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REGULAR ARTICLE

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

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Abstract

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. ANCOVAs were conducted in secondary analyses utilizing a continuous composite representation of MetS.

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 = .037). HF-HRV cluster interacted significantly with sex (p < .001) to predict MetS. In women, those with significant 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 = .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 = .004). Results using a continuous measure of MetS were generally consistent with these findings.

Conclusion Among older participants with CAD or other noncardiovascular disease, hyperreactivity 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 at greater risk.

Keywords Sex differences • Metabolic syndrome • Stress • Autonomic • Heart-rate variability

Introduction

Metabolic syndrome (MetS) increases the risk of atherosclerosis and mortality from cardiovascular disease (CVD) by approximately two-fold [1–4]. The lifetime prevalence in Canadians is approximately 20%, although this increases to 40% 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]. MetS predicts adverse cardiovascular outcomes, independent of which components show elevations [7–9].

Psychological stress may increase the risk of MetS 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 MetS has

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received less attention. For instance, although 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 only 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 MetS 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 MetS criteria. Our laboratory examined concurrent and prospective associations between BP, HR, and autonomic (assessed by high-frequency HR variability, HF-HRV; and the ratio of low- to high-frequency HR variability (LF/HF)) responses to psychological stressors and metabolic burden in a sample of 193 healthy adults aged 18 to 64 years [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. BP and HR reactivity and/or recovery were not associated with metabolic burden, but men with exaggerated stress-related decreases in HF-HRV displayed an increase in metabolic burden over time. However, the opposite pattern 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 [15] also examined the concurrent and prospective relations between autonomic stress reactivity and components of MetS in adults. Although waist circumference and HDL cholesterol were negatively associated with HR reactivity to a cognitive task, greater decreases in HF-HRV were associated with an increased number of MetS components [32]. This association was particularly robust 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 MetS 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 MetS. 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 MetS may further contribute to morbidity or mortality risk. MetS was examined both as a dichotomous and continuous variable. 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. We expected that heightened and blunted (i.e., non-normative) parasympathetic stress responses would be associated with the presence of MetS and that this association would differ according to sex. Specifically, we believed that blunted responses would be associated with MetSyn in women and heightened responses with MetSyn in men as per results of our previous investigation in healthy individuals [31].

Methods

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

Participants

In total, 1,121 men and women were recruited from the André and France Desmarais Hospital Cohort of the Montreal Heart Institute (MHI), which aims to recruit and follow 30,000 individuals with the goal of determining genetic and other markers of cardiovascular outcomes. Any member of the MHI community, including patients with or at risk of CVD, individuals attending the hospital for routine blood tests, family members of patients, and employees, may participate in this cohort. Individuals were excluded from participating in BEL-AGE 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, other than CAD, 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) previously participated in BEL-AGE or was scheduled to participate. In addition, we recruited a similar number of participants with CAD and without CVD. CAD at the time of enrollment into BEL-AGE was documented by the presence of coronary angiography (at least 50% stenosis), prior myocardial infarct, coronary artery bypass graft, or percutaneous coronary angioplasty. Absence of CVD was defined as no current or past history of CAD, angina,

arrhythmia, congenital heart disease, heart failure, cardiomyopathy, and stroke. Medical history was obtained through self-report and corroborated by consultation of participants' medical file in the case of CAD. 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 1,093 individuals.

Procedure

Participants were scheduled for a laboratory appointment between 8:00 AM 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 hr prior to testing. They were also asked to refrain from using illicit drugs or alcohol 24 hr 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. Approximately 25 min later, electrodes for electrocardiographic (ECG) monitoring were attached in a bipolar configuration to the lower side of the participant's rib cage and a ground electrode was placed under the right clavicle. BP was assessed using a noninvasive instrument fastened to the participant's wrist, as well as a sensor wrapped around the index finger of the nondominant hand (Finapres Finometer, Amsterdam, the Netherlands). Participants were then asked to complete a questionnaire quietly for a period of 5 min as they acclimated to the equipment. A brief stress protocol ensued, consisting of a 5-min baseline period, a 2-min preparation phase, a 5-min anger recall task, and a 5-min recovery period. ECG and BP were obtained continuously throughout the baseline period and stress protocol. 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 min to choose and think about the event and then were asked to speak about it for 5 min 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

These 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 the 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

This was defined as per the National Cholesterol Education Program, ATP III [1]. Plasma samples were analyzed for lipids and glucose. 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. To measure waist circumference, the participant's waistline was exposed and the bottom of a measuring tape was

aligned with the top of the hip bone and stretched across the midsection over the navel [47]. The 5 min resting SBP and DBP values obtained with Finapres Finometer and analyzed offline in LabChart were used for the BP component of the MetS construct.

Affect and arousal

These were assessed during the baseline, stress, and recovery phases of the protocol using the Self-Assessment Manikin (SAM) [48].

Psychological variables

The Perceived Stress Questionnaire. The Perceived Stress Questionnaire (PSQ) consists of 30 items quantifying perceived stress over the last 2 years. Each item is composed of a four-point Likert scale, ranging from 1 (almost never) to 4 (almost always). Higher scores indicate greater perceived stress. The test–retest reliability of the PSQ measured over a 6-month period is excellent ($r = 0.82$) [49].

The Center of Epidemiological Studies Depression Scale Revised. The Center of Epidemiological Studies Depression Scale Revised [50] consists of 20 items measuring the presence of depressive symptoms over the last 2 weeks. Scores range from 0 to 60, with higher scores reflecting greater severity of depressive symptomatology. It has excellent internal consistency reliability ($\alpha = 0.85$–0.91) and moderate test–retest reliability ($r = 0.54$) over a 6-month period [51, 52].

The State-Trait Anxiety Inventory. The State-Trait Anxiety Inventory (STAI) [53] assesses both state anxiety and trait anxiety by means of two 20-item self-report scales. The STAI "state" scale assesses the participants' current state, whereas the STAI trait assesses how participants tend to feel in general. Each item is based on a 4-point Likert scale, ranging from *not at all* to *very much* for the STAI State, and from *almost never* to *almost always* for the STAI Trait. The STAI has excellent internal consistency reliability (average $\alpha = 0.89$) as well as good test–retest reliability ($r = 0.75$) over a 3.5-month period [54, 55].

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 MetS categorization relied partly on SBP and DBP obtained at baseline, BP response patterns were excluded from analyses.

Preliminary analyses

Covariates were selected based on prior research indicating an association with MetS and the results of bivariate correlations between MetS and other variables in the dataset. Specifically, those variables that were significantly associated with MetS ($p < .05$) 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 poststress periods) were chosen. This approach was selected to (1) accommodate the possibility that relationships between reactivity and MetS may not be linear, for example, that both exaggerated and blunted reactivity are related to MetS, 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, 56, 57]. 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 poststress 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 MetS in the main analyses will be described. The final solution for HR yielded two groups of participants depicted in 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.

The final solution for HF-HRV yielded three groups of participants depicted in Figure 2. 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.

No significant sex difference emerged ($\chi^2 = 0.92$, $p = .63$) in HF-HRV cluster composition, although a

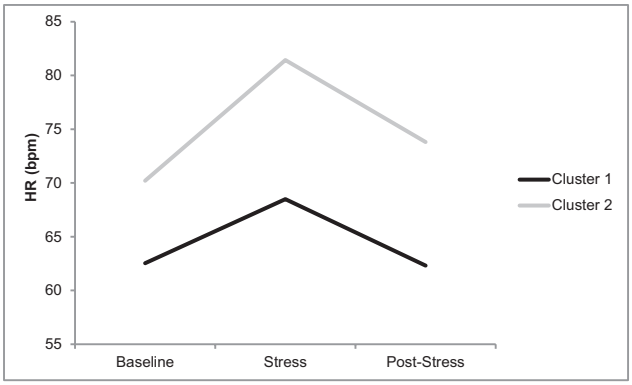

Fig. 1 Stress Response Clusters: HR.

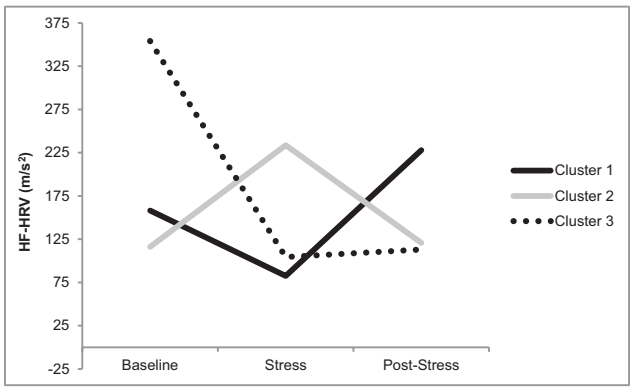

Fig. 2 Stress Response Clusters: HF-HRV. The geometric mean of HF-HRV is presented on the y-axis.

sex difference was observed for HR Cluster (χ^2 = 7.95, p = .005). Specifically, although participants fell predominantly within Cluster 1, men are represented to a slightly greater extent in HR Cluster 1 and women are represented to a greater extent in HR Cluster 2. For the number of participants per HR and HF-HRV cluster and the breakdown of men and women in each cluster, please refer to Table 1.

Presence of CAD, sex, and age were examined as potential moderators of the relation between autonomic stress responses and MetS in preliminary analyses. Only sex was retained for further analyses as presence of CAD or age did not emerge as significant moderators. Since it is well-documented that basal HRV is frequently altered in individuals with CAD [58] versus healthy counterparts, chi-square analyses were performed to verify whether there were differences in cluster membership between those with and without CAD. As no significant differences in cluster membership were found in the current sample (p = .46 and p = .12 for HR and HF-HRV, respectively), performing analyses in the combined group of patients was deemed appropriate.

Main Analyses

To examine associations between response to the stress protocol and MetS, multiple logistic regressions were performed

Table 1 Number of participants per HR and HF-HRV cluster

HR	Total sample	Men *n* (%)	Women *n* (%)
Cluster 1	756	503 (80%)	253 (72%)
Cluster 2	224	126 (20%)	98 (28%)
HF-HRV	**Total Sample**	**Men *n* (%)**	**Women *n* (%)**
Cluster 1	383	247 (39%)	136 (39%)
Cluster 2	429	279 (44%)	150 (43%)
Cluster 3	169	103 (17%)	66 (18%)

There is a significant sex difference in HR cluster composition, χ^2 = 7.95, p = .005.
There is no significant sex difference in HF-HRV cluster composition, χ^2 = 0.92, p = .63.

using the presence of the MetS (yes, no) as the dependent variable, and cluster, sex, and the interaction between cluster and sex as independent variables. If the interaction terms were not significant, they were removed from the equation. Thus, odds ratios for cluster within sex were only computed in the presence of a significant cluster * sex interaction. 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 MetS parameters, other medications, and presence of sex hormone therapy. BMI was included as a covariate to control for confounding of central obesity by obesity elsewhere in the body.

Since dichotomization of continuous variables can result in loss of information regarding severity of related metabolic risk and/or may lead to an under or overestimation of associations as a result of restricted range or chance positioning of cut-off points [59], additional analyses were performed using a continuous representation of MetS. The individual components of MetS were standardized and then summed (z((SBP + DBP)/2) + z(waist circumference) + z(glucose) + z(triglycerides) +z(−1*HDL cholesterol)), as per previous research [60–63]. ANCOVAs were conducted using cluster, sex, and the interaction between them as the independent variables and continuous metabolic risk as the dependent variable. The covariates were entered as per the logistic regressions.

For all tests, $p < .05$ was considered significant. Cluster analyses and logistic regressions were performed by a biostatistician using SAS 9.4 (SAS Institute Inc., Cary, NC). All other tests were performed using IBM SPSS Statistics 24 (Armonk, NY: IBM Corp).

Results

Descriptive Statistics

Nearly 54% of the sample met the NCEP ATP III criteria for MetS and approximately 54% had CAD. Men,

who constituted 62% of the sample, were more likely to have CAD and MetS 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 2.

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) = 1,486.63, $p < .001$); HF (F(1, 1034) = 4.66, $p < .05$); LF/HF (F(1, 1034) = 63.05, $p < .001$); and HF_{nu} (F(1, 1040) = 223.42, $p < .001$). It also resulted in significant decreases in positive affect (F(2, 2180) = 1,354.66, $p < .001$), and significant increases in subjective arousal (F(2,2180) = 1,654.65, $p < .001$).

Table 2 Summary of participant characteristics, M (SD)

	Men	Women
	(*n* = 700)	(*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 (48.3%)
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%)
Metabolic parameters		
SBP*** (mm Hg)	143.9 (20.0)	138.4 (22.2)
DBP*** (mm Hg)	73.2 (13.0)	70.1 (13.7)
Waist circumference*** (cm)	102.9 (13.6)	92.7(15.4)
Glucose*** (mmol/L)	6.4(1.4)	5.9 (1.2)
Triglycerides (mmol/L)	1.7 (0.8)	1.6 (0.8)
HDL cholesterol*** (mmol/L)	1.2 (0.3)	1.5 (0.4)
Baseline physiological measures		
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)

N may vary slightly depending on measure. CAD = coronary artery disease, SBP = systolic blood pressure, DBP = diastolic blood pressure, HDL = high-density lipoprotein cholesterol, HR = heart rate, HF-HRV = high-frequency heart-rate variability, HF_{nu} = high-frequency heart-rate variability in normalized units. Significant sex differences for each variable are indicated with asterisks, *$p < .05$, **$p < .01$, ***$p < .001$.

Physiological Response Patterns and MetS

In the logistic regression analysis predicting MetS from HR Cluster, a significant main effect of HR emerged (complete results are summarized in Table 3). Those in Cluster 2 (who exhibited both high tonic and phasic HR activation) were significantly more likely to have MetS 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], $p = .04$.

In the logistic regression predicting MetS from HF-HRV Cluster, the HF-HRV by Sex interaction was significant; full results are presented in Table 4. Evaluation of the interaction revealed that this was due to the significant associations between HF-HRV response to the stress protocol and MetS in women. Women in Cluster 3 (who displayed a large decrease in HF-HRV) were significantly more likely to suffer from MetS 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], $p = .01$. Women in Cluster 2 (who displayed a stress-related increase in HF-HRV), were also more likely to

Table 3 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)	.04
Sex (male vs. female)	1.35 (0.94–1.93)	.10
Age (1 SD = 7.0 year increase in age)	1.04 (0.89–1.22)	.64
Presence of CAD	0.98 (0.69–1.39)	.91
BMI (1 SD = 5.3 kg/m^2 increase in BMI)	3.46 (2.77–4.32)	<.001
Exercise (hours/week) (1 SD=3.6 hour increase in exercise)	0.92 (0.79–1.06)	.25
Household income		
$40,000–59,999 vs. ≤$39,999	0.80 (0.51–1.27)	.35
$60,000–99,999 vs. ≤$39,999	0.66 (0.42–1.03)	.07
≥$100,000 vs. ≤$39,999	0.57 (0.34–0.93)	.03
Years of school	0.95 (0.80–1.11)	.50
Medication influencing MetS parameters	1.19 (0.72–1.94)	.50
Other medications	1.61 (0.80–3.23)	.18
Presence of comorbid medical conditions	1.50 (1.10–2.04)	.01
Sex hormone therapy	0.63 (0.32–1.27)	.20

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

Table 4 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†		.005
Cluster 2 vs. Cluster 1 within female	2.30 (1.30–4.07)	.004
Cluster 3 vs. Cluster 1 within female	2.57 (1.22–5.41)	.01
Cluster 2 vs. Cluster 3 within female	0.90 (0.44–1.84)	.77
Cluster 2 vs. Cluster 1 within male	0.69 (0.46–1.02)	.06
Cluster 3 vs. Cluster 1 within male	0.59 (0.35–1.00)	.05
Cluster 2 vs. Cluster 3 within male	1.16 (0.69–1.92)	.58
Cluster†		.40
Sex (male vs. female)ψ	1.32 (0.92–1.90)	.13
Age (1 SD=7.0 year increase in age)	1.02 (0.86–1.19)	.85
Presence of CAD	0.94 (0.66–1.33)	.72
BMI (1 SD=5.3 kg/m^2 increase in BMI)	3.50 (2.80–4.37)	<.001
Exercise (hours/week) (1 SD=3.6 hour increase in exercise)	0.91 (0.78–1.05)	.21
Household income		
$40 000–59,999 vs. ≤$39,999	0.83 (0.52–1.32)	.42
$60,000–99,999 vs. ≤$39,999	0.68 (0.43–1.07)	.09
≥$100,000 vs. ≤$39,999	0.59 (0.36–0.97)	.04
Years of school	0.94 (0.77–1.10)	.43
Medication influencing MetS parameters	1.29 (0.78–2.13)	.32
Other medications	1.54 (0.76–3.11)	.23
Presence of comorbid medical conditions	1.52 (1.11–2.07)	<.01
Sex hormone therapy	0.62 (0.30–1.25)	.18

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

have MetS than women in Cluster 1, OR = 2.30, [95% CI = 1.30–4.07], p = .004.

No significant main or interaction effects emerged for the LF/HF or HF_{nu} clusters (see Supplementary Tables S1 and S2).

Physiological Response Patterns and Continuous Metabolic Risk

A significant main effect of HR cluster emerged, F(1, 946) = 10.54, p = .001. Individuals in Cluster 2 had a greater metabolic risk score, (M = 0.14, SE = 0.16) than those in Cluster 1 (M = −0.47, SE = 0.09) when adjusted for covariates.

A significant main effect of HF-HRV cluster also emerged, F(2, 945) = 5.70, p = .003, with those in Cluster 2 (stress-related increases in HF-HRV) showing the highest adjusted MetS score (M = −0.02, SE = 0.13), compared to those in Cluster 1 (M = −0.59, SE = 0.12), and Cluster 3 (M = −0.49, SE = 0.19). There was a trend for an interaction between HF-HRV cluster and sex, F(2, 945) = 2.62, p = .07. Women in Cluster 2 (M = −0.83, SE = 0.20) had significantly higher adjusted metabolic risk scores than Women in Cluster 1 (M = −1.78, SE = 0.21), p = .001. Women in Cluster 3 showed a risk score intermediate to the other two groups (M = −1.32, SE = 0.31). In men, there were no significant differences in adjusted MetS risk between those in Cluster 1 (M = 0.64, SE = 0.15), Cluster 2 (M = 0.79, SE = 0.14), or Cluster 3 (M = 0.34, SE = 0.23). No significant main or interaction effects were observed for LF/HF or HF_{nu} clusters.

Given reviewer concerns regarding the inclusion of BMI as covariate, analyses were repeated without BMI. In general, results were consistent with the initial findings, although somewhat less pronounced.

Post Hoc Analyses

Additional ANOVA and chi-square analyses were performed to better characterize the participants in the HF-HRV clusters. HF-HRV clusters also did not differ significantly with regard to age, or other sociodemographic, medical, and/or behavioral variables. However, differences in psychological characteristics were observed. Given the sex difference observed in the main analyses, we examined whether differences in psychological factors across HF-HRV clusters differed as a function of sex. Women in Cluster 3 scored significantly higher on the CES-D (F(2,351) = 6.20, p = .002); PSQ, (F(2.351) = 5.06, p = .01); and STAI-State (F(2, 351) = 4.02, p = .002) than women in Clusters 1 and 2. In men, no significant differences in psychological factors across HF-HRV clusters were observed. Repeated measures ANOVAs were also conducted on self-reported stress, arousal, and affect in order to examine whether HF-HRV clusters differed in their subjective report of the stress protocol. No significant cluster or cluster*period effects emerged.

Discussion

The objective of this study was to examine associations between autonomic response patterns to psychological stress and MetS among a large heterogeneous sample of older men and women suffering from CAD or other noncardiovascular illness. Both men and women with elevated HR and incomplete recovery across the stress protocol were more likely to meet MetS 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 MetS. Women exhibiting greater 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 MetS. Analyses using a continuous representation of metabolic risk were mostly consistent with these results.

Men and women with greater tonic and phasic HR had a higher metabolic risk score and were nearly 50% more likely to meet MetS criteria than those displaying more moderate activation across the stress protocol. The literature pertaining to HR stress responses and MetS is scarce, although elevated HR at rest has been associated with MetS and/or its components in both concurrent and prospective research [32, 64–67]. 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. [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 poststress, were more than two times more likely of having MetS compared with women showing intermediate decreases in activity. This effect was less pronounced when using the continuous metabolic risk score. 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 in whom greater parasympathetic withdrawal to stress was associated with a poorer metabolic profile [32]. Though 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 large stress-related decreases in parasympathetic activity showed significantly more distress across a number of psychological parameters as compared to those in the other clusters. In men, no psychological differences between clusters were observed. Depression, anxiety, and stress have all been associated with MetS [68–72]. It is thus possible that the combination of heightened parasympathetic responses to stress and greater psychological vulnerability may have increased risk of MetS in these women, although this remains to be verified. It is equally possible that hyperreactivity 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].

Consistent with our prior investigation [31], absence of parasympathetic withdrawal in women was also associated with a higher metabolic risk score and with more than two times the odds of meeting MetS criteria compared to those exhibiting intermediate response styles. Absence of parasympathetic response has been associated with adverse health outcomes in this and other laboratories [73, 74]. For example, we observed that lack of parasympathetic stress response to an autonomic challenge (Valsalva maneuver) was related to more complications during and after cardiovascular surgery [73]. 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 HR and contractility [75, 76]. Activation of both ANS branches in response to stress may facilitate cardiovascular functioning in the short-term [73], but come at a price to the individual, as reflected in greater metabolic dysfunction and peri- or postsurgical complications. Furthermore, a growing body of research suggests that phasic HRV enhancement, or increases in parasympathetic activity during a stressor, may reflect emotional regulation efforts [77]. Typically, in the presence of a stressor, defense systems are activated and parasympathetic withdrawal occurs [78]. However, in situations requiring emotional regulation or self-regulatory behavior, phasic HRV enhancement may occur in order to facilitate successful regulation [78]. It is possible then that a sub-group of participants made effortful attempts to regulate their emotions during the anger recall task, resulting in increased vagal activity during the stressor. This is consistent with one study in which increased parasympathetic activation was observed while participants were exposed to an anger-provoking stimulus [79]. Research suggests that continuous attempts to repress or alter emotions at a surface level, rather than deeper emotional regulation aimed at truly changing internal states, creates dissonance and is linked to emotional exhaustion [80]. 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 including hypertension and cardiovascular disease [81–83].

It is noteworthy that women displayed less parasympathetic activation at rest compared with men in our sample. This was somewhat surprising as research suggests that women tend to have higher tonic HRV than men which is thought to protect women in part from

CVD and other adverse health outcomes [84]. This discrepancy may be attributed to the fact that the women in our sample were more psychologically compromised compared to men (manuscript in preparation). Indeed, psychological distress has been independently associated with lower HRV in prior research (e.g., [85, 86]). As mentioned above, survival bias in men may have also influenced the results, in essence excluding men who were more physiologically vulnerable as a function of lower baseline HRV.

Several factors limit the conclusions that can be drawn from this study. Although not uncommon of large epidemiological studies, only one stressor task was used [24, 87]. However, 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 ethnicities. 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 MetS. However, the results of our previous prospective investigation in healthy individuals suggested an etiological role of stress responses in MetS [31]. As BEL-AGE is ongoing and prospective, it will be possible to eventually examine the clinical significance of the current findings. Given the potential limitations in dichotomizing variables [59], MetS was defined and analyzed not only in categorical (using established criteria as per the National Cholesterol Education Program, ATP III [1]) but also continuous (sum of standardized scores) terms, with similar results, which increases confidence in the results obtained. Additionally, men and women differed on a number of sociodemographic and health-related variables at baseline, which may have confounded results. However, these differences are largely consistent with what is typically observed in the general population and are to be expected in a large heterogeneous sample. The use of cluster analysis may have led to reduced power to detect significant differences and/or artificial exaggeration of differences in scores across participants [59]. Its prognostic significance and reproducibility to other samples will need to be demonstrated in future research. Nevertheless, previous research in our laboratory suggest that findings using recovery change scores may be greatly misleading in the absence of their associated reactivity data [31]. Indeed, "greater recovery" (or mean change scores approaching zero) may actually reflect blunted reactivity, which may be overlooked if reactivity and recovery change scores are examined separately. Moreover, the use of cluster analyses revealed the existence of a sub-group of individuals displaying parasympathetic activation during stress, a group that has been rarely discussed in stress response research. Indeed, it may be that previous studies showing an association between individual parameters of MetS and "reduced" stress reactivity might instead have been showing the potentially noxious effect of increased vagal activation during stress [24–26].

These limitations notwithstanding, 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 MetS in adults, and the first to employ cluster analysis to characterize stress response patterns. It also included 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 [65, 67, 88]. Our results further highlight their potential role in MetS. The fact that findings differed significantly between men and women reinforces the importance of evaluating sex differences in this field of research. The ecological validity of our stress protocol is also noteworthy, as the anger recall task more closely resembles stressors encountered in everyday life, as compared to more artificial cognitive tasks [89, 90]. Finally, our investigation included a large sample size of individuals at elevated cardio-metabolic risk and was sufficiently powered to control for highly relevant medical, demographic, and behavioral covariates.

To conclude, this study corroborates research suggesting that hyperreactivity to and delayed recovery from stress of the autonomic nervous system is associated with MetS, 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 [56, 91]. Moderate reactions to stress may reflect the system's ability to adapt to frequently changing environmental or internal demands, whereas more extreme responses, whether heightened or blunted, may suggest maladaptive responses that increase risk for various disease states [91]. 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 MetS. Preliminary data from our laboratory suggests that this may indeed be helpful (manuscript in preparation).

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Compliance with Ethical Standards

Author(s) Statement of Conflict of Interest and Adherence to Ethical Standards Christina Gentile, Blaine Ditto, Alain Deschamps, and Bianca D'Antono have no conflicts of interest to report. All procedures, including the informed consent process, were conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

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