, stress, and post-stress periods) were chosen. This approach was selected to 1) accommodate the possibility that relationships between reactivity and metabolic syndrome may not be linear, for example, that both exaggerated and blunted reactivity are related to metabolic syndrome, and 2) empirically determine overall patterns of response in order to capture how individuals react and then recover from the stress protocol. Our previous work (31) illustrated that examining autonomic reactivity or recovery change scores separately may be misleading; for example, a recovery change score approaching zero, typically interpreted as "better recovery", may actually reflect a lack of response to stress. Blunted stress responses have been increasingly documented as maladaptive (24-26, 51, 52). In addition, examining the pattern of response across the protocol had the added advantage of increased parsimony by halving the number of statistical tests performed.

The SAS procedures ACECLUS and FASTCLUS were used to distinguish clusters of participants showing similar patterns of activation across baseline, stress, and post-stress periods. The "best" number of clusters was identified by comparing the pseudo F statistic, approximate expected overall R square, and cubic clustering criterion (CCC), and by running PROC FASTCLUS with different values for the MAXCLUSTERS=option. Only the clusters that were significantly associated with metabolic syndrome in the main analyses will be described. The final solution for HR yielded two groups of participants depicted in Figure 1 on page 112. Cluster 1 participants displayed lower HR at baseline, moderate stress-related increases in HR, with full recovery. Cluster 2 participants exhibited higher HR at baseline, a larger stress-related increase in HR, and less recovery. The final solution for HF-HRV yielded three groups of participants depicted in Figure 2 on page 113. Cluster 1 participants displayed presumably "adaptive" responses to the stress protocol characterized by moderate activity at baseline, followed by moderate stress-related decreases in HF-HRV and full recovery. Cluster 2 participants displayed similar activation at baseline, but demonstrated an unusual response involving an increase in HF-HRV across the rest of the stress protocol. Finally, Cluster 3 participants were characterized by higher baseline values, followed by large stress-related decreases in HF-HRV and incomplete recovery.

Presence of CAD, sex, and age were examined as potential moderators in preliminary analyses. Only sex was retained for further analyses as presence of CAD or age did not emerge as significant moderators. While it is well-documented that basal HRV is frequently altered in individuals with CAD (53) versus healthy counterparts, in the current sample, no significant differences were found in cluster membership between those patients with and without CAD. Performing analyses in the combined group of patients was thus deemed appropriate.

Main Analyses

To examine associations between response to the stress protocol and metabolic syndrome, multiple logistic regressions were performed using presence of the metabolic syndrome (yes, no) as the dependent variable, and cluster, sex, and the interaction between cluster and sex as independent variables. The analyses included the following covariates: age, household income, years of schooling, hours of exercise per week, presence of CAD, BMI, presence of comorbid medical conditions, medications influencing metabolic syndrome parameters, other medications, and presence of sex hormone therapy as covariates. For all tests, $p < 0.05$ was considered significant. Statistical analyses were performed by a biostatistician using SAS 9.4 (SAS Institute Inc., Cary, NC).

Results

Descriptive Statistics. Nearly 56 percent of the sample met the NCEP ATP III criteria for metabolic syndrome, while approximately 54 percent had CAD. Seventy percent of those without CVD suffered from at least one medical condition. Men, who constituted 62 percent of the sample, were more likely to have CAD and metabolic syndrome than women, were more likely to be smokers, had a higher average BMI, and had significantly higher BP, HR, and HF-HRV at baseline.   Men also had higher incomes, completed more years of schooling, and were more likely to be married or living with someone. For full participant characteristics, see Table 1 on page 106.

Validation that the protocol was stressful. The anger recall task yielded significant increases (decreases for HF and HF_{nu}) in all parameters across the stress protocol: HR ($F(1, 1033)=1486.63$, $p < 0.001$); HF ($F(1, 1034)=4.66$, $p < 0.05$) ; LF/HF ($F(1,1034)=63.05$, $p < 0.001$); and HF_{nu} ($F(1, 1040)=223.42$, $p < 0.001$). It also resulted in significant decreases in positive affect ($F(2, 2180) = 1354.66$, $p < 0.001$), and significant increases in subjective arousal ($F(2,2180) = 1654.65$, $p < 0.001$).

Physiological Response Patterns and Metabolic Syndrome

In the logistic regression analysis predicting metabolic syndrome from HR Cluster, a significant main effect of HR emerged (complete results are summarized in Table 2 on page 107). Those in Cluster 2 (who exhibited both high tonic and phasic HR activation) were significantly more likely to have metabolic syndrome than those in Cluster 1 (who displayed lower baseline HR and a more adaptive stress response), OR = 1.45, [95% CI =1.02-2.07], p =0.037.

In the logistic regression predicting metabolic syndrome from HF-HRV Cluster, the HF-HRV by Sex interaction was significant; full results are presented in Table 3 on page 108. Evaluation of the interaction revealed that this was due to the significant associations between HF-HRV response to the stress protocol and metabolic syndrome in women. Women in Cluster 3 (who displayed an exaggerated decrease in HF-HRV) were significantly more likely to suffer from metabolic syndrome compared to women in Cluster 1 (who exhibited the expected modest stress-related decrease in HF-HRV with full recovery), OR = 2.56, [95% CI

=1.23-5.41], *p* =0.013. Women in Cluster 2 (who displayed a stress-related increase in HF-HRV), were also more likely to have metabolic syndrome than women in Cluster 1, OR = 2.30, [95% CI =1.30-4.07], *p* = 0.004.

No significant main effects or interactions emerged for the LF/HF or HF_{nu} clusters (see Supplemental Materials, Tables 4 and 5 on pages 109 and 110, respectively).

Additional analyses performed on individual stress reactivity and recovery change scores produced results for HR recovery and HF-HRV reactivity consistent with the cluster approach used above (data not shown).

Post-hoc Analyses

Additional ANOVA and Chi-Squared analyses were performed to better characterize the participants in each HF-HRV cluster. No significant sex difference emerged (χ^2= 0.92, *p* = 0.63) in HF-HRV cluster composition. HF-HRV clusters also did not differ significantly with regard to age, or other socio-demographic, medical, and/or behavioral variables. However, differences in psychological characteristics were observed. Given the sex difference observed in the main results, we examined whether differences in psychological factors across HF clusters differed as a function of sex. Women in Cluster 3 scored significantly higher on the CES-D (F(2,351)=6.20, p=0.002); PSQ, (F(2.351)=5.06 p=0.007); and STAI-State (F(2, 351)=4.02, p=0.002) than women in Clusters 1 and 2. In men, no significant differences in psychological factors across HF clusters were observed. Repeated measures ANOVAs were also conducted on self-reported stress, arousal, and affect in order to examine whether HF clusters differed in their subjective experience of the stress protocol. No significant cluster or cluster*period effects emerged.

Sex differences in the perception of the stressor task were examined by repeated measures ANOVA. Significant sex*period interactions emerged for affect and self-reported arousal; women experienced greater decreases in positive affect [$F(2,2178)=5.15$, $p=0.008$], and greater increases in arousal [$F(2,2178)=8.29$, $p<0.001$] than men in response to the stressor.

Discussion

The objective of this study was to examine associations between autonomic response patterns to psychological stress and metabolic syndrome among a large heterogeneous sample of older men and women suffering from CAD or other non-cardiovascular illness. Both men and women with elevated HR and incomplete recovery across the stress protocol were more likely to meet metabolic syndrome criteria than those with lower baseline HR and adaptive responses. On the other hand, significant sex differences emerged in the relation between parasympathetic stress responses and metabolic syndrome. Women exhibiting exaggerated parasympathetic withdrawal during stress followed by poor recovery, or alternatively, stress-related increases in parasympathetic activity in response to stress, were more likely to have metabolic syndrome.

Men and women with greater tonic and phasic HR activation were nearly 50 percent more likely to meet metabolic syndrome criteria than those displaying more moderate activation across the stress protocol. The literature pertaining to HR stress responses and metabolic syndrome is scarce, although elevated HR at rest has been associated with metabolic syndrome and/or its components in both concurrent and prospective research (32, 54-57). Heightened HR reactivity has been associated with greater BP (14), higher levels of overall cholesterol and triglycerides (18) and less central adiposity (24, 25). In contrast to our findings, Hu et al., (2016) (32) recently reported that greater HR reactivity to a cognitive stressor was associated with higher HDL cholesterol and lower waist circumference in concurrent analyses, though these results were not maintained over a four year follow-up (32). Inconsistencies in results involving HR response may reflect differences in the types of stressors used (for example, interpersonal vs. cognitive) and sample characteristics.

In addition, women (but not men) who showed pronounced parasympathetic withdrawal in response to stress, coupled with poor recovery post-stress, were more than two times more likely of having metabolic syndrome compared to women showing intermediate decreases in activity. We had previously shown the importance of excessive parasympathetic withdrawal to stress in predicting development of metabolic abnormalities in healthy men (31). Results are also consistent with recent data in participants with either a current or past history of mental health disturbance suggesting that hyper-reactive parasympathetic responses to stress are associated with a poorer metabolic profile (32). While a sex difference did not emerge as significant in the latter investigation, relations appeared strongest for women. Sex differences in psychological characteristics across parasympathetic response clusters may partially explain our findings in women and men. Indeed, women in the third cluster who exhibited the exaggerated stress-related decreases in parasympathetic activity showed significantly *more* distress across a number of psychological parameters in comparison to those in the other clusters. In men, no psychological differences between clusters were observed. Depression, anxiety, and stress have all been associated with metabolic syndrome (58-62). It is thus possible that the combination of exaggerated parasympathetic responses to stress and greater psychological vulnerability may have increased risk of metabolic syndrome in these women, although this remains to be verified. It is equally possible that hyper-reactivity was a result of greater distress, or that both reflect some other underlying process in women. Alternatively, the results may reflect a survivor effect in men, who typically develop CAD (for example) and die at an earlier age than women. More specifically, in this older sample, men for whom stress may have been the most pathological may already have died, essentially leaving more stress-resilient men in the investigation. Differences in methodology (cross-sectional vs. prospective) and sample characteristics relating to age and health status between this and our prior study may have also contributed to mixed findings in men (31).

In women, absence of parasympathetic withdrawal or increases in stress-related vagal activation were also associated with more than two times the odds of meeting metabolic syndrome criteria in comparison to those exhibiting intermediate response styles. Absence of parasympathetic withdrawal (or blunted response) has been associated with adverse health outcomes in emerging research in this and other laboratories. Blunted autonomic responses to stress had increased risk of future metabolic burden in healthy women in our prior investigation (31). We similarly observed that lack of parasympathetic stress response to an autonomic challenge (valsalva maneuver) was related to more complications during and after cardiovascular surgery (63). Given that so little research has examined autonomic indices of stress reactivity, it is unclear what parasympathetic activation in response to stress may represent. In the current sample, parasympathetic activation was accompanied by co-activation of sympathetic processes during stress. Such co-activation has been posited to have a synergistic effect on cardiac output, maximizing heart rate and contractility (64, 65). Activation of both ANS branches in response to stress may facilitate cardiovascular functioning in the short-term (63), but come at a price to the individual, as reflected in greater metabolic dysfunction and peri- or post-surgical complications.

Several factors limit the conclusions that can be drawn from this study. While not uncommon of large epidemiological studies, only one stressor task was used (24, 66). On the other hand, we have previously shown robust correlations between this task and other interpersonal stressors and with their aggregate score (41). The majority of participants were French-speaking Caucasians, which limits the extent to which findings can be generalized to individuals of different ethnicity. Given the advanced age of our sample, we cannot exclude the possibility that those most vulnerable to stress may already be deceased. The cross-sectional design obviously precludes conclusions regarding the stress response styles as causing metabolic syndrome. However, the results of our previous prospective investigation in healthy individuals strongly suggested an etiological role of stress responses in metabolic syndrome (31). As BEL-AGE is ongoing and prospective, it will be possible to eventually examine the clinical significance of the current findings.

Several strengths of the present manuscript merit mention. To our knowledge, this is only the second study to investigate the relation between physiological stress responses and presence of metabolic syndrome in adults, and the first to employ cluster analysis to characterize the pattern of stress responses. Use of clusters proved to be a parsimonious and informative means of evaluating the relation of parasympathetic response patterns and metabolic syndrome risk, as it accounted for the fact that reactivity and recovery are interconnected constructs that may yield misleading findings if examined separately. Moreover, our investigation includes autonomic indices of stress response, which have been largely omitted in research examining stress reactivity and metabolic outcomes, despite the importance of ANS activity to metabolism (55, 57, 67). Our results further highlight their potential role in metabolic syndrome. That women differed significantly from men reinforces the importance of evaluating sex differences in this field of research. The ecological validity of our stress protocol is also noteworthy; the anger recall task more closely resembles stressors encountered in everyday life, as compared to more artificial cognitive tasks (68, 69). Finally, our study was sufficiently powered to control for highly relevant medical, demographic, and behavioral covariates.

To conclude, this study corroborates research suggesting that hyper-reactivity to and delayed recovery from stress of the autonomic nervous system is associated with metabolic syndrome, and further suggests increased risk among older women with blunted parasympathetic responses or activation. This and other research substantiates the emerging hypothesis that a moderate or "healthy" level of reactivity exists (51, 70). Moderate reactions to stress may reflect the system's ability to adapt to frequently changing environmental or internal demands, while more extreme responses, whether exaggerated or blunted, may suggest maladaptive responses that increase risk for various disease states (70). The reason for the sex differences in the relation between parasympathetic stress responses and metabolic dysfunction requires further exploration but may involve differential perception of or coping with stress. Targeting individuals with non-normative parasympathetic response styles for stress management may be a means to protect those with or at risk for metabolic syndrome. Preliminary data from our laboratory suggests that this may indeed be helpful.

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Table 1

Summary of Participant Characteristics, M (SD)

	Men (*n* = 700)	**Women** (*n* =393)
Age (years)	65.3 (6.9)	64.9 (7.5)
Body Mass Index* (kg/m^2)	29.5 (4.8)	28.8 (6.2)
Presence of CAD***, *n* (%)	475 (68%)	112 (28.5%)
Presence of metabolic syndrome**, *n* (%)	414 (59.1%)	190 (52.2%)
Smoker*, *n* (%)	82 (11.7%)	31 (7.9%)
Hours of exercise/week	3.2 (3.8)	3.1 (3.2)
Years of schooling*	14.5 (3.7)	14.0 (3.7)
Marital Status***, *n* (%)		
Single	52(7.4%)	46 (11.7%)
Married/living with someone	544 (77.7%)	259 (65.9%)
Separated/divorced/widowed	104 (14.9%)	88 (22.4%)
Annual household income***, *n* (%)		
≤ $39 999	120 (17.2%)	93 (23.7%)
$40 000 - 59 999	153 (21.9%)	115 (29.3%)
$60 000 - 99 999	230 (32.9%)	104 (26.5%)
≥ $100 000	194 (27.7%)	69 (17.6%)
Physiological Baseline Measures		
SBP*** (mm Hg)	143.9 (20.0)	138.4 (22.2)
DBP*** (mm Hg)	73.2 (13.0)	70.1 (13.7)
HR*** (bpm)	62.3 (9.8)	67.4 (9.4)
HF-HRV** (ms^2)	827.0 (2990.3)	365.1 (1014.3)
LF/HF	2.51 (6.34)	2.43 (2.83)
HF_{nu}	0.43 (0.2)	0.41 (0.2)

Note . N may vary slightly depending on measure. CAD = coronary artery disease, SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, HF-HRV = high frequency heart rate variability, HFnu = high frequency heart rate variability in normalized units. Significant sex differences for each variable are indicated with asterisks, *p<0.05, **p<0.01, ***p<0.001.

Table 2

Multiple Logistic Regression Model for Metabolic Syndrome using HR Cluster as Independent Variable

	OR (95% CI)	***p***
HR Cluster		
Cluster 2 vs. Cluster 1	1.45 (1.02-2.07)	**0.04**
Sex	1.35 (0.94-1.93)	0.10
Age (for 1 SD=7.0 increase)	1.04 (0.89-1.22)	0.64
Presence of CAD	0.98 (0.69-1.39)	0.91
BMI (for 1 SD=5.3 increase)	3.46 (2.77-4.32)	<0.001
Exercise (hours/week) (for 1 SD=3.6 increase)	0.92 (0.79-1.06)	0.25
Household income		
40 000 - 59 999$ vs. <= 39 999$	0.80 (0.51-1.27)	0.35
60 000 - 99 999$ vs. <= 39 999$	0.66 (0.42-1.03)	0.07
>= 100 000$ vs. <= 39 999$	0.57 (0.34-0.93)	0.03
Years of school	0.95 (0.80-1.11)	0.50
Medication influencing MetS parameters	1.19 (0.72-1.94)	0.50
Other medications	1.61 (0.80-3.23)	0.18
Presence of comorbid medical conditions	1.50 (1.10-2.04)	0.01
Sex hormone therapy	0.63 (0.32-1.27)	0.20

Note . OR = odds ratio, CI = confidence interval. SBP = systolic blood pressure, BMI = body mass index, CAD = coronary artery disease

Table 3

Multiple Logistic Regression Model for Metabolic Syndrome using HF-HRV Cluster as Independent Variable and Sex as Moderator

	OR (95% CI)	***p***
Sex × HF Cluster		**0.005**
Cluster 2 vs. Cluster 1 within female	2.30 (1.30-4.07)	**0.004**
Cluster 3 vs. Cluster 1 within female	2.57 (1.22-5.41)	**0.013**
Cluster 2 vs. Cluster 3 within female	0.90 (0.44-1.84)	0.77
Cluster 2 vs. Cluster 1 within male	0.69 (0.46-1.02)	0.06
Cluster 3 vs. Cluster 1 within male	0.59 (0.35-1.00)	0.05
Cluster 2 vs. Cluster 3 within male	1.16 (0.69-1.92)	0.58
Age (for 1 SD=7.0 increase)	1.02 (0.86-1.19)	0.85
Presence of CAD	0.94 (0.66-1.33)	0.72
BMI (for 1 SD=5.3 increase)	3.50 (2.80-4.37)	<0.001
Exercise (hours/week) (for 1 SD=3.6 increase)	0.91 (0.78-1.05)	0.21
Household income		
40 000 - 59 999$ vs. <= 39 999$	0.83 (0.52-1.32)	0.42
60 000 - 99 999$ vs. <= 39 999$	0.68 (0.43-1.07)	0.09
>= 100 000$ vs. <= 39 999$	0.59 (0.36-0.97)	0.04
Years of school	0.94 (0.77-1.10)	0.43
Medication influencing MetS parameters	1.29 (0.78-2.13)	0.32
Other medications	1.54 (0.76-3.11)	0.23
Presence of comorbid medical conditions	1.52 (1.11-2.07)	<0.01
Sex hormone therapy	0.62 (0.30-1.25)	0.18

Note . OR = odds ratio, CI = confidence interval. SBP = systolic blood pressure, BMI = body mass index, CAD = coronary artery disease

Supplemental Table 4

Multiple Logistic Regression Model for Metabolic Syndrome using LF/HF Cluster as Independent Variable

	OR (95% CI)	*p*
LF/HF Cluster		
Cluster 2 vs. Cluster 1	0.81 (0.57-1.13)	0.21
Sex	1.32 (0.92-1.89)	0.13
Age (for 1 SD=7.0 increase)	1.02 (0.87-1.20)	0.76
Presence of CAD	0.94 (0.67-1.33)	0.73
BMI (for 1 SD=5.3 increase)	3.43 (2.74-4.29)	<0.001
Exercise (hours/week) (for 1 SD=3.6 increase)	0.92 (0.79-1.07)	0.27
Household income		
40 000 - 59 999$ vs. <= 39 999$	0.82 (0.51-1.30)	0.39
60 000 - 99 999$ vs. <= 39 999$	0.66 (0.42-1.04)	0.08
>= 100 000$ vs. <= 39 999$	0.57 (0.35-0.94)	0.03
Years of school (for 1 SD=3.7 increase)	0.96 (0.82-1.13)	0.62
Medication influencing MetS parameters	1.13 (0.69-1.87)	0.62
Other medications	1.51 (0.75-3.05)	0.25
Presence of comorbid medical conditions	1.51 (1.11-2.06)	0.01
Sex hormone therapy	0.61 (0.30-1.23)	0.17

Note . OR = odds ratio, CI = confidence interval. SBP = systolic blood pressure, BMI = body mass index, CAD = coronary artery disease

Supplemental Table 5

Multiple Logistic Regression Model for Metabolic Syndrome using HF_{nu} Cluster as Independent Variable

	OR (95% CI)	*p*
HF_{nu} Cluster		
Cluster 2 vs. Cluster 1	1.01 (0.69-1.46)	0.98
Cluster 3 vs. Cluster 1	1.14 (0.79-1.63)	0.47
Cluster 2 vs. Cluster 3	0.88 (0.57-1.36)	0.57
Sex	1.31 (0.91-1.86)	0.14
Age (for 1 SD=7.0 increase)	1.02 (0.87-1.20)	0.78
Presence of CAD		0.80
BMI (for 1 SD=5.3 increase)	3.43 (2.75-4.28)	<0.001
Exercise (hours/week) (for 1 SD=3.6 increase)	0.92 (0.79-1.06)	0.26
Household income		
40 000 - 59 999$ vs. <= 39 999$	0.80 (0.50-1.26)	0.34
60 000 - 99 999$ vs. <= 39 999$	0.67 (0.43-1.05)	0.08
>= 100 000$ vs. <= 39 999$	0.57 (0.34-0.93)	0.03
Years of school (for 1 SD=3.7 increase)	0.95 (0.81-1.11)	0.51
Medication influencing MetS parameters	1.18 (0.72-1.94)	0.50
Other medications	1.61 (0.80-3.23)	0.18
Presence of comorbid medical conditions	1.51 (1.11-2.05)	<0.01
Sex hormone therapy	0.64 (0.32-1.28)	0.21

Note . OR = odds ratio, CI = confidence interval. SBP = systolic blood pressure, BMI = body mass index, CAD = coronary artery disease

Figure Legend

Figure 1. Stress Response Clusters: HR

Figure 2. Stress Response Clusters: HF-HRV.

Figure 1. Stress Response Clusters: HR.

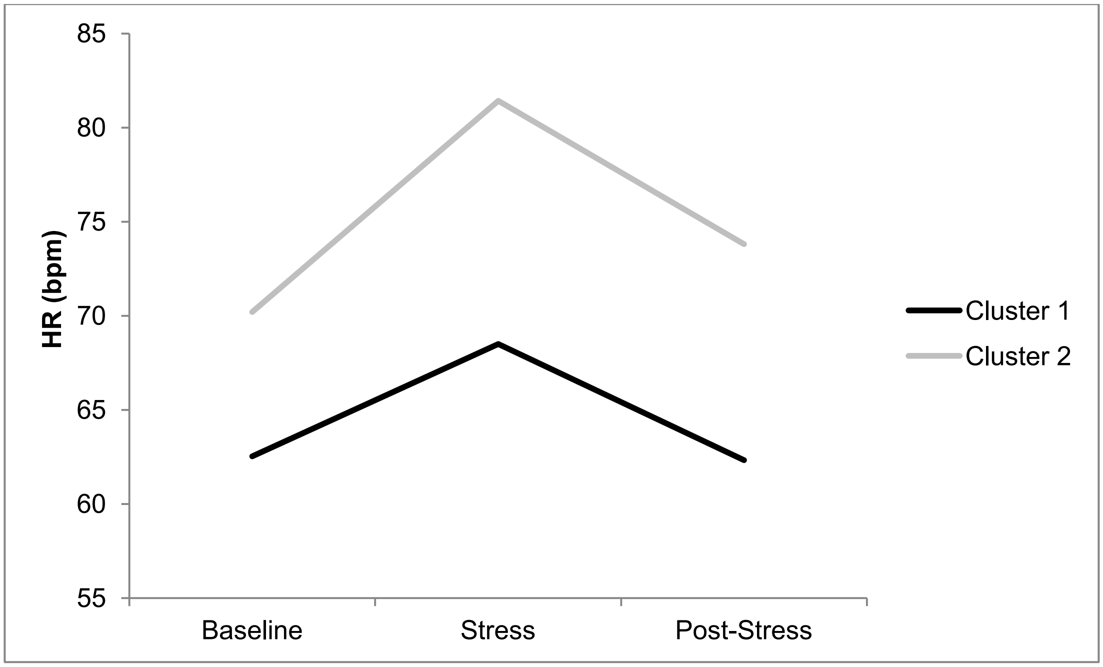

Figure 1. Cluster 1 participants displayed lower HR at baseline, moderate stress-related increases in HR, with full recovery. Cluster 2 participants exhibited higher HR at baseline, a larger stress-related increase in HR, and less recovery.
HR = heart rate, bpm = beats per minute.

Figure 2. Stress Response Clusters: HF-HRV.

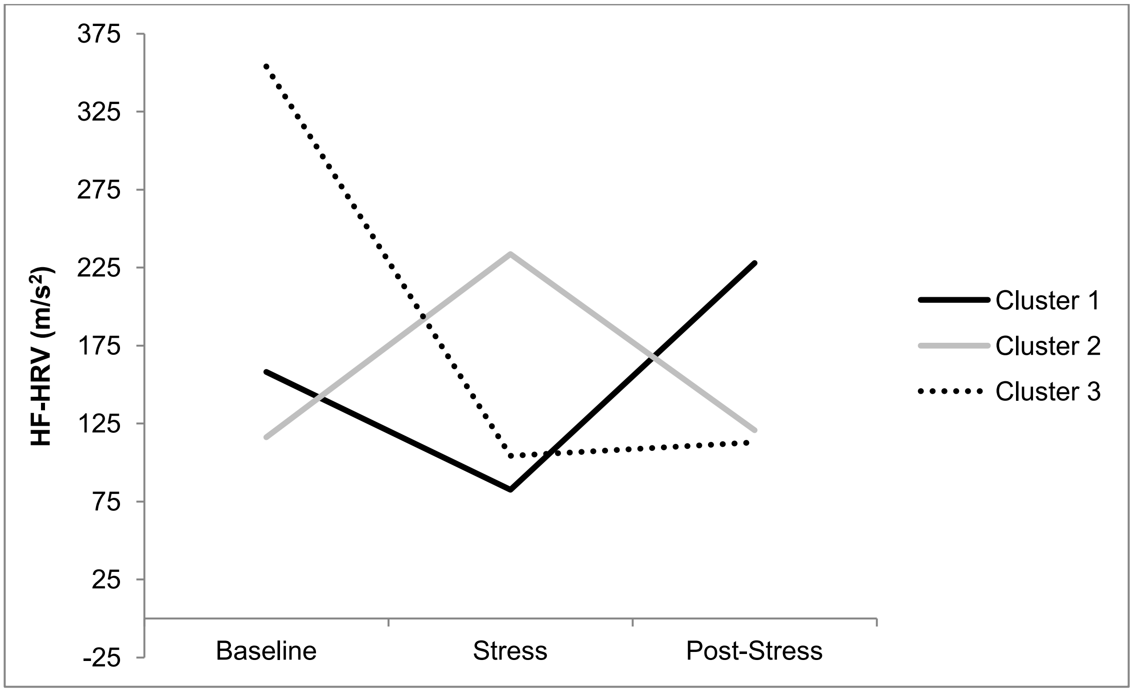

Figure 2. Cluster 1 participants displayed presumably "adaptive" responses to the stress protocol characterized by moderate activity at baseline, moderate stress-related decreases in HF-HRV and full recovery. Cluster 2 participants displayed similar activation at baseline, but demonstrated an unusual response involving an increase in HF-HRV across the rest of the stress protocol. Cluster 3 participants were characterized by higher baseline values, followed by large stress-related decreases in HF-HRV and incomplete recovery
The geometric mean of HF-HRV is presented on the y-axis.
HF-HRV = high frequency heart rate variability

CHAPTER 3

Gentile C., Starnino L., Dupuis, G., & D'Antono B., (2017) *Feasibility and Acceptability of Mindfulness-Based Stress Reduction in Older Adults with Current or Past Metabolic Syndrome: A Pilot Study*

Feasibility and Acceptability of Mindfulness-Based Stress Reduction in Older Adults with Current or Past Metabolic Syndrome: A Pilot Study

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Findings from Articles 1 and 2 strongly suggest that autonomic stress responses may be implicated in the development or progression of metabolic abnormalities. Interestingly, both exaggerated *and blunted* responses were associated with poor metabolic outcomes. Specifically, a pattern including hyper-reactivity of HR was cross-sectionally associated with incidence of metabolic syndrome in older individuals with compromised health. In healthy men, exaggerated parasympathetic withdrawal was associated with future metabolic burden, while non-normative autonomic response styles including heightened, blunted, and stress-related vagal activations were linked to greater concurrent and prospective risk of metabolic dysfunction in women. Given that non-normative autonomic responses were adverse for both healthy individuals and those with cardiovascular or other disease, it reinforced our initial interest in testing whether an established stress reduction intervention, MBSR, was appropriate for both blunted and heightened stress responders. Although some limited evidence suggested that MBSR reduces BP hyper-reactivity to stress (Nyklíček, Mommersteeg, Van Beugen, Ramakers, & Van Boxtel, 2013), whether it had potential to normalize (or increase) blunted stress responses had never been investigated, and very little was known about its impact on autonomic indices of stress response. Furthermore, given that autonomic stress responses were associated with both concurrent and future metabolic syndrome/burden, it seemed increasingly plausible that MBSR could improve metabolic parameters. These are the questions and reflections that led to the development of the objectives for the final study of this thesis.

However, whether the program would be feasible and acceptable to older adults with current or past metabolic syndrome as an adjunct to usual treatment needed to first be determined. With the exception of this pilot study and other work in our laboratory involving yoga and cardiac patients, no research at the Montreal Heart Institute (MHI) has investigated the influence of stress management in patients with or at risk for CAD. Unlike other fields in health psychology (e.g. oncology) wherein mind-body interventions including MBSR are increasingly researched and more readily available to patients (Haller et al., 2017; Shaw, Sekelja, Frasca, Dhillon, & Price, 2018), the importance of stress management interventions in those at risk of cardiovascular disease, and especially those exhibiting metabolic dysfunction, is less established and accepted (Abbott et al., 2014). It was thus important to collect feasibility and acceptability data in order to further corroborate an eventual large-scale RCT at the MHI and to illustrate demand for an adjunct, non-medical intervention in individuals with cardiovascular disease risk factors. In addition, this pilot study enabled us to examine the extent to which recruitment through mailed letters was effective in recruiting a sufficient number of participants. Due to ethical considerations, contacting participants directly by phone was not allowed, and reliance on referrals from cardiologists had not proven fruitful in our previous work.

Objectives

Primary objectives. The current pilot study sought to examine the feasibility and acceptability of MBSR for generally older adults with current or past metabolic syndrome and non-normative autonomic stress responses recruited from BEL-AGE, an ongoing large-scale longitudinal investigation on psychological burden and pathological aging.

Secondary objectives. We aimed to investigate whether MBSR training a) improves metabolic profile (i.e. waist circumference, blood pressure, glucose, triglycerides, and cholesterol) and b) "normalizes" reactivity to stress in individuals who exhibited either a heightened or blunted autonomic response at the time of previous participation in BEL-AGE.

We also examined c) whether changes in metabolic parameters were associated with changes in physiological reactivity post-intervention.

Hypotheses. *Primary.* We expected this study to be both feasible and acceptable, as measured by calculating response rate, recruitment rate, and refusal rates, as well as examining program completion rate, attendance, completion of daily practice logs, and acceptability ratings. *Secondary*. We hypothesized that MBSR would result in clinically significant changes in metabolic profile, particularly for blood pressure, as previous MBSR intervention studies tend to report positive changes in this parameter. We also anticipated that MBSR would help reduce stress reactivity in heightened responders and normalize (increase) reactivity in blunted responders. Finally, we believed that changes in metabolic syndrome parameters would be associated with changes in stress reactivity.

Methods

This pilot study is a randomized-controlled trial with a repeated measures (pre-test/post-test) experimental design.

Participants

Seven men and twelve women (*total n* = 19) without presence or history of cardiovascular disease were recruited from an ongoing large scale project, BEL-AGE, in the "Heart and Mind: Research Unit in Behavioral and Complementary Medicine" laboratory directed by Dr Bianca D'Antono at the Montreal Heart Institute. On average, 743.63 ± 209.61 days (or 2.03 years) elapsed since their participation in BEL-AGE. For BEL-AGE inclusion criteria, please refer to pages 87-88 (Article 2) of this thesis.

Participants were invited to participate through a letter sent to their home if a) they met criteria of metabolic syndrome as specified by the National Cholesterol Education

Program (Alberti et al., 2009) at the time of their participation in BEL-AGE, and b) if they exhibited exaggerated or blunted sympathovagal response (as measured by membership in the lower or higher tertile of LF/HF) to an acute stressor (anger recall task) in previous BEL-AGE testing, please see page 89 (Article 2) for details. Recovery responses from stress were prioritized over reactivity responses given evidence from our laboratory that autonomic stress recovery responses predicted worsening of metabolic profile (Gentile, Dragomir, Solomon, Nigam, & D'Antono, 2014), and data suggesting that abnormal stress recovery responses are not only independent of stress reactivity responses, but may reveal impairments in cardiovascular functioning in addition to or in the absence of non-normative reactivity (for a review, see Chida & Hamer, 2008). LF/HF was chosen as preliminary evidence from the BEL-AGE study suggested that a blunted LF/HF reactivity response to an anger recall stress task was associated with a higher number of metabolic syndrome parameters (Gentile & D'Antono, 2015).

Individuals were excluded from the current study if they a) had a significant cognitive or psychological condition limiting the extent to which they could participate in the research study and intervention program (e.g. delirium, psychosis, bipolar disorder, dementia), b) had cancer, HIV, or any other significant illness with the potential to impact longevity and capacity to participate in follow-up, c) were concurrently participating in psychotherapy, d) were regular yoga or meditation practitioners, and e) had cardiovascular disease, as defined by coronary angiography (at least 50% stenosis), prior myocardial infarct, coronary artery bypass grafting, or percutaneous coronary intervention.

Procedure

A recruitment letter was sent to individuals who met initial criteria for BEL-AGE. Following receipt of the recruitment letter (for a copy of the letter, see Appendix A, on page I), interested individuals were invited to contact the laboratory. They were then screened by phone to ensure that they met eligibility criteria for the current study before they were invited to participate. Once they were deemed eligible, their availabilities for the MBSR intervention were collected, and a final schedule was chosen in an attempt to accommodate the greatest number of participants. Participants who were available during the timeslot chosen for MBSR were then scheduled for their first laboratory appointment between 8:00 a.m and 9:00 am on a weekday. Testing was done in the morning to control for circadian rhythms and to keep the fasting period to a minimum. In addition to abstaining from eating and drinking (with the exception of water) for 12 hours prior to testing, participants were instructed not to smoke or engage in any strenuous exercise. They were also asked to refrain from the use of drugs or alcohol 24 hours prior. Once participants provided written consent, anthropomorphic data (weight, height, and waist circumference) were obtained. Participants then underwent a blood draw, followed by a structured interview in which additional demographic and medical information were collected. The electrodes for electrocardiographic (ECG) monitoring were then attached in a bipolar configuration to the lower side of the participants' rib cage, while a ground electrode was placed under the right clavicle; ECG was obtained using PowerLab (ADInstruments, Oxford, UK). In order to continuously measure blood pressure throughout the stress protocol, a Finopres Finometer (Amsterdam, The Netherlands) was placed on the middle finger of the participant's non-dominant hand. A thoracic belt was also secured around the participant's thorax to measure respiration rate. Participants then underwent a stress protocol involving a 5 min baseline period, and two 5 min psychological stressors: the Paced

Auditory Serial Addition Test (PASAT) and a debate task. Each stressor was followed by a 5 min recovery period. Participants completed measures of affect, arousal, and stress perceptions before and after each stressor task. ECG, blood pressure, and respiration were recorded continuously throughout the baseline, stress, and recovery periods. Following the stress protocol, participants completed a battery of psychological questionnaires. They were also asked to complete a short daily mood log for the duration of their participation in the study. This study was approved by the Research and Ethics Board of the Montreal Heart Institute.

Laboratory tasks. In order to increase stress, participants were informed that they would be video recorded during the PASAT and debate, and that their performances would be evaluated and compared to participants of their sex and age group. These tasks led to significant affective and physiological reactivity in prior studies (e.g. Carroll, Phillips, & Der, 2008; Carroll, Phillips, Der, Hunt, & Benzeval, 2011; Gentile et al., 2014; Steffen & Larson, 2015).

PASAT *(5 min):* During the PASAT, a series of single digit numbers were presented to the participants from a standardized audio-recording, and they were instructed to add the number they just heard with the number presented immediately prior to it. The participants were asked to answer out loud and were told that correct answers would be recorded as an indicator of performance. The first phase of numbers was presented at 3 second intervals, and the second phase at 2.4 second intervals.

Debate task *(5 min):* Participants were instructed to engage in a non-scripted debate with the research assistant on a socially salient topic such as abortion (session 1), the right to die (session 2), and same-sex marriage (session 3). Once participants chose the side they wished to argue, they were given a list of sample arguments to consult and were allowed to prepare for two minutes. This period was allotted to ensure that participants would have sufficient arguments for the duration of the debate, and also to increase stressfulness in anticipation of the task. During the debate, the participant and research assistant alternated between speaking and listening for one minute periods. This resulted in three minutes of active debate for the participant, and two minutes of listening.

Follow-up Visits

Evaluation 2 was performed approximately two months following the first (baseline) appointment. The procedures for Evaluations 2 and 3 were nearly identical to that of Evaluation 1, with the exception that the topics of debate were changed, and full socio-demographic, medical and health behavior questionnaires were not re-administered unless changes in the participant's profile had occurred. The 2-month follow-up data obtained at Evaluation 4 was not included in this thesis due to time constraints.

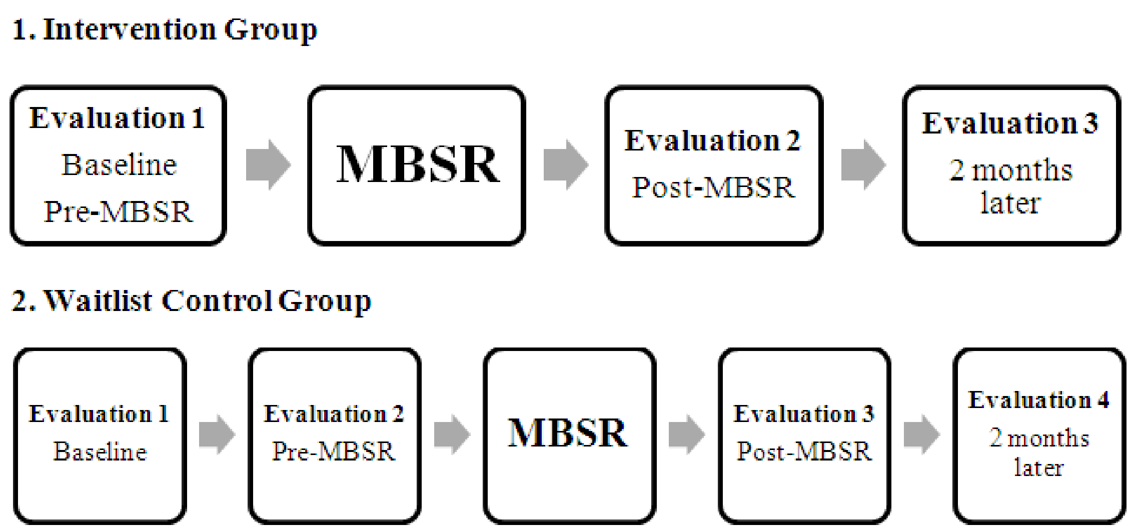
Randomization

Participants were randomly assigned to either the MBSR intervention group or wait-list control group. Randomization to either group was stratified according to sex and type of physiological stress response (exaggerated versus blunted) exhibited by the participant in previous testing. The intervention group and wait-list controls were recruited and tested within a similar time period to limit group differences resulting from the passage of time and differential exposure to weather, socioeconomic, political, or medical variables. Laboratory technicians conducting the blood draws were blind as to the participants grouping and stress response style for the duration of the study. The psychologist administering the MBSR intervention was also blind to the participants' physiological grouping and metabolic status.

Those administering the stress protocol and entering the data were blind until the end of the second evaluation, when feedback concerning their intervention experience was collected.

Participants in the intervention group underwent three evaluation sessions, while those in the control group participated in four evaluations. For more information on study flow, please see Figure 1 below.

Figure 1. Study Flow



The Intervention

Mindfulness-Based Stress Reduction (MBSR) is a standardized eight week program developed by Dr. Jon Kabat-Zinn, PhD. Participants attended eight weekly two and a half hour sessions at a community center adjacent to the Montreal Heart Institute. They also attended an additional five hour "retreat" between weeks 7 and 8 which sought to further integrate the skills acquired until that point. The nine sessions of MBSR were delivered over nine weeks rather than the standard eight in order to avoid holding a session on a religious holiday. Sessions were animated by a psychologist and MBSR teacher with over 25 years of psychotherapy experience. They were audio-recorded and reviewed by Dr. Bianca D'Antono, who has over 20 years of experience in stress management and mindfulness-based stress interventions, in order to ensure adherence to the standardized MBSR program.

Every session typically began and ended with meditation; the first meditation lasted approximately 10 minutes and the second lasted from 20 to 25 minutes. Meditations included body-scan, walking meditation, loving-kindness meditation, yoga, and others. The rest of the session was devoted to teacher instruction and group discussions centering on stress management. Please see Appendix B on page III for a breakdown of the topics covered every session.

Participants were assigned weekly homework activities and instructed to practice mindfulness skills for 25 to 45 minutes a day. They were asked to complete daily logs of their mindfulness practice in order to increase adherence. These practice logs were also used as indicators of acceptability of the program. Audio recordings of mindfulness exercises were provided to the participants in order to facilitate daily practice at home.

Measures

Feasibility. Feasibility was examined via response rate, recruitment rate, and refusal rates. *Response rate* refers to the number of participants that responded to our initial recruitment letter, divided by the total number of participants approached. *Recruitment rate* was defined as the number of participants that agreed to participate after contacting the laboratory and learning about the study, divided by the total number that responded. *Refusal rate* refers to the number of participants who refused to participate divided by the total number that responded.

Acceptability. Acceptability was measured via the program completion rate, program attendance, as well as completion of daily practice logs. An adapted version of the Treatment

Acceptability and Preferences Questionnaire (Sidani, Epstein, Bootzin, Moritz, & Miranda, 2009) was also administered; it consisted of 11 questions measuring the extent to which participants perceived the intervention as efficacious, appropriate and acceptable by means of Likert scales ranging from 0 *(not at all)* to 4 *(extremely).* Participants also indicated how beneficial they perceived each MBSR component to be (teacher instruction, meditation, yoga, group discussions, etc), using the same Likert scale. They were also queried with open-ended questions regarding the intervention (e.g. w*hy did you participate in this project on stress management; what aspect(s) of the MBSR program did you particularly enjoy; what aspect(s) of the MBSR program did you particularly dislike*) and their responses were recorded. For a copy of this questionnaire, see Appendix C on page V).

Sociodemographic variables. Data on sex, age in years, ethnicity, weight, height, marital status, income, and years of schooling were obtained. Behavioral risk factors such as daily tobacco and alcohol consumption as well as weekly hours of physical activity were also assessed.

Affect and arousal. Affect and arousal was assessed by means of the Self-Assessment Manikin (SAM) (Hodes, Cook, & Lang, 1985). Participants were asked to rate their affect and arousal during baseline and immediately following the stress tasks and recovery periods.

Biological outcome variables. ***Blood pressure.*** Baseline BP obtained during the stress protocol was utilized as resting BP. ***Blood sample plasma.*** Blood samples were analyzed for cholesterol, triglycerides and glucose at the Montreal Heart Institute. These determinations were made using respective reagent Flex on the multianalyzer Dimension RxL Max (Dade Behring Diagnostics, Marburg, Germany) with heparinized plasma. The samples were analyzed upon reception. ***Heart rate variability.*** HRV parameters were obtained from the electrocardiogram (ECG) and were analyzed offline in LabChart (ADInstruments, Dunedin, New Zealand). The analysis was performed semi-automatically and artifacts were corrected by hand. HRV was characterized by the high frequency (HF; 0.15–0.40 Hz) and the low frequency components (LF; 0.04– 0.15 Hz) as recommended by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996). HF was assessed in both absolute and normalized units (nu). LF/HF ratio was used as a measure of sympathovagal balance. LF/HF ratios greater than one are thought to reflect greater sympathetic versus parasympathetic activation of the heart.

Data reduction

SBP, DBP, HR, HF-HRV, HF_{nu}, and LF/HF readings were averaged over each baseline, stress, and post-stress period. The two stress periods (PASAT, debate) and recovery periods were then averaged to create composite scores. Stress reactivity (stress-baseline) and recovery (recovery-baseline) change scores were computed for each parameter.

Statistical Analyses

This pilot study was not powered to detect significant differences. Means, standard deviations, and percentages were obtained in order to address primary objectives. For secondary objectives, effect sizes, direction of effects, and **clinical** significance were of interest.

In preliminary analyses, independent samples t-tests were conducted to assess whether the intervention group and control group differed on variables of interest at baseline.

In order to evaluate between-group differences in the extent to which metabolic parameters changed over the first two evaluations, ANOVAs were conducted using change scores (Evaluation 2 – Baseline), with Grouping (MBSR or waitlist control) as a between-subjects factor.

To examine within-group changes in metabolic parameters as a function of participation in MBSR, a repeated measures ANOVA was performed comparing the evaluation period immediately prior to MBSR to that immediately post MBSR. Given that the final post two-month evaluation could not be completed in time for the preparation of the thesis, the follow-up data was not included in the analyses. An intention to treat approach was used.

To investigate whether MBSR "normalizes" reactivity to stress in individuals who exhibited either a heightened or blunted ANS response in BEL-AGE, repeated measures ANOVA's were conducted separately for heightened and blunted responders. Reactivity pre-MBSR was compared to reactivity post-MBSR within each responder group. To examine whether changes in metabolic parameters were associated with post-intervention changes in physiological reactivity, Pearson correlations between percent change in reactivity and percent change in metabolic parameters post-intervention were employed separately for each reactivity grouping.

Results

Feasibility of MBSR

Response rate, refusal rate, and recruitment rate. For a summary of participant recruitment, please refer to Figure 2 on page 160. Eighty-one participants from the original BEL-AGE sample were contacted by letter and invited to participate in the study. The second mailing (to the same individuals) was conducted approximately six weeks after the first mailing. A total of 33 total individuals contacted the laboratory after receiving the letter, a response rate of nearly 41 percent. Of these individuals, 79 percent consented to participate. Seven (21 percent) refused to participate, mostly due to the time commitment and weekly travel demands of the MBSR sessions. However, two were excluded following the phone screening as they were current regular meditation practitioners. Once the final list of interested and eligible participants was compiled (n = 24), we collected the participants' availabilities (preferred day of the week and time of day) for the weekly MBSR program. Based on this information, we scheduled the sessions at a time accommodating the greatest number of participants. Five participants were consequently unable to partake in the study due to scheduling conflicts, which included work commitments or planned vacations abroad exceeding two weeks. This resulted in a final total of 19 participants. One participant who was randomized to the waitlist control group withdrew from the study prior to the start of intervention, citing that she had become too occupied to participate. She only attended the first evaluation session, and thus was removed from the main analyses.

Participant Characteristics

Participants were mostly retired, older adults (M_{age} = 67) with an average BMI of 30.9 kg/m^2. Although many participants were on medication capable of reducing MetS or its constituents, a total of 47 percent still met metabolic syndrome criteria at first evaluation, while 74 percent met criteria for at least two components. For a full summary of participant characteristics, please refer to Table 1 on page 153.

Acceptability of MBSR

Completion rate. Completion rate of the MBSR program was 68 percent (13 out of 19). Specifically, 7 out of 9 completed the MBSR program in the intervention group, while 6 out of 10 completed the program in the wait-list control group. All completers of the MBSR program attended at least seven out of nine sessions. Reasons for non-completion included difficulty with commute (n=1), work scheduling conflicts (n=1), too busy (n=2), and the belief that program would not be beneficial (n=2). All individuals who did not complete the program nevertheless agreed to attend their subsequent evaluation sessions in the laboratory. For a summary of MBSR completion, please refer to Figure 3 on page 161.

Completion of practice logs. Participants were instructed to keep a log of the number of minutes they formally practised their mindfulness skills per day. Participants completed a total of 87 percent of their practise logs from weeks 1 to 9. Most missing logs were those of week 9, when participants were exceptionally asked to return completed logs at their next evaluation session or by mail. Excluding week 9, participants completed 94 percent of their logs.

Practice performed. On average, participants reported practising 40.6 ± 16.4 minutes a day.

Attendance of MBSR. Overall attendance by *completers* of the MBSR program was 97 percent. Missed sessions were due to prior engagements or illness.

Attendance of evaluations. All participants attended the first and second evaluation sessions, with the exception of one individual who withdrew from the study after Evaluation 1 and who was removed from analyses. A total of 89 percent of participants attended the third evaluation. One participant in the intervention group decided not to attend Evaluation 3 due to the burden of a third blood test. One of the control participants who withdrew from MBSR did not arrive in a fasting state to Evaluation 3, and this individual did not agree to reschedule or to participate in Evaluation 4. All other control participants were present for the fourth and final evaluation.

Acceptability questionnaire post-intervention. For full results of the acceptability questionnaire, please refer to Table 2 on page 154. In sum, the majority of participants rated the program as *moderately*, *very,* or *extremely* efficacious, appropriate, and acceptable in the reduction of stress (94%, 88% and 96%, respectively). The most appreciated components of the MBSR program were the teacher instruction, with 94% agreeing it was *very* or *extremely* beneficial, and the sitting meditation, with 69% indicating it was *very* or *extremely* beneficial. The least appreciated components of MBSR were the walking meditation, with 26% agreeing it was *not at all* or *a little bit* beneficial, and the 5 hour retreat, with 23% indicating it was *not at all* or *a little bit* beneficial. A total of 64% of participants indicated that they would be *very* or *extremely* likely to participate in the program again, while 76% were *moderately*, *very* or *extremely* likely to continue their mindfulness practise. Participant verbal feedback is summarized in Appendix D on page IX.

Secondary Objectives: Metabolic Outcomes

The intervention and control groups did not differ significantly in age, weight, BMI, or any of the metabolic syndrome parameters at baseline (waist circumference, SBP, DBP, total cholesterol, LDL, HDL, glucose, and triglycerides).

Between-subjects effects. For all results, please refer to Table 3 on page 155. In summary, those participating in MBSR exhibited greater decreases in total cholesterol and especially LDL, compared to controls, with moderate to large effect sizes. Although triglycerides in the MBSR group were nearly unchanged post-intervention, control participants exhibited a notable increase in triglycerides over the two-month period.

Within-subjects effects. With the exception of glucose, all metabolic parameters decreased post-MBSR. The greatest decreases were observed in LDL and total cholesterol, with large effect sizes. For full summary of results, please refer to Table 4 on page 156.

A second analysis was conducted with *only* those who completed the MBSR program. The direction of effects remained nearly identical; however, percent change decreases in LDL and total cholesterol were larger. For a full summary of results for MBSR completers, please refer to Table 5 on page 157.

Secondary Objectives: Stress Response Outcomes

Psychological stressfulness of the protocol. The protocol elicited significant increases in subjective stress (arousal) at the first, second, and third evaluations (all *p*'s < .01), (see Table 6 below). It also elicited significant decreases in positive affect across all three evaluations, (all *p*'s < .01). Given that half the participants were specifically recruited because of their blunted autonomic responses to stress, changes in physiological parameters across the overall sample were not utilized as an indicator of task stressfulness in this study.

Table 6

Subjective Stressfulness of the Protocol at Each Evaluation Session

	Affect Valence				Arousal			
	Baseline	*Stress*	ANOVA	η^2	*Baseline*	*Stress*	ANOVA	η^2
Evaluation 1	6.22	4.97	F(1,17)=17.30**	.50	4.50	5.83	F(1,17)=14.70**	.46
Evaluation 2	6.39	4.86	F(1,17)=14.50**	.46	4.33	6.17	F(1,17)=10.13**	.37
Evaluation 3	6.81	5.37	F(1,15)=8.34*	.36	4.56	6.22	F(1,15)=11.38**	.43

For affect, 1 represents "extremely negative affect" and 9 represents "extremely positive affect". For arousal, 1 represents "very low arousal" and 9 represents "extremely high arousal". $*p < .05$, $**p < .01$. All effect sizes are large (Cohen 1988).

Impact of Bel-AGE (LF/HF) stress response pattern. For baseline values across all stress parameters in the heightened and blunted LF/HF response groups, please see Appendix E on page XV. For a full summary of results, please see Table 7a and 7b on page 158. Briefly, there was little change in SBP and DBP reactivity post-intervention in heightened LF/HF responders, while BP reactivity decreased in blunted LF/HF responders. Those in the heightened LF/HF response group became *less* reactive in HR, HF, and HF_{nu} upon completion of the intervention, while those in the blunted LF/HF response group became *more* reactive in HR, HF, and HF_{nu}. Both the heightened LF/HF response group and the blunted LF/HF response group exhibited reductions in LF/HF reactivity post-MBSR.

Changes in stress response and in metabolic parameters (separately by stress reactivity grouping). For a full summary of Pearson correlations, please see Tables 8a and 8b on page 159. In hyper-reactors, change in SBP reactivity was positively correlated with percent change in glucose and triglycerides. Percent change in HF reactivity was also negatively correlated with percent change in total and LDL cholesterol. In blunted reactivity responders, percent change in DBP reactivity was negatively correlated with percent change in glucose. Percent change in HF reactivity was positively correlated with percent change in triglycerides.

Post-hoc Analyses

Influence of practice time and frequency on metabolic parameters. For a full summary of correlations between home MBSR practice and change in MetS parameters, please refer to Table 9 below. The most robust correlations were obtained between number of minutes practiced per week and percent change in HDL and total cholesterol (r = -.57, r = -

.52, respectively). In other words, the more participants practiced, the greater the drop in total cholesterol, including HDL.

Table 9

Correlations between MBSR Home Practice and Percent Change in Metabolic Parameters

	WC	SBP	DBP	Glucose	Total Cholesterol	HDL	LDL	Triglycerides
Frequency of practice per week	.10	-.11	.01	.01	-.15	-.14	.17	-.33
Minutes of practice per week	.16	.20	.22	-.23	-.52	-.57*	-.18	-.29

$^*p < .05$, $^{**}p < .01$, bolded values represent trends, $p < .10$; $r = .1$: small effect, $r = .3$: moderate effect, $r > .5$= large effect

Discussion

The primary goal of the pilot study was to assess the feasibility and acceptability of MBSR for older adults with current or past metabolic syndrome and non-normative autonomic stress responses recruited from BEL-AGE, an ongoing large-scale study in our laboratory. Secondary objectives included examining whether MBSR improves metabolic syndrome components, and whether it normalizes heightened and blunted responses to stress. We also verified whether changes in metabolic parameters post-MBSR were correlated with changes in stress responses.

The recruitment for this study was moderately feasible and the methods and intervention largely acceptable to participants. Over 40 percent of individuals invited to participate responded to the recruitment letter. Of those who responded, nearly 80 percent accepted to participate, resulting in a potential sample of 26 individuals (before exclusions). Response rates may have been higher if potentially eligible participants were contacted directly by phone rather than by mail. Indeed, in a study offering a 15 week restorative yoga program for overweight adults with metabolic syndrome, the response rate using phone screenings was 73 percent (Cohen, Chang, Grady, & Kanaya, 2008). However, constraints imposed by our institutional ethics board prohibited recruitment through phone contact. It is difficult to compare our response rate with those of other MBSR intervention studies utilizing clinical samples specifically, as eligible participants in those investigations tended to be referred directly from physicians or other health care providers after in-person visits (Campbell, Labelle, Bacon, Faris, & Carlson, 2012; la Cour & Peterson, 2015; Lengacher et al., 2012). However, our response rate is high compared to studies utilizing invitation letters for other intervention types. For instance, the response rate for an exercise advice program in a similar sample of elderly participants was 32 percent (Halbert, Silagy, Finucane, Withers, & Hamdorf, 1999). For a web-based nutritional intervention trial and an online smoking cessation program, response rates to invitation letters were 15 and 7 percent, respectively (McClure et al., 2006; Stopponi et al., 2009).

Of the total number of participants that were contacted, 32 percent consented to participate. This is similar to what was reported by other authors utilizing a similar sample of 92 elderly individuals with metabolic syndrome (Kim, Park, & Park, 2014). Specifically, in their study employing an 8-week community-based intervention consisting of health behavior counseling, the recruitment rate was 29 percent (Kim et al., 2014). Similarly, Cohen et al., (2008) obtained a recruitment rate of 38 percent in their study examining the impact of a 15 week restorative yoga program in overweight adults with metabolic syndrome. Recruitment rates for MBSR studies in cancer patients tend to be higher (between 40 and 60 percent) (Campbell et al., 2012; Lengacher et al., 2009). However, this may be because these patients are already making frequent trips to medical centers, and thus participation in a complimentary MBSR program does not represent an additional commute. Indeed, the primary reason for refusal to participate in our study was the 9-week time commitment and the significant commute required for some individuals who would not otherwise be visiting the hospital. Scheduling conflicts were also a barrier to feasibility; five participants who were interested in participating were unable to attend the MBSR sessions at the scheduled time and were excluded, despite efforts to accommodate the greatest number of individuals. Given that the majority of those who accepted to participate were older adults who were either working part-time or retired, a weekday afternoon was chosen for the program.

Acceptability of MBSR was high. Completion rate of program was nearly 70 percent, which is comparable to what is observed in other MBSR studies. Completion rates of this intervention tend to be elevated, ranging from 75 to 90 percent in various populations (Campbell et al., 2012; Kabat-Zinn, 1982; Kabat-Zinn & Chapman-Waldrop, 1988; Kabat-Zinn, Lipworth, & Burney, 1985; la Cour & Peterson, 2015; Lengacher et al., 2012; Miller, Fletcher, & Kabat-Zinn, 1995). In a similar sample of older individuals with metabolic syndrome, completion rate of a community-based health counseling intervention program was 77 percent (Kim et al., 2014). The fact that it was only possible to offer one timeslot for MBSR sessions hindered the completion rate in our study. Indeed, three out of the five individuals who did not complete MBSR were individuals working at least 30 hours a week and who had scheduling conflicts. Challenges related to group homogeneity also played a role for at least one participant. During evaluation post-intervention, the youngest participant

(41 years old) expressed that she did not feel she could relate to the rest of the group, who were 65 years old on average, as she did not share the same concerns. Cullen (2011) suggests that homogeneity of participants within the MBSR program may lead to greater bonding, empathy, and support, which may facilitate program completion. However, group heterogeneity may also be advantageous in certain contexts, and research examining the acceptability and/or impact of MBSR on health outcomes does not generally favor one approach over the other (Cullen, 2011; Dobkin, Irving, & Amar, 2012; Rosenzweig et al., 2010; Van den Brink, & Koster, 2015). The completion rate for the intervention group was higher than that of the control group; this appears to be explained by participant characteristics. For instance, two of the four controls who did not complete the MBSR intervention were full-time workers who had less time to devote to the program. Adherence to MBSR in our study was excellent; completers attended 97 percent of sessions and completed nearly 90 percent of their practice logs. On average, participants practiced mindfulness 41 minutes a day at home, which was near the upper limit (25-45 minutes a day) of recommended practice time, and higher than what is typically reported (18-33 minutes a day) in other studies (Campbell et al., 2012, Lengacher et al., 2012; Lengacher et al., 2009; Parsons, Crane, Parsons, Fjorback, & Kuyken, 2017). This is not particularly surprising, as most of our sample was retired and possibly had greater time available for practice. Given that our recruitment method also required an active response on the part of participants, it is possible that our sample represented a particularly motivated group of individuals who were prepared to adhere to study guidelines.

The MBSR program was also well-received by participants; the majority rated the program as very efficacious, appropriate, and acceptable in the reduction of stress. This is consistent with other literature suggesting that generally, those who undergo MBSR tend to report high levels of satisfaction and seem to believe that their mindfulness experience was important and valuable (Kieviet-Stijnen, Visser, Garssen, & Hudig, 2008). A total of 64 percent of participants would be very or extremely likely to participate in the program again. Traffic and significant commute to the hospital were stated as primary reasons for unwillingness to hypothetically participate a second time.

Participants also provided rich verbal feedback regarding the MBSR program. Several mentioned that it bought them a sense of calm, helped them connect with their loved ones, and made them more aware of their movements, facilitating physical activities. MBSR also helped participants become more in tune with their emotions, which was pleasant for most participants but distressing for one individual. Certain participants expressed the conviction that MBSR should be widely available for older adults or those working in high-stress jobs. Interestingly, participants appeared to grasp that mindfulness is a skill that is developed over time and must be incorporated into everyday life in order to have a lasting impact. To quote one of our participants, "*mindfulness meditation is like taking vitamins; you may not recognize the benefits every day, but if you stop practicing, you will notice the difference*".

MBSR & Metabolic Outcomes

A secondary objective of this work was to examine the size and direction of effects of MBSR on metabolic parameters. The most notable impact of MBSR was observed for cholesterol. Specifically, the MBSR group exhibited a 15 percent decrease in LDL cholesterol and a 10 percent decrease in total cholesterol post-intervention, while controls displayed little to no change in these parameters. Effect sizes associated with these changes were large. A meta-analysis conducted by Gould, Rossouw, Santanello, Heyse, & Furberg,

(1998) reported that a reduction of 10 percent in total cholesterol results in a 10 to 11 percent decrease in the risk of all-cause mortality, and a 13 to 15 percent decrease in CVD-related mortality, indicating substantial clinical significance of these findings. Moreover, these reductions were in addition to benefits already achieved by medication, (58 percent of the sample were taking dyslipidemic agents), which is particularly noteworthy. In general, regular use of statins tends to reduce LDL cholesterol by 40 to 60 percent (for a meta-analysis, see Law, Wald, & Rudnicka, 2003).

Reductions of 15 percent observed in this study are comparable and even superior to decreases reported in cholesterol after dietary and physical activity changes in earlier studies (Schaefer & Brousseau,1998; Stefanick, 1998). However, although diet and exercise are typically promoted as ways to reduce LDL cholesterol, consistent adherence to these methods in out-patient settings is difficult to achieve (Schaefer & Brousseau, 1998). The fact that attendance and adherence to daily mindfulness practise was excellent in this pilot study further supports the usefulness of MBSR as an adjunct to treatment of metabolic dysfunction.

The influence of MBSR on the remaining metabolic syndrome components was also mostly positive. While SBP decreased to a similar extent post-MBSR independent of the group participants were randomized to, reductions in DBP were larger in the MBSR group than in controls. Waist circumference also decreased in the whole sample post-intervention, with a large effect size. Although triglycerides remained nearly unchanged post-intervention in the overall sample, participants in the control group exhibited an increase in triglycerides over the waiting period, compared to the MBSR group whose triglyceride levels remained equivalent. In contrast, both groups displayed increases in blood glucose levels post-intervention, though effect sizes were small. The overall pattern of results suggests that

MBSR shows substantial promise in altering the different components of metabolic syndrome.

As mentioned, MBSR resulted in clinically significant reductions in cholesterol. Both acute and chronic stress have been associated with increases in LDL and total cholesterol, yet we are the first to investigate the effects of MBSR on these parameters (Bacon, Ring, Lip, & Carroll, 2004; Muldoon et al., 1995; Patterson, Gottdiener, Hecht, Vargot, & Krantz, 1993; Shahnam, Roohafza, Sadeghi, Bahonar, & Sarrafzadegan, 2010). Changes in cholesterol may reflect changes in physiological responses to stress, as was initially proposed by Articles 1 and 2 of this thesis. Preliminary data from this study suggest that changes in parasympathetic reactivity are associated with changes in total and LDL cholesterol, although the direction of the association differs according to the initial stress response style (heightened versus blunted responder). Changes in SBP reactivity were also robustly associated with improvements in glucose and triglycerides among heightened reactivity responders. Although findings are preliminary and must be replicated on a larger scale before conclusions can be drawn, these data support the notion that alterations in physiological stress responses may be a pathway by which MBSR influences metabolic outcomes.

MBSR may have also positively impacted metabolic parameters (i.e. cholesterol, waist circumference, and triglycerides) through the teaching of greater attention control. It is well documented that those reporting high levels of stress are also more likely to engage in poor health behaviors to cope, such as overeating, consuming alcohol, smoking, or being sedentary (Dallman, 2010; Epel, Lapidus, McEwen, & Brownell, 2001; Kouvonen et al., 2005; Roberts, Campbell, & Troop, 2014; Soloman, Jankord, Flak, & Herman, 2011; Stetson et al., 1997; Tomiyama, Dallman, & Epel, 2011). MBSR may thus mitigate the harmful impact of these health behaviors on one's metabolic profile by enabling individuals to become aware of the associated negative or unpleasant sensations (Loucks et al., 2015). Indeed, in "auto-pilot" mode, these sensations may have been inaccessible or unconsciously avoided, thus maintaining these maladaptive coping strategies (Loucks et al., 2015). This seemed to be the case for at least one participant, who reported that MBSR allowed him to become conscious of his frequent mindless eating and alcohol consumption, which resulted in the reduction of these tendencies and subsequent weight loss. Interestingly, greater number of minutes of MBSR practised per week was associated with greater decreases in total cholesterol. These findings are in line with Carlson and colleagues (2001) and Lengacher et al., (2009), who reported that greater number of minutes practised of MBSR was associated with greater improvements in pain, physical functioning, and mood, as well as reductions in perceived stress. However, frequency of mindfulness practise (rather than duration of each individual practise session) has also been associated with better health outcomes in other research (Crane et al., 2014; Pradhan et al. 2007; Soler et al., 2014). Taken together, data demonstrate that the need for practise outside the weekly MBSR sessions should be strongly emphasized to participants in order for them to derive maximum benefits from the program.

Decreases in SBP in both groups post-MBSR may be explained by the fact that participants habituated to the testing environment and research personnel by the second evaluation. Indeed, BP is volatile and tends to increase acutely in medical and laboratory contexts, especially in older adults (Franklin, Thijs, Hansen, O'Brien, & Staessen, 2013; Pickering, 1996). As a result, greater effects of habituation of baseline BP may be observed across consecutive evaluations, particularly in individuals with higher BP initially (Pickering, 1996). Consistent with our within-subjects findings for SBP, Hartmann et al., (2012) also reported no change SBP post-MBSR in a randomized-controlled trial of individuals with Type 2 diabetes (Hartmann et al., 2012). It has been suggested that null results in BP after MBSR completion may be attributed to floor effects (Loucks et al., 2015). Indeed, largest decreases in BP post-MBSR tend to be observed in individuals specifically recruited with un-medicated stage 1 or stage 2 hypertension (de la Fuente et al., 2010), while smaller changes or null results tend to be reported in participants with pre-hypertension and/or on medication (Hughes et al., 2013; Hartmann et al. 2012). Indeed, the mean SBP of our sample was 133.6 mm Hg, indicating pre-hypertension, and 60 percent of our sample was taking blood pressure medication. This may have dampened the extent to which MBSR influenced SBP. As for DBP, our results are in line with two other studies reporting modest decreases in this parameter following participation in MBSR (Hughes et al., 2013; Nyklicek et al., 2013). Indeed, the reduction of 3.5 mm Hg observed in the experimental group and 2 mm Hg observed in the whole sample in our study is slightly higher than post-MBSR decreases of 1.9 mm Hg in DBP reported by Hughes and colleagues (2013).

The fact that participants exhibited small increases in glucose post-MBSR regardless of which group they were randomized to is somewhat surprising, given that MBSR tended to result in improvements in all other metabolic syndrome parameters. It is unclear why this is the case at this time. Nevertheless, our findings for glucose are consistent with Daubenmier et al., (2012), who also reported that participants in both a mindfulness-based eating awareness program and waitlist group displayed increases in glucose post-intervention (but no change in BMI or weight). It remains to be determined whether this finding replicates in a future large-scale RCT. Further investigation in this case would be warranted.

MBSR & Physiological Stress Responses

This study provides preliminary evidence that participating in a stress reduction intervention may "normalize" physiological stress responses in those with heightened or blunted response styles at outset. Consistent with hypotheses, those in the blunted LF/HF group response groups became *more* reactive in HR, HF, and HF_{nu} upon completion of MBSR, while those who were initially more reactive became *less* reactive on these same measures. Both exaggerated and blunted LF/HF responders exhibited further decreases in LF/HF reactivity post-MBSR. Moreover, while there was little change in SBP and DBP reactivity post-intervention in heightened LF/HF responders, SBP and DBP reactivity further decreased in blunted LF/HF responders. Given that decreases were observed in *both* groups for LF/HF and BP indices, it is unlikely that the overall findings can be explained by regression towards the mean. Only one previous study examined the impact of MBSR on cardiovascular and autonomic reactivity specifically. In their randomized-controlled trial of 88 healthy individuals, Nyklicek and colleagues (2013) reported that participation in MBSR resulted in significant decreases in SBP and DBP reactivity compared to waitlist controls, but no change in LF, HF, or LF/HF post-intervention. However, these authors did not stratify their sample according to initial stress response; if reactivity groupings had been combined in our analyses, changes observed for HR and HF may have been occluded.

Despite initial promising results, limitations of this pilot study need to be considered. An average of approximately two years (± 6 months) elapsed between participation in Study 2 and the first evaluation of Study 3, allowing substantial time for changes in initial stress response style. However, we previously reported in a longitudinal study with three year follow-up that cardiovascular and autonomic stress responses represent individual traits that are stable over time (Dragomir, Gentile, Nolan, & D'Antono, 2014). Possible habituation or practice effects across repeated administrations of the stress protocol may have also occurred. However, participants reported significant increases in subjective stress and decreases in positive affect across all three evaluation sessions; in fact, the highest level of arousal (and lowest positive affect) was reported during the third administration of the stress protocol. Finally, the investigation consisted of a very small sample size. Results need to be replicated on a grander scale before reliable conclusions about the impact of MBSR on metabolic parameters and stress reactivity outcomes can be made.

On the other hand, this pilot study was a randomized controlled trial that employed rigorous methodology. The sample was clustered by initial stress response grouping and sex, and the randomization groups did not differ significantly from each other at baseline. The MBSR program was animated by an experienced psychologist who was widely appreciated by participants. Participants also had access to high quality materials (e.g. yoga mats, meditation cushions, chairs) in order to facilitate mindfulness practice during sessions. Different debate topics were also chosen for each evaluation of the stress protocol, which limited participants' ability to practice in between sessions.

Future directions and clinical relevance associated with this study are addressed in the general discussion, beginning on page 162.

Conclusion

This investigation revealed that implementing MBSR in an elderly population with current or past metabolic syndrome is largely feasible and highly acceptable to participants. This illustrates the pertinence of conducting a larger-scale replication study in order to further investigate whether MBSR impacts metabolic profile and stress responses in heightened and blunted responders. Preliminary evidence from this chapter suggests that MBSR may yield positive changes in metabolic parameters, especially cholesterol, to a clinically significant level. MBSR also appears to have potential with regard to normalizing stress responses, particularly those of the autonomic system. In sum, this pilot study corroborates the pathogenic role of stress responses in metabolic dysfunction, and generally supports the potential reversibility of such effects through stress management.

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Table 1

Participant characteristics (Mean ± SD) at Evaluation 1 (Baseline)

	***n* = 19**
Sex (*n*, % male)	7 (37%)
Age (years)	67.2 ± 7.70
Weight (kg)	82.8 ± 13.54
Body Mass Index (kg/m^2)	30.9 ± 4.50
Years of schooling	14.1 ± 2.90
Marital Status *n* (%)	
Single	4 (21%)
Civil union/married	11 (58%)
Separated/divorced	4 (21%)
Employment Status *n* (%)	
Full-time	4 (21%)
Part-time	3 (16%)
Retired	11 (63%)
Annual family income *n* (%)	
≤ $29 999	5 (26%)
$30 000 - $59 999	6 (32%)
$60 000 - $99 999	4 (21%)
≥ $100 000	4 (21%)
Smoker *n* (%)	0 (0%)
Hours of exercise/week	3.9 ± 3.79
Medications	
BP agents	11 (58%)
Blood glucose regulators	4 (21%)
Dyslipidemic agents	11 (58%)
Anxiolytics	4 (21%)
Baseline Metabolic Parameters	
SBP (mm Hg)	133.6 ± 12.9
DBP (mm Hg)	64.9 ± 9.05
Waist circumference (cm)	102.4 ± 10.3
Glucose (mmol/L)	5.8 ± 1.14
Triglycerides (mmol/L)	1.5 ± 0.69
HDL (mmol/L)	1.4 ± 0.29
LDL (mmol/L)	2.6 ± 1.03
Total cholesterol (mmol/L)	4.7 ± 1.18
Baseline ANS Measures	
HR (bpm)	71.5 ± 9.7
HF-HRV (ms^2)	958.4 ± 2609.5
LF/HF	2.09 ± 2.07
HF_{nu}	0.46 ± 0.26

Note. SBP = systolic blood pressure, DBP = diastolic blood pressure, HDL = high-density lipoprotein cholesterol, LDL = low-density lipoprotein cholesterol, HR = heart rate, HF-HRV = high frequency heart rate variability, HF_{nu} = high frequency heart rate variability in normalized units.

Table 2

Acceptability of MBSR Program

	n	*0 Not at all*	*1 A little bit*	*2 Moderately*	*3 Very*	*4 Extremely*
*1. To what extent did you find the MBSR program **efficacious**?*	17	0%	6%	29%	53%	12%
*2. To what extent did you find the MBSR program **appropriate**?*	17	0%	12%	12%	64%	12%
*3. To what extent did you find the MBSR program **acceptable**?*	17	0%	6%	18%	70%	6%
*4. To what extent did you find each of the following components of MBSR to be **beneficial?***						
a) Teacher instruction	17	0%	0%	6%	82%	12%
b) Meditation – lying down	17	18%	0%	29%	47%	6%
c) Meditation – sitting	16	12.5%	12.5 %	6%	50%	19%
d) Meditation – walking	15	6%	20%	47%	27%	0%
e) Meditation – loving-kindness	13	15%	8%	23%	31%	23%
f) 5 hour meditation retreat	13	8%	15%	31%	38%	8%
g) Yoga postures	16	6%	19%	19%	56%	0%
h) Group discussion	16	6%	6%	31%	50%	6%
i) Home exercises	17	6%	12%	35%	29%	18%
5. To what extent would you participate in the MBSR program again?	16	12%	12%	12%	29%	35%
6. How likely are you to continue your mindfulness practice?	16	0%	13%	25%	56%	6%
7. To what percentage of people would you recommend MBSR? M (SD)	12	89% (15.09)				

Note . For a full copy of the questionnaire, see Appendix C. The Likert Scale ranged from 0 (not al all) to 4 (extremely). As of question 3c, the number of respondents per question varies, as those who dropped out of MBSR did not respond to questions regarding aspects they did not participate in.

Table 3

MBSR Group Versus Waitlist Control Group Differences in Metabolic Parameter Change Scores from Evaluation 1 (Baseline) to Evaluation 2 Using an Intention to Treat Approach

	MBSR Group (n = 9)			Waitlist Group (n =9)					
Change Scores	*M change*	*SD*	*% change*	*M*	*SD*	*% change*	*p*	*Cohen's d*	*Size of Effect*
Waist circumference (cm)	-1.00	1.80	-1.00%	0.08	2.87	-0.07%	p = .36	.45	Medium
SBP (mm Hg)	-5.91	15.60	-4.44%	-6.17	15.04	-4.59%	p = .82	.02	Very Small
DBP (mm Hg)	-3.49	7.85	-5.5%	-0.90	6.19	-1.37%	p = .33	.37	Small to Medium
Glucose (mmol/L)	0.23	0.66	+4.04%	0.32	0.53	+5.54%	p = .63	.15	Small
Triglycerides (mmol/L)	0.01	0.21	+0.55%	0.21	0.35	+11.5%	p = .23	.71	Medium to Large
HDL (mmol/L)	-0.08	0.13	-5.49%	0.04	0.25	+2.78%	p = .11	.29	Small
LDL (mmol/L)	-0.40	0.54	-14.97%	-0.12	0.34	-4.54%	p = .64	.64	Medium to Large
Total cholesterol (mmol/L)	-0.49	0.68	-10.44%	-0.05	0.56	-0.94%	p = .90	.72	Medium to Large

Note . SBP = systolic blood pressure, DBP =diastolic blood pressure, HDL = high density lipoprotein cholesterol, LDL = low density lipoprotein cholesterol

Effect sizes near .2 are considered small, near .5 are considered medium, and near .8 are considered large (Cohen 1988).

Table 4

Differences in Metabolic Parameters (Immediately Pre- and Post-MBSR) Using an Intent-to-Treat Approach (n = 19)

	Pre-MBSR	*Post-MBSR*					
Change Scores	*M (SD)*	*M (SD)*	*% change*	*F*	*p*	η^2	*Size of Effect*
Waist circumference (cm)	102.39 (10.8)	100.83 (10.9)	-1.52%	F(1,17)=10.82	p = .004	0.39	Large
SBP (mm Hg)	128.50 (14.9)	127.71 (19.8)	-0.61%	F(1,16)=0.04	p = .84	.00	Negligible
DBP (mm Hg)	62.27 (6.6)	60.00 (0.08)	-3.65%	F(1,16)=1.46	p = .25	.08	Medium
Glucose (mmol/L)	5.98 (1.2)	6.15 (1.6)	+2.84%	F(1,16)=1.20	p = .29	.07	Medium
Triglycerides (mmol/L)	1.56 (0.6)	1.55 (0.7)	-0.64%	F(1,16)=0.03	p = .87	.00	Negligible
HDL (mmol/L)	1.42 (0.3)	1.41 (0.3)	-0.70%	F(1,16)=0.07	p = .80	.00	Negligible
LDL (mmol/L)	2.67 (1.0)	2.40 (1.0)	-9.45%	F(1,16)=5.64	p = .03*	.26	Large
Total cholesterol (mmol/L)	4.78 (1.1)	4.51 (1.0)	-5.65%	F(1,16)=3.82	p = .07	.19	Large

Note. Waist circumference is missing for one participant; BP, glucose, triglycerides, and cholesterol are missing for two participants, as two individuals did not complete Evaluation 3.
SBP = systolic blood pressure, DBP =diastolic blood pressure, HDL = high density lipoprotein cholesterol, LDL = low density lipoprotein cholesterol

Table 5

Differences in Metabolic Parameters (Pre- and Post-) for Completers of MBSR Only (n=13)

	Pre-MBSR	*Post-MBSR*				
Change Scores	*M (SD)*	*M (SD)*	*% change*	*p*	η^2	*Size of Effect*
Waist circumference (cm)	104.15 (11.1)	102.46 (10.8)	-1.62%	p = .01	.45	Large
SBP (mm Hg)	129.14 (14.8)	129.49 (19.6)	+0.27%	p = .93	.00	Negligible
DBP (mm Hg)	61.33 (5.64)	59.43 (7.8)	-3.10%	p = .33	.08	Medium
Glucose (mmol/L)	6.21 (1.3)	6.33 (1.7)	+1.98%	p = .53	.03	Small
Triglycerides (mmol/L)	1.60 (0.7)	1.60 (0.8)	0.00%	p = .99	.00	Negligible
HDL (mmol/L)	1.41 (0.3)	1.36 (0.2)	-3.55%	p = .30	.09	Medium
LDL (mmol/L)	2.62 (1.0)	2.30 (0.9)	-12.21%	p = .03	.33	Large
Total cholesterol (mmol/L)	4.75 (1.2)	4.39 (1.0)	-7.58%	p = .05	.28	Large

Note . SBP = systolic blood pressure, DBP =diastolic blood pressure, HDL = high density lipoprotein cholesterol, LDL = low density lipoprotein cholesterol

Tables 7a and 7b

Within-Subjects Analysis using Reactivity Change Scores in Heightened LF/HF Responders (n=10)

	Pre-MBSR	*Post-MBSR*				
Change Scores	*M (SD)*	*M (SD)*	*% change*	*p*	η^2	*Size of Effect*
SBP (mm Hg)	21.08 (10.6)	22.80 (11.3)	+8.2%	p = .59	.03	Small
DBP (mm Hg)	8.31 (8.7)	8.85 (6.2)	+6.5%	p = .80	.01	Small
HR (bpm)	4.65 (1.7)	4.18 (2.2)	-10.1%	p = .44	.07	Medium
HF-HRV (m/s^2)	-0.16 (0.4)	-0.15 (0.2)	+7.5%	p = .92	.00	Negligible
LF/HF (m/s^2)	0.36 (0.27)	0.24 (0.29)	-32.0%	p = .34	.10	Medium to Large
HFnu	-0.16 (0.16)	-0.10 (0.14)	+6.0%	p = .28	.13	Medium to Large

Within-Subjects Analysis using Reactivity Change Scores in Blunted LF/HF Responders (n=7)

	Pre-MBSR	*Post-MBSR*				
Change Scores	*M (SD)*	*M (SD)*	*% change*	*p*	η^2	*Size of Effect*
SBP (mm Hg)	26.60 (12.5)	17.68 (12.2)	-33.5%	p = .03	.58	Large
DBP (mm Hg)	12.14 (5.1)	7.33 (4.4)	-39.6%	p = .03	.58	Large
HR (bpm)	4.41 (4.8)	5.41 (6.2)	+22.7%	p = .32	.20	Large
HF-HRV (m/s^2)	0.10 (0.14)	-0.08 (0.42)	-17.7%	p = .23	.27	Large
LF/HF (m/s^2)	0.06 (0.21)	0.04 (0.48)	-37.5%	p = .84	.01	Small
HFnu	-0.04 (0.09)	-0.06 (0.18)	-40.0%	p = .70	.03	Small

Note **.** HF and LF/HF were log transformed in order to increase the normality of their distributions.
Change scores = stress score minus baseline score for every parameter. Parasympathetic activation (HF) is expected to decrease during stress; in hyper-responders, we expected *less* parasympathetic withdrawal following participation in MBSR. In contrast, in hypo-responders, we expected *greater* parasympathetic withdrawal. Stress response data is missing for one participant due to error during testing.

Table 8a

Pearson Correlations (r) between Percent Change in Reactivity Parameters and Percent Change in Metabolic Parameters in Heightened LF/HF Responders (n=10)

	WC	SBP	DBP	Glucose	Total Cholesterol	HDL	LDL	Triglycerides
ΔSBP (mm Hg)	.36	-.19	.20	.78**	.44	-.12	.15	.68*
ΔDBP (mm Hg)	.16	-.21	-.44	-.32	-.02	.46	.07	-.59
ΔHR (bpm)	.10	-.00	-.07	.31	.03	-.03	-.10	.13
ΔHF-HRV (m/s^2)	.29	.32	-.14	.11	-.73*	-.17	-.66*	-.48
ΔLF/HF (m/s^2)	.23	.20	.33	-.25	.37	.49	.30	-.05
ΔHFnu	-.13	-.20	-.13	.16	.08	-.44	.25	.35

Note . HF and LF/HF were log transformed in order to increase the normality of their distributions.
*p<0.05, **p<0.01; *r*=0.1: small effect, *r*=0.3: moderate effect, *r*>0.5: large effect

Table 8b

Pearson Correlations (r) between Percent Change in Reactivity Parameters and Percent Change in Metabolic Parameters in Blunted LF/HF Responders (n=7)

	WC	SBP	DBP	Glucose	Total Cholesterol	HDL	LDL	Triglycerides
ΔSBP (mm Hg)	.02	.06	-.26	-.63	.52	.44	.13	.63
ΔDBP (mm Hg)	-.29	-.27	-.62	-.80*	.22	.07	-.14	.48
ΔHR (bpm)	-.16	.05	.19	-.63	.41	.31	.06	.63
ΔHF-HRV (m/s^2)	-.33	.07	-.37	-.29	.44	.26	.01	.90*
ΔLF/HF (m/s^2)	.23	.20	.33	-.25	.37	.49	.30	-.05
ΔHFnu	.27	.32	.25	-.20	.52	.59	.42	.04

Note . HF and LF/HF were log transformed in order to increase the normality of their distributions.
*p<0.05, **p<0.01; r=0.1: small effect, *r*=0.3: moderate effect, *r*>0.5: large effect

Figure 2. Breakdown of participant recruitment.

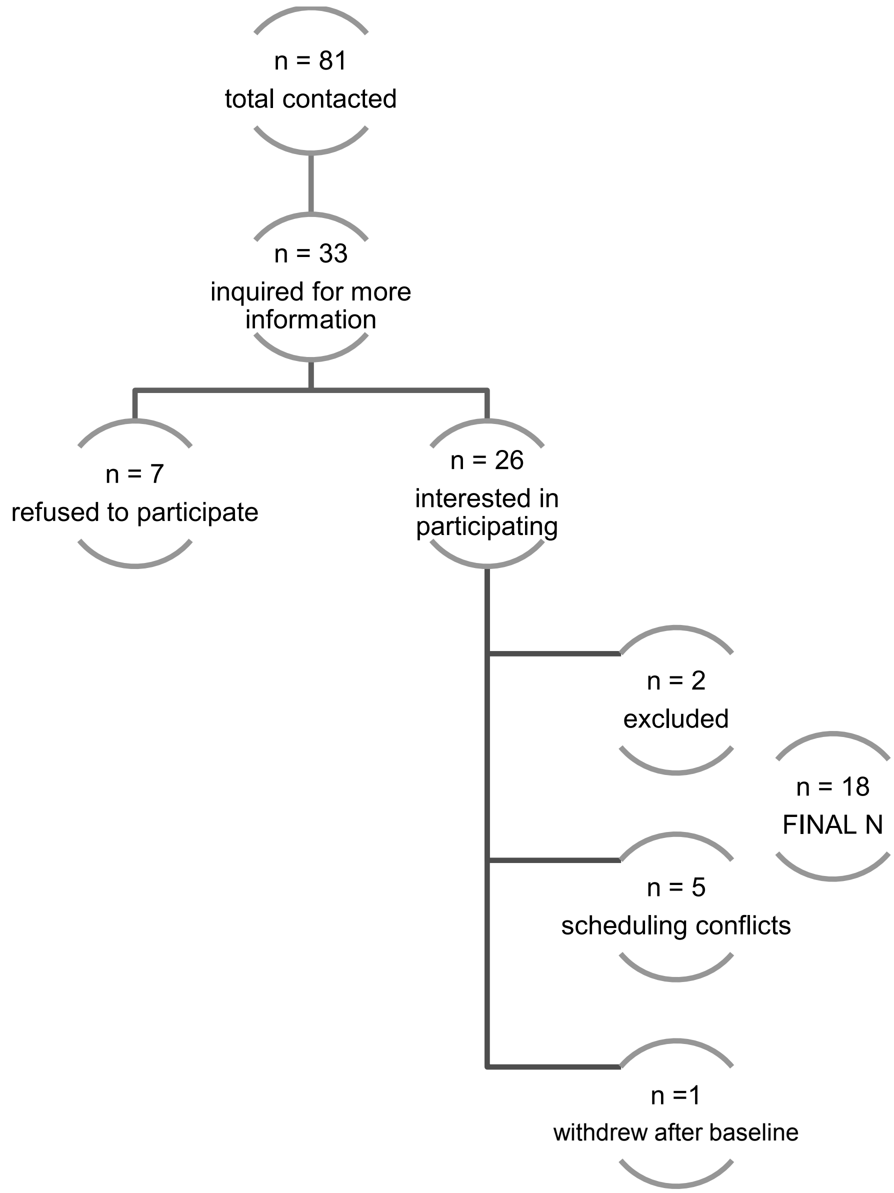
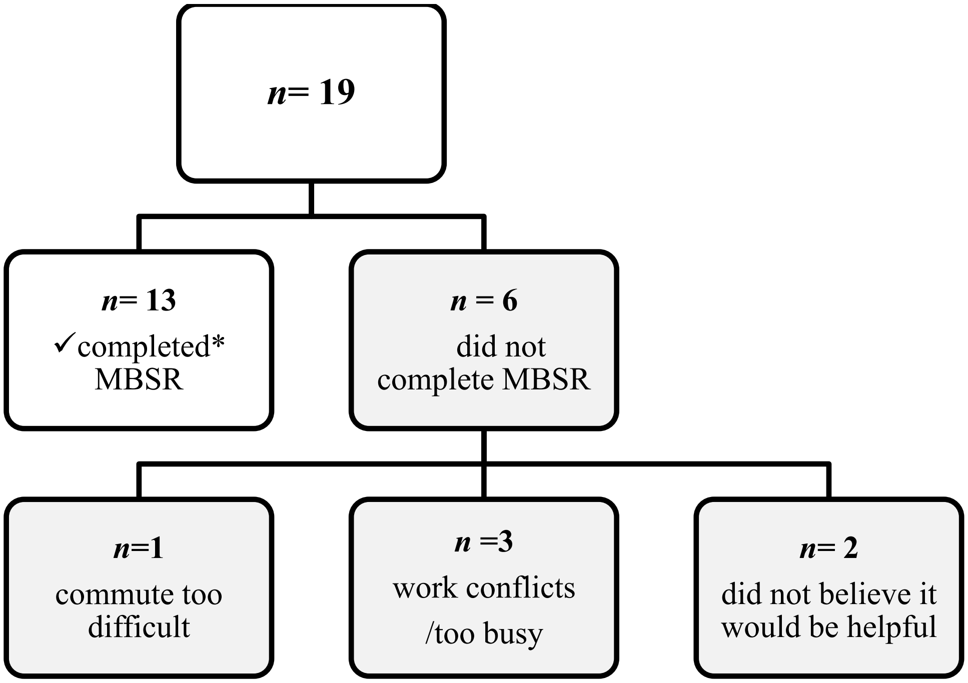


Figure 3. Summary of MBSR Program Completion



Note. *Attendance of at least 7 out of 9 sessions was required for program completion. Program completers (*n*=13) attended 97% of total MBSR sessions.

GENERAL DISCUSSION

This thesis aimed to elucidate the role of physiological stress responses in metabolic dysfunction and examine whether sex differences exist in this regard. This was achieved through three independent investigations. The first two evaluated whether physiological responses to psychological stress were concurrently (Study 2) and prospectively (Study 1) associated with metabolic disturbances while examining the moderating effect of sex. The third study was a randomized controlled pilot trial which sought to assess the feasibility and acceptability of mindfulness-based stress reduction in an older sample of individuals with current or past metabolic syndrome and heightened or blunted autonomic response styles. This thesis provides robust evidence for the importance of autonomic stress responses to metabolic activity and identified notable sex differences in these associations.

More specifically, a pattern involving hyper-reactivity of the autonomic nervous system and incomplete recovery from stress (as measured via larger increases in HR and exaggerated withdrawal of parasympathetic activity) was associated with greater risk of metabolic burden or metabolic syndrome in concurrent and prospective analyses. This was observed in both women (Study 2) and men (Studies 1 and 2). In women, however, additional stress response patterns involving either blunted autonomic responses or stress-related increases in parasympathetic activity also increased metabolic risk. Finally, the pilot investigation suggested that stress reduction via MBSR is largely feasible and acceptable in an older population with compromised metabolic profiles and non-normative stress responses, and provided preliminary evidence supporting the reversibility of metabolic dysfunction through stress management. The latter further illustrates the importance of stress responses to metabolic health.

Results in Context

The fact that associations between stress responses and metabolic outcomes were specific to the autonomic nervous system in both cross-sectional and longitudinal investigations of this thesis strongly supports the role of autonomic stress responses in the pathogenesis of metabolic abnormalities. Hu, Lamers, de Geus, and Penninx (2016) are the only other authors to our knowledge to investigate the contribution of autonomic stress responses to metabolic syndrome risk. In their recent longitudinal study, a large sample of middle-aged individuals with current or past history of mood disorders underwent a stress protocol comprised of a 45 minute psychiatric interview and the n-back task, a cognitive stressor. Exaggerated parasympathetic reactivity (as indicated by greater decrease in respiratory sinus arrhythmia) during the stress protocol was associated with concurrent elevations in triglycerides, glucose, waist circumference, and number of overall metabolic syndrome components met. In longitudinal analyses (4 years later), individuals who demonstrated greater parasympathetic reactivity (withdrawal) to the cognitive stressor met a greater number of metabolic syndrome components. Informed by our first study, (Gentile, Dragomir, Solomon, Nigam, & D'Antono, 2014), Hu and colleagues (2016) also tested the interaction between sex and autonomic responses in their model. Cross-sectional and prospective relations between parasympathetic reactivity and number of metabolic syndrome components were more robust in women.

These results are highly consistent with what was observed in our second study in which women demonstrating exaggerated parasympathetic withdrawal during stress were more likely to meet the criteria for metabolic syndrome. Interestingly, women displaying this stress response style in Study 2 reported greater levels of psychological distress compared to women exhibiting intermediate levels of parasympathetic withdrawal or blunted/stress-related increases in parasympathetic activation. As mentioned above, all participants recruited by Hu et al. (2016) had a current or past history of mood and/or anxiety disorders. Depression, anxiety, and stress, even at sub-clinical levels, have all been associated independently with metabolic syndrome (Chandola, Brunner, & Marmot, 2006; Cohen, Panguluri, Na, & Whooley, 2010; Goldbacher & Matthews, 2007; Roohafza, Sadeghi, Talaei, Pourmoghaddas, & 2012; Steptoe & Kivimaki, 2013). This thesis and results from Hu et al. (2016) suggest that exaggerated parasympathetic responses to stress and greater psychological vulnerability may be a particularly adverse combination with regard to metabolic syndrome risk in women, though this remains to be verified. It is equally possible that hyper-reactivity may be a manifestation of increased psychological distress in these individuals. For instance, anger and hostility have been associated with greater reactivity to stress, especially in response to interpersonal stressors (Suls & Wan, 1993; Vella & Friedman, 2009). Alternatively, both heightened reactivity and increased psychological distress may reflect some other underlying problem that has not yet been elucidated in research.

The results of this thesis also suggest increased risk for metabolic burden in healthy men as a result of greater autonomic stress reactivity. In Study 1, exaggerated parasympathetic withdrawal predicted greater metabolic burden in healthy men after a three year follow-up. This is consistent with previous research indicating that heightened blood pressure reactivity to stress increases risk for hypertension in various populations including healthy individuals (Chida & Steptoe 2010; Carroll et al., 2012). Moreover, in Study 2, an overall heightened HR response profile (i.e. higher basal HR, followed by greater HR reactivity and less HR recovery) was associated with increased odds of meeting metabolic syndrome criteria in men (and women). The data pertaining to HR responses and metabolic outcomes in the literature are mixed; while some authors report that elevated HR reactivity is adverse for BP, cholesterol, and triglyceride levels (Chida & Steptoe, 2010; Jorgensen, Nash, Lasser, Hymowitz, & Langer, 1988), others have demonstrated that greater HR reactivity is associated with *less* central adiposity both cross-sectionally and prospectively (Carroll, Phillips, & Der, 2008; Hu et al., 2016; Phillips, Roseboom, Carroll, & de Rooij, 2012). Of note, HR responses were not associated with metabolic burden in Study 1; this may be because residual change scores controlled for HR at baseline in that investigation. Indeed, high resting HR is considered a marker of autonomic imbalance, and has been associated with greater risk of metabolic abnormalities (Hu et al., 2016; Licht, de Geus, & Penninx, 2013). However, baseline HR was also controlled for in large-scale studies reporting significant negative associations between HR reactivity and central adiposity, suggesting that results were driven by stress-induced changes in HR rather than HR at rest (Carroll et al., 2008; Phillips et al., 2012). Supplemental analyses utilizing HR change scores in Study 2 (instead of clusters) suggested that delayed HR recovery may be a risk factor for metabolic syndrome independent of baseline HR. In Chida & Steptoe's meta-analysis examining 30 associations of cardiovascular recovery responses and negative cardiovascular endpoints, poor HR recovery similarly emerged as a consistent predictor of poor future cardiovascular status, such as greater carotid intima-media thickness (marker of atherosclerosis) and higher resting BP (Chida & Steptoe, 2010).

Exaggerated or prolonged parasympathetic responses are thought to reflect disturbances in prefrontal functioning (Park & Thayer, 2014). The prefrontal cortex is responsible for self-regulation, which refers to the ability to regulate thoughts, emotions, and behaviors in response to fluctuating external demands (Gross, 1998; Park & Thayer, 2014; Segerstrom & Nes, 2007; Thayer & Lane, 2000). For instance, in a potentially dangerous situation, feeling fear is adaptive as it is coupled with heightened sympathetic activation in preparation to cope with the possible threat (Thayer & Lane, 2000). Once the danger has subsided, the prefrontal cortex identifies safety cues in the environment, fear diminishes, and parasympathetic dominance is restored (Park & Thayer 2014; Thayer & Lane, 2000). However, prefrontal deficiencies may lead to the faulty interpretation of non-aversive stimuli as threatening or failure to identify safety cues upon dissolution of the stressor. This in turn results in exaggerated parasympathetic withdrawal and/or poor parasympathetic recovery post-stress. This contributes to or is associated with hyper-active sympathetic activity and prolonged activation of defense mechanisms including hyper-vigilance and rumination (Brosschot, Gerin, & Thayer, 2006; Thayer, Åhs, Fredrikson, Sollers, & Wager, 2012; Thayer & Lane 2000). Unnecessary and prolonged activation of sympathetic processes can lead to inflammation and facilitates disease processes consistent with allostatic load (McEwen, 1998). It is also not surprising that prefrontal inhibitory disturbances have been linked to deficits in psychological flexibility as well as various psychopathologies including anxiety disorders (Johnstone, van Reekum, Urry, Kalin, & Davidson, 2007; Kim & Whalen, 2009; Lewis, Hashimoto, & Volk, 2005; Li & Sinha, 2008). This is in line with our Study 2 data in which women with exaggerated parasympathetic response styles also had higher levels of psychological distress.

The Importance of Sex Differences

Sex moderated the relation between autonomic stress response patterns and metabolic outcomes in the first two articles of this thesis. While autonomic reactivity to psychological stress has been seldom examined in general, sex differences in overall HRV in healthy individuals has received considerable attention (for a meta-analysis, see Koenig & Thayer, 2016). Specifically, women tend to exhibit greater parasympathetic activation at rest whereas in men, sympathetic activity is dominant (Koenig & Thayer, 2016). Greater tonic parasympathetic activity is generally regarded as a protective factor against cardiovascular disease and other adverse health outcomes (Jarczok et al., 2015). This rationale is often used to explain why women tend to be less at risk for cardiovascular disease, diabetes, hypertension, stroke, and all-cause mortality compared to men (Thayer & Lane, 2007; Thayer, Yamamoto, & Brosschot, 2010). Interestingly, women in Study 2 (but not Study 1) displayed significantly *less* parasympathetic activity at baseline than men. This difference may be attributable to sample characteristics. Women in Study 2 were more compromised than men with regard to their mental health and psychological distress has been independently associated with lower HRV (Carney, & Freedland; Kemp, Quintana, Felmingham, Matthews, & Jelinek, 2012).

Sex differences in stress perception across the protocol were also observed across studies; women consistently rated the stressors as more subjectively arousing and negative than men. This is in line with previous research indicating that although men and women are exposed to an equivalent number of acute stressors in their daily lives, women tend to rate these events as more stressful than men (Allen, Bocek, & Burch, 2011; Brougham, Zail, Mendoza, & Miller, 2009; Bebbington, 1996; Maciejewski, Prigerson, & Mazure, 2001). Additional analyses (not shown) indicated that while men reported subjective increases in anger and stress during the stress task in Study 2, they returned to baseline levels in these parameters once the stressor subsided. Women, regardless of their stress response style, continued to report higher levels of stress and anger during the recovery period of the stressor, indicative of possible rumination. Although many definitions exist, rumination is generally characterized as a cognitive process including repetitive, intrusive, and negative thoughts in the absence of immediate external demands requiring these thoughts (Martin & Tesser, 1996; Papageorgiou & Siegle, 2003). Prolonged rumination in response to stressors has been associated with elevated BP, low HRV, and various other adverse cardiovascular, immune, and neuroendocrine outcomes (for a review, see Brosschot, Gerin, & Thayer, 2006). Sex differences in stress perception and rumination may shed light as to why women appeared to be more vulnerable to the adverse impact of non-normative stress responses, particularly blunted reactions and stress-related vagal increases.

Theoretical Implications of Thesis Findings

The stress reactivity hypothesis revisited. This thesis provides partial support for the stress reactivity hypothesis which posits that individuals displaying greater physiological reactivity to acute stressors are more likely to experience hypertension and other adverse cardiovascular endpoints (Obrist, 1981). However, the stress reactivity hypothesis in its original formulation is incomplete; not only does it fail to address the importance of recovery, but is also does not account for non-normative responses at the other end of the reactivity spectrum. Discussion of such responses is newer to the literature. Lovallo (2011) spoke of "*blunted"* stress responses in cases where individuals showed little or no physiological arousal in response to a stressor. Although the reactivity hypothesis does not address blunted responses explicitly, it was initially assumed that low or blunted reactivity was benign or protective against disease (Brindle, Ginty, Phillips, & Carroll, 2014). However, a growing body of evidence suggests that blunted stress responses are associated with or may predispose individuals to poor physical and mental health (Carroll et al., 2008; Cohen et al., 1998; Deschamps et al., 2013; Lovallo, 2011; Phillips et al., 2012; Singh & Shen, 2013; Thayer & Lane, 2007; Thayer, Yamamoto, & Brosschot, 2010; Weinberg, Klonsky, & Hajcak, 2009). For instance, blunted cardiovascular reactivity has been associated with abdominal obesity in a few large-scale longitudinal studies (Carroll et al., 2008; Phillips et al., 2012; Singh & Shen, 2013). Depression has also been linked with blunted stress responses in both cross-sectional and prospective investigations and across various samples including undergraduate students and individuals with CVD (Brinkmann, Schüpbach, Joye, & Gendolla, 2009; Carroll, Phillips, Hunt, & Der, 2007; Gordon, Ditto, & D'Antono, 2012; Phillips, Hunt, Der, & Carroll, 2011; Salomon, Clift, Karlsdottir, & Rottenberg, 2009; Schwerdtfeger, & Rosenkaimer, 2011; York et al. 2007). Other mental health issues such as borderline personality disorder (Weinberg et al., 2009), post-traumatic stress disorder (Cohen et al., 1998), and bullimia nervosa (Ginty, Phillips, Higgs, Heaney, & Carroll, 2012; Koo-Loeb, Pedersen, & Girdler, 1998) have also all been associated with blunted stress responses. However, in these investigations, stress responses were examined as outcomes of psychological distress, not as its predictor. It is thus possible that psychological distress may be contributing to blunted physiological response patterns rather than the reverse.

Blunted autonomic stress responses in women were associated with metabolic abnormalities both concurrently and prospectively in our studies. Few authors have examined blunted autonomic responses to challenges in relation to health outcomes. A study from our group demonstrated that patients with a blunted parasympathetic response to an autonomic challenge (valsalva maneuver) had higher rates of complications during and after cardiac surgery, independent of ANS activation at baseline, compared to patients with greater autonomic responses to the same task (Deschamps et al., 2013). Research by Park and Thayer (2014) may shed light as to what blunted parasympathetic responses represent in our work. Typically, in the presence of a stressor, defense systems are activated and parasympathetic withdrawal occurs, a process described by the authors as phasic HRV suppression (Park & Thayer, 2014). In other words, parasympathetic activity is suppressed or withdrawn, allowing for the successful activation of sympathetic mechanisms to cope with the stressor. However, in situations requiring emotional regulation (e.g. suppressing anger in a work meeting) or self-regulatory behavior (e.g. choosing to eat carrots over cookies), phasic HRV *enhancement* occurs resulting in lack of vagal withdrawal or blunted vagal response, which facilitates successful regulation (Park & Thayer, 2014). The interpersonal stressors included in this thesis may have evoked unpleasant emotional experiences in our participants (e.g. anger, feelings of failure) which they may have attempted to *suppress* in the presence of the research assistant administering the protocol. Although only a hypothesis, it is possible that efforts to suppress emotions were related to greater phasic HRV enhancement or a blunted vagal response. Although the ability to suppress anger or other emotional experiences may be adaptive in the short-term, repeated suppression has been linked to various adverse health endpoints (Mauss, & Gross, 2004; Quartana, Bounds, Yoon, Goodin, & Burns, 2010; Vögele, Jarvis, & Cheeseman, 1997).

Interestingly, greater HRV enhancement has typically been observed in individuals with higher resting HRV (Segerstrom & Nes, 2007). This was the case in Study 1 in which elevated baseline HRV was associated with blunted autonomic response, which was in turn associated with greater metabolic burden among women. High baseline levels of parasympathetic activity may reflect the organism's attempt to limit repeated disturbances to homeostasis, the long-term cost of which may be the inability of the parasympathetic system to adapt sufficiently to regular life demands (Porges, 1992). Indeed, in our prior study in patients undergoing cardiac surgery, predictors of autonomic dysfunction (or blunted response) also included higher baseline parasympathetic activation (Deschamps et al., 2013).

Other mechanisms by which blunted stress responses lead to adverse health outcomes have also been proposed. For instance, blunted responses have been said to reflect an inability of the individual to physiologically adapt to stress due to an overall deteriorating stress response as a result of chronic exposure to stressful conditions (Phillips et al., 2012). Indeed, chronic and prolonged exposure to stressful conditions may lead to a down-regulation of beta-adrenergic receptors (or stress receptors) in an attempt to guard against the consequences of repeated sympathetic activation. This in turn may result in a blunted stress response which may lead to compensatory inflammatory action, increasing vulnerability to disease (de Rooij, 2013; McEwen, 1998). However, our pattern of results does not support an overall failing stress response as blunted responses were observed for LF/HF and HF indices only, and not BP or HR measures, across both articles.

Others have posited that blunted responses may reflect the perception of elevated task difficulty. If a task is deemed too challenging, the individual may feel helpless and engage in passive coping; that is, invest little physiological or behavioral resources to cope resulting in a blunted stress response (Carroll, Turner, & Prasad, 1986; Richter, Friedrich, & Gendolla, 2008; Richter & Gendolla, 2006). On the other hand, during active coping (i.e. when an individual makes an effort to cope with challenges),there is mobilization of resources which leads to increases in cardiovascular activity due in part to increased beta-adrenergic stimulation (Wright, 1996). In support of this, Richter and colleagues (2008) tested the impact of four levels of task difficulty (low, moderate, high, impossible) on SBP reactivity to the Sternberg item-recognition task in 64 undergraduate students. During the impossible condition, the task was perceived as unreasonable and/or unachievable, resulting in little mobilization of physiological resources and a diminished SBP response (Brehm & Self, 1989; Richter, Friedrich, & Gendolla, 2008). Elevated task difficulty has also resulted in less cardiovascular reactivity in earlier research (Smith, Baldwin, & Christensen, 1990), although some conflicting results have emerged (Willemsen, Ring, McKeever, & Carroll, 2000). Results from this thesis also do not support this hypothesis; although the stressors were rated as subjectively stressful and arousing by participants, the tasks were not perceived as impossible or overly difficult.

This thesis and other research reporting associations between blunted responses and metabolic outcomes highlight the importance of including subjective measures of task stressfulness when examining acute stress responses. Specifically, the addition of affect, arousal, and self-reported stress measures in this thesis provided useful information as to how the stressors were perceived despite little change in autonomic response in some individuals. Justifying task stressfulness by solely examining significant increases in physiological parameters may not be appropriate for blunted responders; as we have shown, these individuals may be subjectively stressed by the task, but not physiologically responsive across all measures. Indeed, depending on the array of measures obtained by any particular study, one might inappropriately presume an overall lack of physiological response when in fact there was a lack of response across a limited number of measures.

Does A Healthy Level of Reactivity Exist?

This thesis provided considerable evidence indicating that autonomic responses on both ends of the reactivity spectrum are disadvantageous for metabolic health. This begs the question: does a healthy level of reactivity exist? Authors have speculated that *moderate* reactions may be the most adaptive responses to stress, especially in healthy individuals (Chumaeva et al., 2015; Lovallo, 2013; Phillips, Ginty, & Hughes, 2013). According to some, moderate or "normative" stress responders include individuals in the middle range of stress response situated between the two extremes (Lovallo, 2011; Phillips et al., 2013). Indeed, in Article 2, women with a moderate response to stress had the lowest odds of meeting metabolic syndrome criteria, although the same was not true for men. The reasons for this are unclear; however, it is possible that the other metabolic syndrome risk factors men displayed (e.g. significantly higher BMI than women, more likely to smoke) occluded the possible protective effects of a moderate stress response.

Nevertheless, our results are in line with those of Chumaeva et al. (2015) who demonstrated that in participants with good vascular health (as indicated by elasticity of blood vessels), *moderately* high HR reactivity to a mental arithmetic and public speaking task was associated with less incidence of atherosclerosis. The authors suggested that successful activation of sympathetic mechanisms in stressful situations may be adaptive in the short-term in healthy individuals, but incur risk when these activations are chronic and/or prolonged. Porges (1992) also proposed that the ability to exhibit moderate cardiac responsiveness to stress (as indicated by HR and autonomic parameters) as opposed to hyper- or blunted-reactivity may reflect behavioral flexibility and mobilization of resources indicative of successful coping. For instance, when a potential danger is identified, physiological and behavioral changes consistent with the "fight or "flight" response ensue, enabling the individual to respond to the threat. This may include rapid changes in cardiovascular and autonomic reactivity. However, in the case of generalized anxiety disorder for example, individuals are less able to shift their emotions, behaviors, and thoughts to match the demands of the environment, resulting in over-active sympathetic responses (Friedman, & Thayer, 1998; Thayer, & Friedman, 1997). In other words, defensive reactions such as hyper-vigilance and perseverative cognition (e.g. worrying, rumination) may persist even if a real source of danger has not been identified (Brosschot, Gerin, & Thayer, 2006; Park, Vasey, Van Bavel, & Thayer, 2013; Thayer & Lane, 2000; Thayer, Hansen, Saus-Rose, & Johnsen, 2009). This in turn results in behavioral rigidity, as it limits the perceived number of available coping behaviors to deal with the "danger" (e.g. avoidance, escape) (Thayer & Lane, 2000). Although these coping mechanisms may feel adaptive in the short-term, they limit exposure to alternative information related to the perceived threat, which maintains fear and anxiety unnecessarily in the long-term (Kemp et al., 2012; Tallis & Eysenck, 1994; Thayer & Lane, 2000).

Measurement Considerations in Stress Response Literature

This thesis further illustrated that heightened responses to stress cannot be automatically considered pathological (Heponiemi et al., 2007). Whether high cardiac reactivity is followed by quick and efficient recovery, or alternatively, followed by delayed or inadequate recovery, drastically changes the overall response profile and has distinct implications for disease risk. The combination of moderately high reactivity with quick and efficient recovery may represent the most favorable stress response pattern as it reflects the capacity of the individual to adapt adequately to continuously changing demands. In support of this, Heponiemi et al., (2007) reported that high cardiac autonomic reactivity to a mental arithmetic and speech task as well as greater recovery was associated with less preclinical arthrosclerosis even after adjustment for relevant covariates (Heponiemi et al., 2007).

This thesis also demonstrated that examining reactivity and recovery change scores separately may be misleading. In Study 1, for example, both hyper-reactivity and rapid recovery were associated with metabolic burden, which appeared counter-intuitive and contradictory. Thus, post-hoc analyses examining the patterns of response across the stress protocol were conducted to better decipher the meaning of these results. Analyses revealed that “greater recovery” (change scores approaching zero) were actually reflective of blunted reactivity which greatly altered the interpretation of these data. This revelation partly inspired the use of cluster analysis in the second study. The novel use of clusters was not only more parsimonious, but also permitted the evaluation of specific subgroups of individuals who could be empirically distinguished from each other based on the pattern of responses across the entire stress protocol.

Clinical Relevance of Thesis Findings

The first two articles of this thesis provided robust evidence for the contribution of autonomic stress responses to metabolic dysfunction. These results led to the queries that motivated the development of the pilot study of this thesis: Can stress management reduce or reverse some of this dysfunction and can reversal be achieved through normalization of heightened or blunted stress responses?

Although a large-scale replication of this pilot study is required before conclusions can be drawn, preliminary data suggest that MBSR has the potential to reduce metabolic abnormalities, especially LDL and total cholesterol, to a clinically significant degree. This is of particular importance as it suggests that a non-invasive, non-medical intervention with little to no side effects has the potential to reverse cardiovascular risk factors at a physiological level. Moreover, improvements were over and above benefits engendered by medication in those already receiving pharmacotherapy for one or several metabolic syndrome components. This implies that MBSR may be a useful addition or alternative to usual treatment for individuals exposed to high levels of chronic or acute stress, or who do not tolerate certain medications. Its feasibility and acceptability in an older population, those who are the most vulnerable to CAD, is also promising, as it highlights potential for openness and change in individuals who may be more resistant to lifestyle alterations (Carstensen, & Hartel, 2006).

Findings from the pilot study also suggest that MBSR has the potential to alter stress responses, particularly those of the autonomic nervous system. This provides further evidence of the importance of stress and, in particular, non-normative autonomic stress responses to metabolic dysfunction. Furthermore, the fact that changes in reactivity/recovery were robustly associated with changes in metabolic parameters further supports the role of stress responses in the pathogenesis of metabolic syndrome and shed lights as to the pathway by which MBSR may have influenced metabolic outcomes. It is also possible that MBSR acted on psychological factors such as rumination which may have reduced prolonged activation of stress responses. This in turn may have influenced metabolic outcomes. Indeed, participation in MBSR has resulted in decreased rumination in several investigations (Campbell, Labelle, Bacon, Faris, & Carlson, 2012; Chiesa, & Serretti, 2009; Deyo, Wilson, Ong, J., Koopman, 2009; Goldin, & Gross, 2010; Labelle, Campbell, & Carlson, 2010). Moreover, in a small study of women with cancer, reductions in ruminative tendencies were correlated with decreases in resting SBP.

The collection of qualitative data from participants in Study 3 also pointed to an important clinical consideration. One participant stated that becoming increasingly in tune with her emotions over the course of the program was particularly distressing as she had been previously unaware of her repressed anger and resentment towards her partner. This is a common occurrence rarely discussed in MBSR intervention articles but that should be communicated explicitly to participants. As participants learn to become more mindful of their moment-to-moment reality, they may begin to access emotions that were previously experientially avoided which may be uncomfortable and confronting (Shapiro, Carlson, Astin, & Freedman, 2006). Participants are typically informed at the beginning of MBSR that mindfulness may evoke unpleasant emotional experiences and that the goal of the practice is to observe these experiences with non-judgment (Shapiro et al., 2006). However, our study illustrates that perhaps this should be emphasized to a greater degree and addressed more frequently by group facilitators in open discussion.

Limitations of Thesis

This thesis comprises several limitations. First, repeated administration of a similar stress protocol in pilot Study 3 may have yielded habituation or practice effects. However, participants experienced significant increases in subjective stress and arousal across all administrations. Moreover, changes in stress response style may have occurred between participation in BEL-AGE and first evaluation of Study 3 (approximately 2.5 years later). However, data from our laboratory demonstrate that individual responses to psychological stress are stable over a longer period of time (Dragomir, Gentile, Nolan, & D'Antono, 2014).

In addition, LF/HF was utilized as a measure of sympathovagal balance in all three studies of this thesis. The measure of LF-HRV, once largely considered an indicator of sympathetic activity, has now been shown to be influenced by both parasympathetic and sympathetic systems (Reyes del Paso, Langewitz, Mulder, Roon, & Duschek, 2013). As a result, the LF/HF ratio has instead been used as a measure of sympathovagal balance across several disciplines. However, Reyes del Paso and colleagues (2013) report that the interpretation of LF/HF is oversimplified and remains debatable and assert that authors generally disregard conflicting evidence pertaining to its representation of sympathetic activity.

The samples included in this dissertation consisted mostly of francophone Caucasians, and thus results may not be generalizable to other individuals. For instance, racial differences, particularly between African-Americans and Caucasians, have been reported with regard to cardiovascular reactivity to stress (Knox, Hausdorff, & Markovitz, 2002) and prevalence of metabolic syndrome (Smith et al., 2005).

Some authors suggest that it is the individual parameters of metabolic syndrome that account for the increased risk of cardiovascular disease, rather than the syndrome itself (Guembe et al., 2010; Iribarren et al., 2006; Kahn et al., 2005; Sundstrom et al., 2006). However, recent large-scale prospective research has demonstrated that the metabolic syndrome construct is a genuine predictor of adverse cardiovascular outcomes, independently of its individual parameters (Gupta, Dahlof, Sever, & Poulter, 2010; Reilly & Rader, 2003; Scuteri, Najjar, Morrell, & Lakatta, 2005; Scuteri et al., 2004; Simons, Simons, Friedlander, & McCallum, 2011).

The clinical relevance of studying acute stress responses has also been questioned on the basis that it is difficult for individuals to become aware of and alter their physiological responsiveness to stressful events. Yet, our pilot study suggests that MBSR has the potential to normalize both heightened and blunted stress responses, particularly for autonomic indices. A separate study also showed that MBSR reduces BP reactivity in adults with high levels of self-reported stress (Nyklicek et al., 2012). Moreover, other interventions including biofeedback and relaxation have also been repeatedly shown to help individuals voluntarily modify their physiological stress responses (Del Pozo, Gevirtz, Scher, & Guarneri, 2004; Mishima, Kubota, & Nagata, 1999; Miu, Heilman, & Miclea, 2009; Palomba et al., 2011; Prinsloo, Derman, Lambert, & Rauch, 2013; Whited, Larkin, & Whited, 2014). Importantly, it has been posited that acute stressors commonly used in the laboratory (e.g. mental arithmetic and speech tasks) are significantly *less* stressful than those regularly experienced by individuals in daily life (Chumaeva et al., 2015), especially for women (Allen, Stoney, Owens, & Matthews, 1993; Carroll et al., 2008; Lassner, Matthews, & Stoney, 1994; Matthews, Davis, Stoney, Owens, & Caggiula, 1991). These studies may thus be underestimating the contribution of non-normative stress response styles to adverse cardiovascular endpoints. This only further supports the need to continue to study stress responses and explore ways to mitigate exaggerated stress reactivity (or normalize blunted reactivity) as it is not always possible to limit exposure to frequent or prolonged stressors.

Strengths of Thesis

This thesis comprises several strengths that increase the confidence that can be had in the results obtained. First, this is the first body of work to examine the relation between physiological stress responses and a global representation of metabolic syndrome. It included autonomic indices of reactivity and recovery; the latter having been largely ignored to date in the literature. The inclusion of these parameters proved to be of paramount importance; in the first two studies, autonomic responses emerged as robust contributors to

(Study 1) or correlates of (Study 2) metabolic dysfunction. Moreover, this thesis included a prospective investigation with three year follow-up and a large-scale cross-sectional study which produced comparable results despite vastly different samples. The focus on potential sex differences was also novel and led to the discovery of notable differences between men and women in the relation between autonomic response and metabolic outcomes. Rigorous methodology was employed across all three studies; BP and ECG readings were obtained continuously throughout the stress protocols and research personnel were thoroughly trained to remain neutral during stress testing. In the first study, resting BP for metabolic burden criteria was obtained using 24 hour ambulatory monitoring. Twenty-four-hour ambulatory BP measures have been shown to be more predictive of cardiovascular outcomes than laboratory or clinic readings and are considered the best representation of BP for the diagnosis of hypertension and/or metabolic syndrome (Hermida et al., 2013; Linden, Lenz, & Con, 2001; Sherwood et al, 2002). The first two studies were sufficiently powered to control for relevant covariates and employed strict exclusion criteria in order to limit possibility of confounds. The majority of laboratory stressors contained an interpersonal component, which more closely resemble the types of stressors individuals encounter in their daily lives (Kamarck & Lovallo, 2003; Linden, Rutledge, & Con, 1998). Moreover, these stressors have been shown to be relevant to men and women in contrast to purely cognitive stressors which tend to elicit greater motivation and interest in men (Allen et al., 1993; Carroll et al., 2008; Lassner et al., 1994; Matthews et al., 1991). Given that sex differences were of primary interest to this thesis, it was important that the stressors selected were salient to men and women in order to limit the possibility that sex differences in the relation between stress responses and metabolic outcomes were due to task-specific factors.

Finally, this thesis included a randomized controlled pilot study which enabled us to test whether mindfulness-based stress reduction was feasible and acceptable in an older population with current or past metabolic syndrome. The MBSR program was animated by an experienced psychologist and participants had access to a large comfortable setting and high-quality materials conducive to mindfulness meditation. Various debate topics were chosen for each evaluation session, limiting the participants' ability to prepare their arguments in advance. The sample was stratified by sex and initial stress response style and successful randomization was confirmed by the fact that the randomization groups did not differ significantly at baseline. This pilot research provides an example of how theoretical results from the first two articles may be tested (and then eventually applied) in a clinical setting to possibly improve the metabolic health and stress response styles of individuals vulnerable to metabolic dysfunction.

Future Directions

Our data suggest that the role of autonomic stress responses in the pathogenesis of metabolic syndrome may differ according to the sex of the individual. Further research should continue to explore the nature of these sex differences in order to better understand why women (but not men) with blunted autonomic responses in particular seem to be more vulnerable to metabolic dysfunction. Further examination of sex differences at the neuropsychological level may be particularly pertinent given that HRV is thought to reflect the functional integrity of brain regions involved in self-regulation and that notable sex differences exist in HRV. Since our pilot study was not sufficiently powered to make multiple comparisons, it would also be of interest to test in a large-scale study whether the impact of MBSR on metabolic profile and/or stress responses differs as a function of sex.

In a future investigation, it may also be relevant to measure rumination directly using a self-report questionnaire. Women who tended to report greater levels of stress and anger post-stressor in Study 2, indicating possible rumination, were also more susceptible to the harmful impacts of non-normative stress responses on their metabolic profile. Testing the mediating effect of rumination on the associations between stress responses and metabolic outcomes would be of interest given previous research suggesting that rumination is independently associated with various adverse health endpoints (Brosschot, Gerin, & Thayer, 2006). In addition, the inclusion of a measure of anger expression would also be recommended given that suppression has been associated with phasic HRV enhancement, or blunted vagal response.

This thesis demonstrated that MBSR is generally feasible and acceptable for older adults with current or past metabolic syndrome. In order to facilitate recruitment and reach individuals on a larger scale, this pilot study should be replicated in collaboration with health care professionals (e.g. physicians, nurses). Indeed, motivation to engage in stress management may be further increased if individuals were first introduced to the topic by their trusted physician and perceived it as part of their medical care. Other recruitment methods such as presentations to groups of patients in hospital or public postings may also be of interest depending on the type of sample desired. In a larger study, it is recommended that the MBSR program be offered at more than one time period (e.g. day and evening) in order to accommodate both working and retired participants. For older adults, offering the program during the daytime is recommended; an evening class was not feasible for our participants, who expressed concerns regarding driving at night and in the winter.

More research is also needed to determine how to better accommodate individuals who display psychological distress during the intervention. Indeed, one individual who dropped out after 5 sessions reported that MBSR increased her anxiety and stress as well as evoked repeated feelings of failure. One possible way of identifying individuals who are having difficulty early on may be to include occasional phone check-ins by study personnel over the course of MBSR. This would create an early opportunity to answer any questions or concerns and possibly mitigate some distress.

While we have shown that non-normative autonomic responses contribute to concurrent and prospective metabolic syndrome risk, the question remains as to how to identify these response patterns outside the laboratory for the clinical benefit of patients. Indeed, if patients had an indication of their stress response profile and understood the associated risks, they may be increasingly motivated to invest in stress management. One option may be to add a short stressor task (perhaps one that does not require additional equipment, such as anger recall) to the existing exercise ECG stress test. The ECG stress test is already employed for older individuals with a history of or at risk of CAD and/or cardiovascular events in order to assess functionality of the heart during physical exertion as a marker of CAD prognosis (Banerjee, Newman, Van den Bruel, & Heneghan, 2012). Since the metabolic health of younger and/or healthy individuals is equally impacted by non-normative stress responses as we have shown in Study 1, psychological stress testing would also be indicated for these individuals. Some research suggests that inadequate blood flow to the heart (i.e. ischemia) induced by mental/emotional stress is actually a better predictor of fatal and nonfatal cardiac events than ischemia induced by the exercise stress test in those with CAD (Jiang et al., 1996). Future research should aim to validate meaningful clinical thresholds of physiological stress reactivity. Once these have been established, the next step would involve pilot investigations assessing feasibility and acceptability of implementing psychological stress tests in clinical settings for individuals with and without CAD.

Moreover, given debate regarding the interpretation of LF/HF (Reyes del Paso et al., 2013), replicating these studies with blood pressure variability measures, a better measure of sympathetic activity, would increase confidence in results pertaining to LF/HF (Höcht, 2013). It will be also important to verify whether findings from Study 2 are maintained longitudinally. Follow-up testing is currently underway in the Heart and Mind Laboratory at the Montreal Heart Institute (MHI).

Transfer of Knowledge Strategy

Some of these findings have already been disseminated to the scientific community by means of international research conferences or academic publications. Article 1 was published in 2014 in *Annals of Behavioral Medicine*, a high impact journal with notable visibility. Results were also presented at the Society of Behavioral Medicine Conference in San Francisco, California. Preliminary results from Study 2 were presented at the *Psychoneuroendocrinology* conference in Edinburgh, Scotland in 2015, and its abstract was published in the *Psychoneuroendocrinology* journal. Final results from Study 2 were submitted to *Annals of Behavioral Medicine* and I plan to publish findings from pilot Study 3.

Over the last five years, I have been a part of the Heart and Mind: Research Unit in Behavioral and Complementary Medicine Laboratory at the MHI. The mission of our laboratory is twofold; first, to expand knowledge of complementary non-pharmacological and non-invasive means to preventing and managing cardiovascular health and second, to communicate this knowledge to patients and healthcare officials to effectuate change. Dr.

Bianca D'Antono, my thesis supervisor and director of our laboratory, gave seminars in 2016 at the MHI to patients and their families regarding the importance of identifying and treating the psychological causes and consequences of cardiovascular events, particularly in men who are often less likely to seek psychological support when needed. The seminars were attended to full capacity and participants consistently expressed the need for greater psychological support at the MHI. Given the findings of this thesis, I believe that future seminars should aim to increase awareness regarding the stress response and its impact on metabolic syndrome and cardiovascular health as well as provide some basic stress management tools. Once I am a licensed psychologist, I will consider offering these seminars periodically to patients at the MHI and providing them with appropriate referrals to colleagues for individual psychotherapy or stress management programs. In an ideal world, I believe stress management training should be offered free of charge to patients who have experienced cardiovascular events and to patients at risk of developing cardiovascular disease (e.g. with metabolic syndrome). Previously, a mindfulness stress intervention was offered by an MHI affiliated center to patients at a cost of approximately 500 dollars. Recently, I was hired by the psycho-social oncology department at the Glen hospital, where I will holding psychological orientation sessions for women recently diagnosed with breast cancer. This will give me the opportunity to emphasize the importance of stress management in another population of individuals.

In order to further disseminate the results to the general public, I will prepare a summary of my results and submit it to Dr. Martin Juneau, a cardiologist who regularly publishes data related to cardiovascular disease prevention in accessible language on his blog. The director of the MHI Biobank will also be informed so that findings may be published on the official website; in this way, individuals who generously participated in these studies may have access to the non-denominational results.

Finally, it is my conviction that physicians and other health care professionals should communicate the importance of stress management in the same way that exercise and maintaining a healthy diet is often emphasized. In order to disseminate this message, I will consider preparing a list of recommendations based on the results of this thesis and submitting it to the MHI board of directors who will ideally ensure that health professionals are informed of its contents.

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Appendix A: Recruitment Letter

« Le paradis n'est pas un endroit, mais un état de conscience » – Sri Chinmoy

Cher _________,

Nos dossiers indiquent que vous faites partie de la Biobanque de l'Institut de Cardiologie de Montréal. Lors de votre première participation, vous avez consenti à être recontacté pour de futurs projets de recherche. C'est ainsi que vous avez été invité à participer à notre projet **BEL-AGE** : le fardeau psychologique et le vieillissement pathologique chez les individus avec ou sans maladie cardiovasculaire.

Nous tenons à vous remercier de votre participation lors de votre première visite pour le projet BEL-AGE le _____. En nous basant sur les résultats obtenus lors de celle-ci, nous croyons que vous pourriez retirer certains bénéfices en participant à une étude pilote qui se déroulera dans notre laboratoire à partir de l'automne 2015. Celle-ci comporte, entre autre, un **programme de huit semaines sur la gestion du stress.**

L'expérience du stress est associée à de nombreuses conséquences de santé néfastes, incluant le développement des maladies cardiovasculaires. La réduction du stress peut ainsi servir comme facteur protecteur contre certains comportements qui aggravent le risque d'être atteint d'une maladie chronique.

De nombreuses études ont montré l'efficacité de ce programme, non seulement pour la réduction du stress, mais aussi de la douleur, de la pression artérielle, de troubles digestifs et de symptômes psychologiques divers. À ce jour, plus de 17 000 personnes ont suivi ce programme et plus de 5000 médecins et professionnels de la santé à travers le monde s'y réfèrent quotidiennement dans le cadre de leur travail.

Nous vous offrons ce programme gratuitement en retour de votre participation à cette nouvelle étude.

La participation à cette étude pilote pourrait vous aider à réaliser des objectifs importants, soit l'amélioration de votre santé physique, et mentale et plus globalement, de votre qualité de vie. Si vous êtes intéressé à obtenir de plus amples informations concernant ce projet et désirez y participer, veuillez contacter Christina Gentile ou Louisia Starnino au 514-376-3330 poste 2011.

Cordialement,

Dr. Bianca D'Antono, Ph.D, chercheure principale
Christina Gentile & Louisia Starnino, candidates au doctorat en psychologie clinique
Coeurs et âmes: unité de recherche en médecine comportementale et complémentaire

Appendix B: Mindfulness-Based Stress Intervention Program – Weekly Breakdown

Week	Theme
1	Introduction to the program and mindfulness; theory and evidence of mind-body medicine and how to applies in daily life; discussion of personal resources and strengths; body-scan meditation practice
2	Examination of participant assumptions and perceptions of themselves, others, and their environment; mindful hatha yoga practice, body scan; mindful eating; sitting meditation
3	Mindfulness versus mindlessness; discovering the pleasure and power of being present; mindful hatha yoga practice; walking meditation
4	Learn to pay attention with curiosity and openness to a full range of experiences; learn the psychological and physiological bases of stress reactivity; practice mindful strategies of responding to stress in positive and proactive ways
5	Identify repetitive unhealthy patterns for stress management that may be reduced or eliminated via mindful awareness; short sitting meditation
6	Effective interpersonal communication; preparation for silent meditation retreat
7	Silent meditation retreat (5 hours) (sitting meditation, yoga, body scan; love and kind poem; walking meditation)
8	Learn how to integrate mindfulness more fully into daily life; maintaining discipline and flexibility of daily practice as life circumstances change; brief love and kindness meditation
9	Review and keeping up the practice; discussion of available resources; celebration

Appendix C: Acceptability Questionnaire

ÉTUDE MBSR-MS

QUESTIONNAIRE DE PRÉFÉRENCE ET D'ACCEPTABILITÉ DU TRAITEMENT

Vous avez participé à un projet durant lequel vous avez appris à contrer les effets du stress par le biais d'un programme basé sur la réduction du stress par la pleine conscience (MBSR). Maintenant que vous avez pris part à ce projet, nous vous demandons de vous prononcer sur les questions suivantes : répondez spontanément, il n'y a pas de bonnes ou de mauvaises réponses.

1. Jusqu'à quel point ce type de programme a été efficace pour changer votre façon de répondre aux diverses situations stressantes de votre vie ?

Pas du tout	*Un peu*	*Moyennement*	*Beaucoup*	*Extrêmement*
0	*1*	*2*	*3*	*4*

2. Jusqu'à quel point ce type de programme vous a semblé approprié dans la réduction du stress?

Pas du tout	*Un peu*	*Moyennement*	*Beaucoup*	*Extrêmement*
0	*1*	*2*	*3*	*4*

4. Jusqu'à quel point ce type de programme vous a semblé acceptable (sensé) dans la réduction du stress?

Pas du tout	*Un peu*	*Moyennement*	*Beaucoup*	*Extrêmement*
0	*1*	*2*	*3*	*4*

4. Les modalités suivantes ont –elles été bénéfiques pour vous?

Modalités	*Pas du tout*	*Un peu*	*Moyennement*	*Beaucoup*	*Extrêmement*
Enseignement du professeur *(p. ex. qualité de l'enseignement et matériaux fournis)*	*0*	*1*	*2*	*3*	*4*
Méditation :					
Allongée	*0*	*1*	*2*	*3*	*4*
Assise	*0*	*1*	*2*	*3*	*4*
En marchant	*0*	*1*	*2*	*3*	*4*

Bienveillance	*0*	*1*	*2*	*3*	*4*
Retraite *(5 heures de pleine conscience en silence)*	*0*	*1*	*2*	*3*	*4*
Postures de yoga	*0*	*1*	*2*	*3*	*4*
Discussions de groupe	*0*	*1*	*2*	*3*	*4*
Exercices de pleine conscience à la maison *(p. ex. pratiques formelles (méditation) et pratiques informelles (attentif au moment présent dans son quotidien)).*	*0*	*1*	*2*	*3*	*4*

5. Si ce projet était à refaire, seriez-vous d'accord à participer au programme?

Pas du tout *Un peu* *Moyennement* *Beaucoup* *Extrêmement*

0 *1* *2* *3* *4*

6. Maintenant que le programme est terminé, à quel point croyez-vous continuer votre pratique de la pleine conscience dans votre quotidien?

Pas du tout *Un peu* *Moyennement* *Beaucoup* *Extrêmement*

0 *1* *2* *3* *4*

7. Qu'est-ce qui vous a amené à vouloir participer à ce projet de recherche sur la réduction du stress par la pleine conscience?

___

___

___

8. Y a-t-il un aspect ou des aspects du programme MBSR que vous avez moins aimés?

___

___

___

9. Y a-t-il un aspect ou des aspects du programme MBSR que vous avez beaucoup appréciés?

___

___

___

10. Qu'avez-vous appris suite au programme MBSR? Avez-vous aperçu des changements personnels? Si oui, lesquels?

____
____
____
___

11. À quel pourcentage de personnes de votre entourage recommanderiez-vous le programme MBSR?

________%

Appendix D: Summary of Participants' Verbal Feedback Regarding MBSR

What aspects of MBSR did you appreciate?	What didn't you appreciate about MBSR?	What did you learn from MBSR?
« La présentation était simple; le yoga et la méditation étaient bien dosés. La séance passait vite, je ne me sentais pas obligée de parler, tout était fait en douceur, c'était facile. Je sortais de la séance plus légère. J'ai beaucoup apprécié le cartable et le CD».	*« J'ai trouvé qu'il y avait beaucoup de devoirs. Les émotions dans les carnets personnels étaient très similaires et j'avais de la misère à comprendre les différences».*	*« J'ai appris à penser à moi, à moins en mettre sur mes épaules. Je me suis retirée dans mes problèmes avec XX; il y a un bout de chemin que tu peux faire pour les autres, et un bout que tu ne peux pas faire ».*
« Bel accueil, beau groupe, pas de jugement, je ne me sentais pas en compétition avec les autres, j'ai apprécié le CD et les outils pour que nous puissions continuer à pratiquer».	*« La méditation – ça m'a fait penser à des choses désagréables et au lieu de la retraite, j'aurais préféré avoir une séance seule avec Anne. Le local était froid».*	*« Je m'affirme plus avec mon conjoint, ce qui nous amène à avoir plus de conflits. J'ai davantage de colère depuis que je prends plus conscience ».*
«J'ai aimé l'aspect social, les discussions, c'était un bon groupe. La professeure et l'assistante étaient correctes. L'heure de la séance me convenait».	*«J'ai eu de la difficulté avec le yoga, je n'ai pas de souplesse, et c'était difficile de rester couché».*	*« Le programme m'a aidé à être plus calme. Je suis moins fâché lorsque je conduis. Je suis moins réactif; j'ai un meilleur contrôle de ma colère. Le MBSR devrait être offert aux enfants à l'école et aux chauffeurs de camion et pour tout autre emploi où les employés vivent beaucoup de stress».*
«La professeure - elle était très bien, elle avait une voix douce, je continue à faire mes exercices sans obligation. Au début je ne croyais pas beaucoup à la méditation, mais maintenant j'y crois. C'était un bon groupe».	*«C'était un peu dur d'être obligé d'être là chaque semaine; les discussions entre 2 personnes étaient longues parfois ».*	*«Je grignote moins avant de manger mon souper; j'essaie d'être plus conscient quand je mange. J'ai diminué ma consommation d'alcool, et j'ai même maigri de plusieurs livres. Ce n'était pas facile, mais c'est un bon programme. Je suis content*

		d'y avoir participé».
«La professeure et le groupe étaient très bien. J'ai aimé le scan corporel et le concept de la pleine conscience, mais je ne pouvais pas m'allonger, j'avais mal au cœur».	*«Faire des choses au ralenti me stresse davantage. J'ai des problèmes d'audition et sans mon appareil, je suis en silence et donc je n'aime pas la méditation. Je n'ai pas aimé les discussions de groupe, je n'entendais pas bien, je ne comprenais pas et la salle était trop grande».*	*« Je fais les exercices de respiration le matin et en me couchant et j'ai utilisé ces exercices de respiration quand mon mari était à l'hôpital. J'ai obtenu mon meilleur score au bowling après avoir fait mes pratiques informelles, car j'étais plus consciente de mes mouvements ».*
« J'ai bien aimé le scan corporel, et le groupe, ça m'a fait réaliser que je ne suis pas toute seule».	*C'était long. La troisième méditation du CD - j'étais incapable, je l'évitais».*	*« Je faisais beaucoup d'exercice avant, mais je ne me rendais pas compte de ma respiration. Maintenant, ma respiration est meilleure en joggant. Le programme m'a motivée à reprendre l'entrainement, même si je le fais seule ».*
« J'ai beaucoup aimé la professeure et sa façon de présenter. Elle a une voix apaisante. J'ai aimé les discussions, on avait un bon groupe. J'avais hâte à chaque semaine, c'était agréable».	*« La méditation en marchant et assise, ça ne me disait rien. La méditation assise n'était pas confortable».*	*« Je suis plus à l'écoute. Je suis plus conscient des besoins des autres, de leurs joies et de leurs peines ».*
« Rencontrer les gens et voir le cheminement de chacun. On était content de se revoir. Je veux continuer à pratiquer la pleine conscience tous les jours. J'étais impliquée dans le groupe, j'ai adoré faire des improvisations».	*« Je trouvais que la professeure avait un ton monotone sur le CD, elle perdait mon attention. Je n'ai pas aimé la retraite de 5 heures, j'étais en colère en revenant chez moi. Je me sentais coincée, comme si j'étais obligée de faire certaines choses. Je n'ai pas aimé le fait qu'il n'y avait pas d'émotions positives dans les logs quotidiens».*	*«J'ai fait une prise de conscience, j'ai compris ce que veux dire être dans le moment présent. Quand j'arrose mes fleurs, j'arrose mes fleurs. Je goute plus à la nourriture. Quand j'étais en colère après la retraite, je me disais, au moins j'en suis consciente. La méditation pleine conscience, c'est comme les vitamines - tu ne vois pas les effets tous les jours, mais si tu n'en fais pas tu vas*

		remarquer la différence».
« J'ai aimé le groupe. Le programme m'a aidée à prendre conscience de certains comportements que je pourrais améliorer».	*« Je ne me sentais pas à l'aise avec le programme. La pleine conscience est devenue comme une obsession ; je pensais toujours à mes comportements, je m'évaluais. Je me sentais comme un échec tout le temps. Je fais déjà toujours une évaluation constante de mon comportement. Peut-être que je suis trop sévère avec moi-même, mais c'est comme ça que j'ai avancé dans la vie. Aussi, je n'ai pas aimé le trafic - ça me prenait 2 heures pour faire l'aller-retour».*	*« Le programme m'a fait réaliser que je suis anxieuse et angoissée plutôt que stressée. Ce programme m'a permis de voir les visions des autres, de réaliser que je ne suis pas toute seule, et que je ne suis si pire que ça».*
« J'ai adoré la méditation. Je n'en avais pas fait depuis 30 ans et j'ai vraiment aimé me remettre dedans. J'ai aimé que j'aie pris le temps de vivre au moment présent, et j'ai réalisé à quel point j'étais en pilote automatique. Je ne portais pas attention à ce que je faisais avant». .	*« Rien en particulier».*	*« J'oublie moins mes clés, je cherche moins mes choses, j'ai changé ma stratégie en bridge depuis que je suis plus consciente. J'arrête quand je prends ma douche, j'observe ce que je suis en train de faire. C'est formidable, je me sens plus vivante, plus calme. Mon conjoint fait de la méditation avec moi, c'est rendu une routine pour nous. Il a observé des changements positifs dans ses résultats de prise de sang depuis qu'il fait la méditation. Je ne rendais pas compte à quel point j'étais stressée avant. Je ressens un manque quand je ne fais pas ma méditation».*
« J'ai aimé l'enseignement de la professeure. Nous avons eu un bon esprit d'équipe».	*« Je n'ai pas aimé la voix monotone de la professeure sur le CD. Ça me faisait la peine que le groupe diminuait- nous avons commencé avec 9 et on a terminé avec 6. Ça m'a brassé un peu la première journée quand le Monsieur a quitté après 30 minutes. Il savait à l'avance dans quoi il s'impliquait, c'était*	*« Le programme m'a aidé dans ma maladie, à être plus calme, et à penser à autre chose. Je me sens plus joyeux après avoir médité. Depuis le programme, ma blonde semble plus souriante, joyeuse, il y a un rapprochement entre nous, peut-être parce que je suis*

	une perte de temps pour nous et pour vous. J'aurais préféré passer à l'hiver (groupe 1) ».	*moins stressé. Elle m'encourage à faire ma méditation. C'est difficile pour moi de trouver un temps fixe durant la journée pour méditer, mais quand je le fais, je dors bien après. J'étais aussi plus conscient durant mes cours d'étirement au gym. Ce programme pourrait aider tout le monde, il faut juste avoir la patience de l'apprendre. C'est un bon travail».*
«La méditation, j'ai toujours voulu en faire plus régulièrement. C'était un bon groupe, ça a bien été après que les deux premiers ont abandonné. J'ai apprécié l'expérience. J'étais bien à l'aise avec la professeure et l'assistante. Même si le programme était difficile parfois, c'était une belle expérience».	*«Remplir les logs des émotions tous les jours, c'était un fardeau. C'était aussi difficile de reconnaitre la différence entre les émotions. J'ai eu de la difficulté avec certains mouvements de yoga».*	*«J'ai appris la pleine conscience - souvent on fait des choses en machine allemande, sans y penser. Maintenant, je prête plus attention à ce que je fais. Le programme m'a aussi rappelé qu'il ne faut pas lâcher les exercices physiques- il est important de continuer à les faire».*
«J'ai aimé la méditation, le recentrage sur la respiration, je le fais tous les jours quand il y a quelque chose qui me dérange, ça me fait un bien immense. Même pour les pensées négatives, je me ramène sur ma respiration et ça m'aide. Qu'elle belle expérience, je suis ravie d'avoir participé. C'était un très bon groupe, c'était bien d'échanger, de se reconnaitre dans des gens de divers milieux. J'ai pris conscience que chacun vit son stress différemment. J'ai adoré l'expérience, même j'avais de la peine quand ça c'est terminé. J'ai aimé la prof, elle avait une voix apaisante - lorsque j'entends sa voix sur le CD, ça me relaxe. Elle	*«Les 5 heures de silence, ça ne m'a pas apporté grand-chose ou bien je n'ai pas trop compris ce que ça m'a apporté. Il y avait beaucoup d'exercice, j'aurais aimé plus de conférence, de bien discuter des certaines choses. J'aurais aimé 30 minutes additionnelles de discussion pour bien approfondir sur certains points».*	*«Je suis plus calme au bureau, plus ouverte. J'ai moins de stress inutile. Je suis moins énervée par mes collègues. Je voulais être moins stressée au départ au travail et je pense que j'ai atteint mon but. Je vois le programme comme un médicament, faut qu'on le donne aux gens qui en ont besoin, qui sont stressés ou malades. Les gens de 50 ans et plus devraient tous suivre le programme. Il est important que les gens soient prêts, par exemple».*

était tellement calme et posée».		
«La professeure, c'est une perle. Elle avait des réponses et des interventions impeccables. C'était un bon groupe aussi. J'ai aimé le programme, l'endroit était propice, le stationnement était facile et la classe était bien. Il y avait beaucoup de respect entre les intervenants et les participants».	*«Rien en particulier».*	*«Je n'ai pas encore intégré la pratique dans ma routine, mais je suis convaincue du bien que ça va m'amener. Je respire plus depuis le programme et suis plus consciente de mes mouvements. Je ne savais rien sur la pleine conscience quand j'ai commencé et je ne regrette pas d'y avoir participé».*

As nearly all of our participants were Francophone, they are quoted here in French

Appendix E. Baseline Values in Stress Parameters According to Reactivity Grouping

	Heightened LF/HF Responders (n=10)	*Blunted LF/HF Responders (n=7)*
	M (SD)	*M (SD)*
SBP (mm Hg)	133.68(12.47)	133.61(15.07)
DBP (mm Hg)	64.29(6.28)	65.10(12.51)
HR (bpm)	71.04(10.29)	72.24(9.56)
HF-HRV (m/s^2)	1377.29(3377.46)	360.07(581.09)
LF/HF (m/s^2)	2.12(2.69)	2.04(0.78)
HFnu	0.55(0.32)	0.35(0.09)