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Mental stress is associated with coronary endothelial dysfunction in women with chest pain and non-obstructive coronary artery disease

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ABSTRACT

Objective: We evaluate the association between chronic mental stress (MS) and coronary endothelial function in patients with chest pain and nonobstructive coronary artery disease (CAD) separately in males and females.
Methods: Patients with nonobstructive CAD (stenosis <40 %) at coronary angiography underwent an invasive assessment for coronary endothelial dysfunction (CED). Macrovascular CED was defined as a percentage change in coronary artery diameter to acetylcholine (%ΔCADAch) ≤ −10 % and microvascular CED was defined as a percentage change in coronary blood flow to acetylcholine (%ΔCBFAch) ≤−50 %. Patients completed a questionnaire within 2 years of the index procedure that included questions regarding chronic MS. The frequency of macrovascular, microvascular and any type of CED was compared across groups. Logistic regression analyses were performed to assess the association between MS and CED.
Results: Between January 2017 and December 2022, 211 patients (mean (sd) age 54.4 (13.6) yrs, 71.0 % female) were included. One hundred forty-two (67.3 %) patients had any type of CED. In females with significant MS there was a higher proportion of individuals with any type of CED compared to without CED (43 (42.6 %) vs. 12 (24.5 %), p = 0.0362). In a multivariable analysis MS was associated with any type of CED in females: OR (95 % CI) 2.70 (1.24–6.25); p = 0.0156.
Conclusion: Chronic MS is associated with CED in females with chest pain and nonobstructive CAD. Chronic MS may underly the mechanism for chest pain in these patients and may play a contributory to cardiovascular disease through its association with endothelial dysfunction.

1. Introduction

Increased mental stress (MS) is associated with an elevated risk of cardiovascular events [1]. Acute experimentally-induced MS has been correlated with myocardial ischemia demonstrated using myocardial perfusion imaging in patients with stable coronary artery disease (CAD) [2] and following a recent myocardial infarction (MI) [3]. Further evidence demonstrates that MS-induced myocardial ischemia is associated with an increased risk of cardiovascular death and MI in patients with stable CAD [4,5] and following a recent cardiac event [6]. The mechanism underpinning MS-induced ischemia and the associated increased risk of cardiac events is multifactorial and is thought to relate to hemodynamic responses, increased vasomotion and endothelial dysfunction [7,8,9].

Stress-induced (Takatsubo) cardiomyopathy often occurs in the setting of acute MS and affects predominantly females with nonobstructive CAD [10]. Women with a history of stress-induced cardiomyopathy exhibited impaired peripheral endothelial function and excessive vasoconstriction in response to acute MS compared to age-matched controls and patients with a prior MI [11]. Women with a history of stress-induced cardiomyopathy also exhibited reduced endothelial-dependent coronary microvascular function in response to

Abbreviations: BMI, Body Mass Index; CAD, Coronary Artery Disease; CBF, Coronary Blood Flow; CED, Coronary Endothelial Dysfunction; CVD, Cardiovascular disease; HDL, High Density Lipoprotein; LDL, Low Density Lipoprotein; MI, Myocardial Infarction; MS, Mental Stress; % Δ CAD Ach, Percentage change in coronary artery diameter in response to acetylcholine; % Δ CBF Ach, Percentage change in coronary blood flow in response to acetylcholine.

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acetylcholine [12], suggesting that chronically impaired coronary vascular reactivity plays a role in stress-mediated cardiovascular disease. Acute MS resulted in reductions in coronary blood flow [13], and constricted epicardial coronary arteries in patients with stable CAD [14]. However, the effects of *chronic* MS on coronary vasomotion in patients with nonobstructive CAD is unknown. Thus, in the current study we evaluate the association between chronic MS on invasively derived measures of macrovascular and microvascular coronary endothelial function in individuals who present with chest pain and nonobstructive CAD and hypothesize that chronic MS is associated with coronary endothelial dysfunction (CED) in women. We also evaluate the association between a number of additional social determinants of health (SDOH), that may confound the relationship between MS and coronary endothelial function.

2. Methods

This cross-sectional was approved by the Mayo Clinic Institutional Review Board, and all study participants provided their informed consent. Patients were referred to our institution by their healthcare provider for the assessment of chest pain, and/or an abnormal noninvasive stress test. Where deemed clinically appropriate, patients were referred for elective coronary angiograms. Patients with nonobstructive CAD (maximal luminal stenosis of any epicardial coronary artery <40 %) proceeded to invasive coronary vasoreactivity testing as outlined below with the following exceptions: acute coronary syndrome; acute renal failure; uncontrolled hypertension; left ventricular ejection fraction of 50 % or less and left ventricular hypertrophy [15,16,17]. Patients who completed the SDOH questionnaire within 2 years of the index cardiac catheterization were included in this study (see below).

2.1. Coronary vasoreactivity testing protocol

Consecutive patients presented to the cardiac catheterization laboratory in the fasting state and all cardiovascular medications, including nitrates and calcium channel blockers, had been discontinued for at least 24 h. Routine diagnostic coronary angiography was performed on all patients using standard clinical protocols. Angiograms were reviewed prior to the infusion of any pharmacological agents. In cases where the severity of stenosis was uncertain, online quantitative coronary angiography was used. All patients underwent evaluation of microvascular and macrovascular coronary endothelial function as previously described [15,16,17]. Following intravenous administration of 5000–7000U of heparin, a Doppler guidewire (Flowire, Volcano) 0.014 in. in diameter within a 3-F. Slip-Cath Infusion Catheter (Cook Medical) was positioned into the mid-portion of the left anterior descending coronary artery, 2–3 mm distal to the tip of the infusion catheter. Heart rate and mean arterial blood pressure were continuously monitored throughout each procedure [15,16,17].

Baseline mean peak velocity was recorded using the intracoronary Doppler wire after which acetylcholine was infused at concentrations of 10^{-6}, 10^{-5} and 10^{-4} M (to achieve estimated coronary bed concentrations of 10^{-8}, 10^{-7} and 10^{-6} M respectively) for 3 min at each concentration to assess endothelial-dependent function as previously described [15,16,17].Infusions were performed using a Harvard pump to maintain infusion rates of less than 1 % of the estimated coronary blood flow (CBF). Doppler measurements of mean peak velocity were performed after each infusion followed by repeat coronary angiography. Coronary artery diameter was measured at baseline and after the infusion with acetylcholine, by an independent investigator blinded to Doppler velocity data using a previously described computer-based image analysis system [18]. Endothelial-dependent CBF was then calculated using the following, as previously described [19]: $\text{CBF} = \pi(\text{mean peak velocity}/2)(\text{coronary artery diameter}/2)^2$. The maximal percentage increase in CBF in response to acetylcholine compared to the CBF at baseline was then calculated (%ΔCBFAch). For quality control, all measurements were performed in the segment 5 mm distal to the tip of the Doppler wire and following each infusion, the diameter was measured in the same segment of the vessel [15,16,17].

2.2. Definition of Terms

Macrovascular CED was defined as a coronary artery diameter in response to acetylcholine (%ΔCADAch) of −10 % or less. Microvascular CED was defined as a maximal percentage increase in CBF in response to any dose of acetylcholine compared to baseline CBF (%ΔCBFAch) of 50 % or less [15,16,17]. Coronary endothelial dysfunction was defined as the presence of impaired endothelial-dependent macrovascular and/or microvascular dysfunction.

2.3. Patient information

Data was collected on conventional cardiovascular risk factors including hypertension, diabetes mellitus, hyperlipidemia, smoking status and body mass index (BMI); biochemical parameters including fasting blood glucose, HbA1c, serum total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), and triglycerides; and medication use including antiplatelet agents, antihypertensive medication, and lipid-lowering therapy. Smoking was categorized as a history of current smoking, former smoking or never smoking; hyperlipidemia was defined by a documented history of hyperlipidemia, treatment with lipid-lowering therapy, a LDL cholesterol level above the target (<130 mg/dL for low risk patients, < 100 mg/dL for moderate-high risk patients, <70 mg/dL for very high risk, and <55 mg/dL for extreme high risk patients based on 10-year atherosclerotic cardiovascular disease risk), high-density lipoprotein cholesterol <40 mg/dL in men or <50 mg/dL in women, or triglycerides >150 mg/dL. Type 2 diabetes mellitus was defined as a documented history of or treatment for type 2 diabetes, or an HbA1c of >6.5, if available. Hypertension was defined as a documented history of or treatment of the condition, or a systolic blood pressure measurement of more than 130 mmHg, or diastolic blood pressure measurement more than 90 mmHg. All blood test results included in this study are based on blood samples obtained on the morning of the index procedure. Information was also collected on past medical history including other vascular diseases (defined as a documented history of peripheral vascular disease, stroke or transient ischemic attack) [15,16,17].

2.4. Mental stress and social determinants of health

Data on SDOH were obtained using a standardized and validated questionnaire from each patient on one occasion within 2 years of the index cardiac catheterization procedure during one of each patient's appointment at Mayo Clinic in Minnesota. The survey captures information on SDOH through 31 multiple-choice questions covering 11 separate domains: physical activity, social connection, housing instability, financial strain, transportation difficulties, alcohol use, smoking, nutrition, employment, education, and MS. The response to each multiple-choice question may be binary or have multiple categories, but in each case the response corresponds to a score on a linear scale with lower scores indicating a less favorable value (i.e., less physical activity, lower social connection, greater housing instability etc.). The net assessment of each domain could vary from one question to three questions (e.g., for physical activity there are two questions: i) on average, how many days per week do you engage in moderate to strenuous exercise (like a brisk walk)? and ii) on average, how many minutes do you engage in exercise at this level? whereas for education there is one question: i) what is the highest level of school you have completed or the highest degree you have received?) Depending on the net score for each domain individuals will be categorized into two groups for each domain, with higher scores placing individuals in one group and lower scores placing them into another.

In the area of MS individuals answered one question as follows: do you feel stress – tense, restless, nervous, or anxious, or unable to sleep at night because your mind is troubled all the time: not at all, only a little, rather much, to some extent, very much? Individuals answering 'not at all' and 'only a little' were categorized in the no MS group whereas those responding with 'rather much,' 'to some extent' and 'very much' were categorized in the significant MS group.

2.5. Statistical analysis

Patients were categorized as having (any) CED versus normal coronary endothelial function and baseline characteristics were compared between groups (Table 1). The %ΔCADAch, as a continuous variable and index of macrovascular coronary endothelial function, and %ΔCBFAch, as a continuous variable and index of microvascular coronary endothelial function were then compared between patients with and without significant MS in all patients and after stratifying by sex. Patients were then subdivided into groups according to if they had normal versus abnormal macrovascular CED (%ΔCADAch ≤ -10 %) and normal versus abnormal microvascular CED (%ΔCBFAch ≤ 50 %). The proportion of individuals with significant MS who had CED (macrovascular, microvascular and any) was compared to those with significant MS without CED, in all patients and across both sexes. We then estimated the odds ratio of having significant MS in individuals with macrovascular, microvascular and any CED as categorical independent variables in univariable and multivariable analyses, in all patients and after stratifying by sex. Last, the frequency of any CED was compared across the 9 SDOH domains (excluding smoking and MS) in all patients and across sexes. Each SDOH was presented as two groups with higher or lower scores depending on the domain and its constituent questions. Continuous variables were presented as a mean (standard deviation), and categorical variables were presented as frequencies (percentages). Differences between groups were analyzed using Student's T test and Wilcoxon rank-sum test for continuous variables and Pearson's chi-squared test for proportions. A p-value less than 0.05 was considered significant and statistical analyses were performed using SPSS Statistics software 2022.

Table 1
Summary of baseline clinical characteristics of patients with normal and abnormal coronary endothelial function.

	Normal coronary endothelial function N = 69 (32.7 %)	Any abnormal endothelial function N = 142 (67.3 %)	*P Value*
Age, years (SD)	52.1 (13.6)	54.8 (13.6)	0.184
Female, n (%)	50 (72.5)	100 (70.4)	0.759
White caucasian, n (%)	66 (95.7)	133 (93.7)	0.419
BMI, kg/m^2 (SD)	28.4 (3.4)	28.7 (4.1)	0.493
Hypertension, n (%)	37 (53.6)	68 (47.9)	0.162
Diabetes mellitus, n (%)	6 (8.7)	7 (4.9)	0.286
Hyperlipidemia, n (%)	38 (55.1)	71 (50.0)	0.510
History of MI, n (%)	4 (5.8)	6 (4.2)	0.614
Obstructive sleep apnea, n (%)	6 (8.7)	21 (14.8)	0.214
History of vascular disease, n (%)	18 (26.1)	33 (23.2)	0.312
History of vasospasm disease, n (%)	21 (30.4)	47 (33.1)	0.698
Smoking status, n (%)			
Never smoked	16 (23.2)	33 (23.2)	
Former smoker	36 (52.2)	74 (52.1)	
Current smoker	17 (24.6)	35 (24.7)	0.992
Hemoglobin, mg/dL (SD)	13.5 (1.1)	13.6 (1.5)	0.848
Leukocytes, x 10^9/L (SD)	6.8 (2.0)	6.6 (2.1)	0.592
Platelets, x 10^9/L (SD)	232.7 (56.6)	254.5 (64.0)	0.018*
Glucose, mg/dL (SD)	105.8 (31.0)	102.7 (25.0)	0.446
HbA1c, % (SD)	5.6 (1.2)	5.4 (1.0)	0.528
Total cholesterol, mg/dL (SD)	175.3 (37.5)	175.0 (43.1)	0.959
HDL-C, mg/dL (SD)	69.0 (46.3)	64.9 (35.3)	0.500
LDL-C, mg/dL (SD)	94.3 (32.7)	94.0 (35.5)	0.952
Triglycerides, mg/dL (SD)	113.9 (79.7)	122.6 (68.9)	0.434
Creatinine, mg/dL (SD)	0.9 (0.2)	1.0 (0.2)	0.324
BUN, mg/dL (SD)	15.5 (5.2)	14.9 (5.2)	0.471
ACE-inhibitor use, n (%)	12 (17.4)	25 (17.6)	0.952
Aspirin use, n (%)	32 (46.4)	74 (52.1)	0.434
Beta-blocker use, n (%)	30 (43.5)	48 (33.8)	0.184
Calcium channel blocker use, n (%)	27 (39.1)	62 (43.7)	0.505
Lipid lowering therapy use, n (%)	31 (44.9)	68 (47.9)	0.686
Psychotropic medication use, n (%)	36 (52.2)	75 (52.8)	0.890
Systolic blood pressure, mmHg (SD)	123.1 (15.9)	123.6 (17.2)	0.832
Diastolic blood pressure, mmHg (SD)	75.6 (13.8)	75.3 (11.0)	0.891

Abbreviations – ACE: Angiotensin Converting Enzyme; BMI: Body Mass Index; eGFR: estimated Glomerular Filtration Rate; HbA1c: Glycosylated hemoglobin; HDL-C: High Density Lipoprotein Cholesterol; LDL-C: Low Density Lipoprotein Cholesterol; MI: Myocardial Infarction

3. Results

3.1. Sample overview

Between January 2017 and December 2022, 211 patients (mean (sd) age 54.4 (13.6) years, 71.0 % female) underwent coronary angiography with invasive testing for CED and completed a SDOH questionnaire that included an assessment of MS within 2 years of the index cardiac catheterization. One hundred forty-two (67.3 %) of all patients had any CED comprising macrovascular and/or microvascular CED. In males 41 (67.2 %) had evidence of any CED and in females 101 (67.3 %) had any CED. Table 1 summarizes the baseline characteristics of all patients with and without any CED. Individuals with any abnormal CED on average had high platelet values than those with normal coronary endothelial function (platelets, x 10^9/L (SD): 254.5 (64.0) vs. 232.7 (56.6), p = 0.018). Otherwise, there were no other significant differences between groups with respect to demographic, clinical or laboratory variables or in medication use.

3.2. Coronary endothelial function according to presence of significant mental stress

Table 2 demonstrates the relationship between the presence versus absence of significant MS and % Δ CAD Ach and % Δ CBF Ach as measures of macrovascular and microvascular coronary endothelial function in all patients and after stratifying by sex. There were no significant differences in the absolute % Δ CAD Ach and % Δ CBF Ach across individuals with versus without significant MS in all patients of separatelly in males or females.

3.3. Frequency of mental stress according to type of coronary endothelial dysfunction

Table 3 demonstrates the proportion of individuals with significant MS who had macrovascular CED, microvascular CED and any type of CED in all patients and by sex. The proportion of patients with significant MS did not vary significantly between those with compared to those without macrovascular CED or between those with compared to those without microvascular CED in all patients and across both sexes. The proportion of patients with significant MS did not vary significantly between those with compared to those without any type of CED amongst

Table 2
Relationship between mental stress and % δ CAD Ach and % δ CBF ach as measures of macrovascular and microvascular coronary endothelial function across all patients and after stratifying by sex.

	No mental stress	Mental stress	*P value*
All patients – mean (SEM)			
% Δ CAD Ach	3.20 ± 1.75	6.04 ± 2.91	0.3798
% Δ CBF Ach	38.31 ± 6.26	53.59 ± 9.31	0.1602
Males – mean (SEM)			
% Δ CAD Ach	6.95 ± 4.07	1.32 ± 3.13	0.2771
% Δ CBF Ach	36.22 ± 11.04	66.09 ± 17.06	0.1468
Females – mean (SEM)			
% Δ CAD Ach	2.45 ± 1.88	9.58 ± 4.30	0.0876
% Δ CBF Ach	42.84 ± 7.83	47.64 ± 11.46	0.7206

Abbreviations – % Δ CAD Ach: Percentage change in coronary artery diameter in response to acetylcholine; % Δ CBF Ach: Percentage change in coronary blood flow in response to acetylcholine

all patients and in males. However, amongst females with significant MS there was a significantly higher proportion of individuals who had any type of CED compared to those without CED (43 (42.6 %) vs. 12 (24.5 %), p = 0.0362). In a univariable analysis, the OR (95 % CI) for the association between MS and any CED was as follows: 2.26 (1.04 – 4.88).

3.4. Coronary endothelial dysfunction and mental stress – Multivariable analysis

Fig. 1 demonstrates the results of multivariable analyses evaluating the association between significant MS and macrovascular CED, microvascular CED and any type of CED in all patients and separately in males and females. Multivariable analyses were adjusted for age, hypertension, diabetes mellitus and smoking status. The association between MS and macrovascular CED and microvascular CED in all patients and in males and females separately was not significant. Further, there was no significant associations between MS and any type of CED in all patients or in males. However, amongst females MS was significantly associated with any type of CED as follows: odds ratio (95 % CI) 2.70 (1.24–6.25); p = 0.0156.

3.5. Frequency with any coronary endothelial function across SDOH domains

Table 4 demonstrates the proportion of individuals with any type of CED whose scores derived from the SDOH questionnaire corresponded to unfavorable compared to favorable socioeconomic outcomes across the 9 domains evaluated. These domains included physical activity, social connection, housing security, financial strain, transportation concerns, alcohol consumption, nutrition concerns, employment status and educational level attained. Frequencies are shown for all patients and after stratifying by sex. There were no significant differences in the proportion of individuals with any type of CED across any of the 9 SDOH domains in all patients or in males or females separately.

Table 3
Univariable analyses of the relationship between mental stress and coronary endothelial dysfunction across all patients and after stratifying by sex.

	No macrovascular CED	Macrovascular CED	*P value*	Odds ratio	95% Confidence interval	*P value*
All patients n=165n=46						
Mental stress	70 (42.4%)	20 (43.5%)	0.8983	1.04	0.54 – 2.01	0.8983
Males n=46n=15						
Mental stress	25 (54.3%)	10 (66.7%)	0.3737	1.70	0.52 – 5.55	0.3737
Females n=119n=31						
Mental stress	45 (37.8%)	10 (32.3%)	0.6218	0.8070	0.34 – 1.89	0.6218
All patients n=88n=123						
Mental stress	42 (47.7%)	69 (56.1%)	0.8905	1.04	0.59 – 1.82	0.8905
Males n=25n=36						
Mental stress	14 (56.0%)	17 (47.2%)	0.6067	0.77	0.28 – 2.11	0.6067
Females n=63n=87						
Mental stress	32 (50.8%)	37 (42.5%)	0.3141	1.44	0.71 – 2.93	0.3141
	No CED	CED	*P value*	Odds Ratio	95% Confidence interval	*P value*
All patients n=69n=142						
Mental stress	25 (36.2%)	65 (45.8%)	0.1886	1.49	0.82 – 2.68	0.1886
Males n=20n=41						
Mental stress	13 (65.0%)	22 (53.7%)	0.7884	1.16	0.40 – 3.31	0.7884
Females n=49n=101						
Mental stress	12 (24.5%)	43 (42.6%)	0.0362*	2.26	1.04 – 4.88	0.0362*

Abbreviations – CED: Coronary Endothelial Dysfunction.

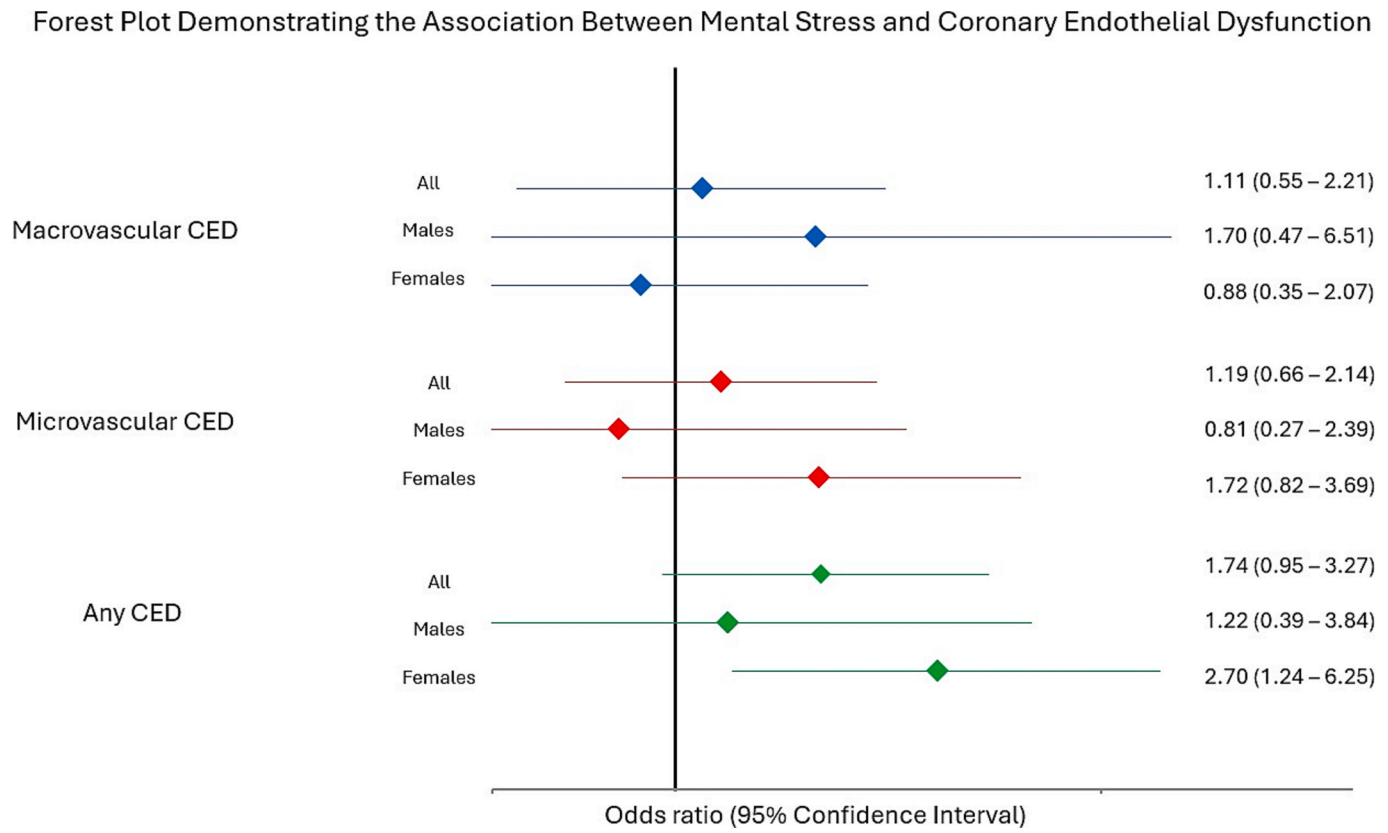

Fig. 1. Forrest Plot Demonstrating Multivariable Analyses of the Relationship Between Mental Stress and Coronary Endothelial Dysfunction Across All Patients and After Stratifying by Sex. Abbreviations – CED: Coronary Endothelial Dysfunction. Multivariable analyses were adjusted for age, hypertension, diabetes mellitus and smoking status.

4. Discussion

In the current study we demonstrate that self-reported chronic MS is associated with CED in women who present with chest pain and/or a positive stress test suggesting the presence of myocardial ischemia and nonobstructive CAD at angiography in both univariable and multivariable analyses. Chronic MS was not associated with CED in males. Further, there were no significant differences in the frequency of CED across the various domains of SDOH that included physical activity, social connection, housing security, nutrition and transportation concerns, financial strain, alcohol consumption, employment status and education level when comparing respondents dichotomized into high and low scoring groups. These SDOH may coexist with and confound the effects of MS [20] yet our findings suggest that these psychosocial variables were not associated with CED in this study sample. Thus, our findings support the notion that chronic self-reported MS may be implicated in CED and might therefore account, at least in part, for the underlying mechanism of the chest pain syndrome with which these patients present. Moreover, these findings suggest that chronic MS could also play a role in increasing the risk of cardiovascular events through its association with endothelial dysfunction.

4.1. Mental stress and endothelial dysfunction

MS is associated with an increased risk of cardiovascular events [1,9,21]. Most of the studies that have evaluated the cardiovascular effects of MS have focused on experimentally induced *acute* MS as the independent variable with exercises such as mental arithmetic or public speaking [4,6,22,23]. These studies have temporally correlated acute MS with myocardial ischemia on myocardial perfusion imaging in patients with CAD [2] and following a recent MI [3]. Moreover, a number of studies have also correlated *acute* stress with endothelial dysfunction measured in the peripheral vasculature both in large vessels using flow-mediated dilatation [22,23,24] and the microcirculation [2,3,25] using peripheral arterial tonometry. The current study differs from these reports in that we evaluated the association of *chronic* self-reported MS on the coronary vascular bed.

There are in fact few studies that have evaluated the effects of MS on coronary endothelial function. Yeung et al. evaluated coronary vasomotion in response to *acute* MS in a study published more than 30 years ago that included 26 subjects (with 4 controls). They demonstrated epicardial vasoconstriction in response to *acute* MS in segments already narrowed with atherosclerosis, but no vasoconstriction in smooth segments without atherosclerosis. Further CBF reduced in response to acute MS in patients with stenosed arteries but increased in those without atherosclerosis. The authors also demonstrated a significant correlation between the vasomotor response to MS and the vasomotor response to intracoronary acetylcholine [13] suggesting that defective endothelial-dependent nitric-oxide release underpins both processes. Another study including 12 subjects with symptomatic myocardial ischemia demonstrated epicardial vasoconstriction after participants were asked to recall a recent event that elicited anger [26]. A further study with 76 individuals (59 of whom had CAD) demonstrated epicardial vasoconstriction in only 18.6 % of participants with CAD after they were asked to perform a mental arithmetic study. The authors ascribed this variance to differences in hemodynamic responses to mental arousal across participants. Interestingly, CBF was attenuated in response to MS in patients with CAD but increased in those without disease [27]. Last, a recent study including 38 patients with stable CAD who were asked to perform mental arithmetic testing demonstrated epicardial coronary vasoconstriction but no changes in CBF [14]. Collectively these findings indicate that *acute* MS may induce variable macrovascular and microvascular

Table 4
Frequency of subjects in social determinants of health categories in all patients and across both sexes.

	Any abnormal endothelial function – N (%)	*P Value*
All		
Physical activity, Low	68 (61.8 %)	0.070
Physical activity, High	63 (74.1 %)	
Males		
Physical activity, Low	18 (56.3 %)	0.055
Physical activity, High	24 (79.3 %)	
Females		
Physical activity, Low	50 (65.8 %)	0.429
Physical activity, High	39 (75.0 %)	
All		
Social connection, Low	72 (72.7 %)	0.112
Social connection, High	68 (62.4 %)	
Males		
Social connection, Low	21 (72.4 %)	0.410
Social connection, High	21 (62.5 %)	
Females		
Social connection, Low	51 (72.8 %)	0.308
Social connection, High	47 (66.1 %)	
All		
Housing security, Low	6 (100.0 %)	0.070
Housing security, High	42 (63.6 %)	
Males		
Housing security, Low	1 (100.0 %)	0.428
Housing security, High	7 (70.0 %)	
Females		
Housing security, Low	5 (100.0 %)	0.103
Housing security, High	35 (66.0 %)	
All		
Financial strain, Yes	20 (62.5 %)	0.586
Financial strain, No	116 (67.4 %)	
Males		
Financial strain, Yes	4 (57.1 %)	0.594
Financial strain, No	37 (67.3 %)	
Females		
Financial strain, Yes	16 (66.7 %)	0.893
Financial strain, No	79 (66.4 %)	
All		
Transportation concerns, Yes	8 (76.9 %)	0.445
Transportation concerns, No	132 (66.7 %)	
Males		
Transportation concerns, Yes	0 (0.0 %)	N/A
Transportation concerns, No	42 (66.1 %)	
Females		
Transportation concerns, Yes	8 (88.9 %)	0.963
Transportation concerns, No	90 (68.1 %)	
All		
Excessive alcohol consumption, Yes	37 (58.7 %)	0.160
Excessive alcohol consumption, No	110 (69.7 %)	
Males	8 (66.7 %)	0.965
Excessive alcohol consumption, Yes	36 (66.0 %)	
Excessive alcohol consumption, No	29 (58.0 %)	0.142
Females	74 (72.0 %)	
Excessive alcohol consumption, Yes		
Excessive alcohol consumption, No		
All		
Nutrition concerns, Yes	10 (71.4 %)	0.714
Nutrition concerns, No	130 (66.7 %)	
Males		
Nutrition concerns, Yes	3 (100.0 %)	0.204
Nutrition concerns, No	39 (64.4 %)	
Females		
Nutrition concerns, Yes	7 (70.0 %)	0.879
Nutrition concerns, No	91 (68.4 %)	
All		
Unable to work/not working	10 (62.5 %)	0.620
Working or voluntary retirement	38 (69.1 %)	
Males	1 (100.0 %)	0.428
Unable to work/not working	7 (70.0 %)	
Working or voluntary retirement	9 (64.3 %)	0.702
Females	31 (72.1 %)	
Unable to work/not working		
Working or voluntary retirement		
All		
Less than college degree education	30 (68.2 %)	0.888
At least college degree education	112 (67.1 %)	
Males	9 (61.5 %)	0.694
Less than college degree education	34 (67.3 %)	
At least college degree education	21 (67.8 %)	0.990
Females	78 (69.6 %)	
Less than college degree Education		
At least college degree education		

vasoconstriction in obstructive coronary disease, while smooth coronary arteries may be protected from this effect. In the current study, we extend these findings by demonstrating an association between MS and impaired endothelial-mediated coronary vasomotion in a large sample of individuals with nonobstructive CAD. These findings suggest that obstructive CAD may not be the necessary substrate for an abnormal endothelial-dependent vasomotor response in the context of MS even if chest pain and ischemia are the clinical manifestations. Further, the current study focusses on *chronic* self-reported MS, which as a risk factor is more relevant to patients and their everyday lives than is *acute* experimentally induced MS. In addition, the effects of MS on CED assessed in the current study did not appear to be driven by a number of additional potentially coexisting [20] SDOH. Last, the association of MS with CED remained significant in female participants even after adjusting for age, smoking, diabetes and hypertension, suggesting that this effect cannot be explained away by the presence of traditional cardiovascular risk factors, which in the case of the modifiable variables, also often cluster with MS [28].

4.2. Mechanism of association between mental stress and endothelial dysfunction

Acute MS elicited from public speaking tasks [29] and anger provocation [30] have been associated with an increase in circulating endothelial cell-derived microparticles. Further, both acute and chronic MS is associated with lower levels of nitric oxide synthase mRNA expression [31,32] leading to endothelial dysfunction. Studies using both functional magnetic resonance imaging and positron MRI and positron emission tomography have demonstrated that stressful stimuli lead to the activation of the amygdala, which through its connections to the hypothalamus results in activation of the hypothalamic-pituitary-axis leading to the release of cortisol and increased sympathetic nervous activity [33,34,35]. Catecholamines bind to surface receptors of macrophages inducing the expression of inflammatory cytokines in a manner that is exacerbated under conditions of chronic MS [36]. MS also enhances the binding of norepinephrine to adrenergic receptors in bone marrow progenitor inflammatory cells resulting in increased leukopoietic proliferation [37,38,39,40]. Newly released inflammatory cells produce further inflammatory cytokines resulting in greater inflammation in a feed-forward loop [41]. This enhanced leukocyte

recruitment and adhesion ("vascular inflammation") results in increased endothelial cell permeability and endothelial dysfunction [42]. Thus the endothelium may be the site where the pathophysiologic effects of MS are transduced [9].

Studies have demonstrated that experimentally induced *acute* MS results in prolonged endothelial dysfunction after the discontinuation of the stressor [22,24]. Repeated encounters with acute stressors over periods of time could therefore result in recurrent episodes of prolonged endothelial dysfunction that accumulates over time and does not fully recover. Epidemiological studies have demonstrated that individuals with chronic MS related to their occupation or to providing prolonged care to family members with chronic illness is associated with peripheral endothelial dysfunction [43,44]. In a similar vein, individuals with a prior MI who reported higher levels of chronic psychological distress had a greater odd of MS-induced myocardial ischemia compared to those with low psychological distress [45]. Endothelial dysfunction is the first step in the atherosclerotic process and is independently associated with an increased risk of CVD events [46] even in individuals with minimal traditional risk factors [46,47,48]. Thus, the findings of the current study support the concept that chronic MS might also result in CED, which in turn may underly the mechanism for chest pain and ischemia and could play a role in the increased risk of cardiovascular events in these patients. Further prospective studies are required to clarify this notion.

4.3. Clinical implications

In the current study we demonstrated that chronic MS was associated with CED in female patients but not in males. When patients with nonobstructive CAD were exposed to *acute* MS females exhibited greater peripheral endothelial dysfunction compared to males [25]. The current study extends these findings to the coronary circulation in women who report *chronic* MS. Women experience adverse CVD events more frequently in the absence of obstructive CAD, which may be explained by a higher prevalence of functional vascular abnormalities such coronary microvascular dysfunction and endothelial dysfunction [49]. Interestingly, stress-induced cardiomyopathy affects predominantly females with nonobstructive CAD and is also associated with impaired peripheral endothelial function and excessive vasoconstriction in response to acute MS [11], as well as reduced endothelial-dependent coronary microvascular function in response to acetylcholine [12]. While the current study is, to our knowledge, the first to demonstrate an association between *chronic* MS and CED our group has previously demonstrated an association between anxiety disorders and CED in females [50]. Thus, sex-based physiological differences may result in an increased vulnerability to the deleterious vascular effects of psychosocial risk factors such as MS in women. Further studies are required to clarify the underlying mechanism of this effect across sexes. Future studies should also evaluate the value of incorporating chronic MS, and other psychosocial disorders, in risk stratification models particularly as management strategies targeting these variables are emerging including stress management training [51], aerobic exercise [52], and antidepressant pharmacotherapy [53]. Novel pharmacotherapeutic agents, such as the sodium glucose transporter empagliflozin [54], L-arginine [55], and NAD + with nicotinamide riboside [56], have also shown promise in improving endothelial function in frail elderly patients with hypertension or peripheral arterial disease. Such agents could therefore be considered to ameliorate the potentially deleterious vascular effects of chronic MS, although further studies will be required to evaluate these therapies.

4.4 Limitations.

The current study has some limitations. First, our sample is made up of patients who were referred for coronary angiography at a tertiary referral center and so comprises a select population. Second, the categorization of MS was based on self-report from a single question that was included in a wider questionnaire addressing SDOH, making this measure vulnerable to misclassification and inherently subjective. Nevertheless, MS *is* a self-reported subjective and individual experience making it challenging to measure this variable using alternative methods. Similarly, given the variable intervals between the completion of the questionnaire and the invasive coronary angiogram across the included patients (all were completed within 2 years of the index procedure), the classification of chronic MS may be influenced by recall bias. Last, this was a cross-sectional study and so we are unable to demonstrate causality between MS and CED.

5. Conclusion

Chronic MS is associated with CED in females presenting with chest pain and nonobstructive CAD. Self-reported chronic MS may thus underly the mechanism for the syndrome of chest pain and/or a positive stress test in these patients. Further, these findings support the notion that chronic MS could, at least in part, play a contributory role to vascular disease and adverse cardiovascular events through endothelial dysfunction. Further studies are required to clarify these findings and to determine if therapies targeting chronic MS reduce the risk of cardiovascular events by impacting endothelial function.

Patient and public involvement

None.

Ethical approval

This study was approved by the Mayo Clinic Institutional Board Review, and all patients provided their informed written consent to participate in this study.

CRediT authorship contribution statement

Jaskanwal Deep S Sara: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Nazanin Rajai:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Scott Breitinger:** Writing – review & editing, Methodology. **Betsy Medina-Inojosa:** Writing – review & editing, Formal analysis, Data curation. **Lilach O Lerman:** Writing – review & editing, Supervision, Conceptualization. **Amir Lerman:** Writing – review & editing, Methodology, Investigation, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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