Published in final edited form as:

Psychosom Med. 2019 January ; 81(1): 57–66. doi:10.1097/PSY.0000000000000636.

Sex-Specific Association Between Coronary Artery Disease Severity and Myocardial Ischemia Induced by Mental Stress

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Abstract

Objective: It is unclear whether mental stress-induced myocardial ischemia (MSIMI) is related to obstructive coronary artery disease (CAD). We examined this question and contrasted results with ischemia induced by conventional stress testing (CSIMI). Because women are more susceptible to ischemia without coronary obstruction than men, we examined sex differences.

Methods: We studied 276 patients 61 years and younger with recent myocardial infarction. CAD severity was quantified using the log-transformed Gensini Score (lnGS) and the Sullivan Stenosis Score. Patients underwent myocardial perfusion imaging with mental stress (public speaking) and conventional (exercise or pharmacological) stress testing. MSIMI and CSIMI were defined as a new or worsening perfusion defect.

Results: The prevalence of MSIMI was 15% in men and 20% in women. The median GS for patients with MSIMI was 65.0 in men and 28.5 in women. In logistic regression models adjusted for demographic and cardiovascular risk factors, CAD severity was associated with CSIMI in the full sample (odds ratio [OR] = 1.49, 95% [CI], 1.14–1.95, per 1-unit increase in lnGS), with no significant difference by sex. Although CAD severity was not associated with MSIMI in the entire sample, results differed by sex. CAD severity was associated with MSIMI among men (OR = 1.95,

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The authors report no conflicts of interest.

SDC Supplemental Content

95% CI, 1.13–3.36, per 1-unit increase in lnGS), but not among women (OR = 1.02, 95% CI, 0.74–1.42, $p = .042$ for interaction). Analysis using Sullivan Stenosis Score yielded similar results.

Conclusions: Findings suggest that CAD severity is related to MSIMI in men but not women. MSIMI in women may therefore be driven by alternative mechanisms such as coronary microvascular disease.

Keywords

coronary artery disease; ischemia; myocardial infarction; sex; stress

INTRODUCTION

There is growing evidence that psychosocial stressors may promote the development and progression of coronary artery disease (CAD) in susceptible individuals (1,2). Experimental studies have demonstrated that acute mental stress may induce myocardial ischemia among patients with CAD regardless of inducible ischemia with a conventional stress test and this phenomenon is associated with activation of brain areas involved in stress response and autonomic regulation (3,4). Mental stress-induced myocardial ischemia (MSIMI) is known to be associated with fatal and nonfatal cardiovascular (CV) events (5–10). Although the prognostic value of MSIMI is similar to that of conventional stress-induced ischemia (CSIMI), its association with CAD severity defined by coronary angiography remains controversial (5,11–14). We have previously shown that MSIMI is not related to CAD severity (11). However, our previous study included a sample of predominantly older patients, with broadly defined CAD, with few women and a large variation in disease severity and in the time between the last coronary angiogram and the mental stress test (median = 3 years).

We have also previously shown that among patients with CAD, women, and especially younger women, are more likely to develop MSIMI than men, despite less severe obstructive CAD and a relatively similar profile of traditional CAD risk factors (15–17). It is possible that coronary microvascular dysfunction, rather than obstructive CAD severity, is a mechanism of MSIMI in women more often than in men (18,19). Consistent with this hypothesis, we have also reported that for women, stress-induced increased vaso-motor tone is a prominent mechanism of MSIMI (17,20), whereas for men, a stress-induced rise in rate-pressure product (RPP) is a more important correlate of MSIMI. This suggests that in men, but not in women, CAD severity plays a role in MSIMI through a supply-demand mechanism triggered by CAD burden (20). However, because of the small number of women included in previous studies of MSIMI and limited data on objective indicators of CAD severity, sex differences in the relationship between MSIMI and CAD severity have not been investigated.

In a well-characterized sample of young and middle-aged patients with a recent myocardial infarction (MI), including a large proportion of women, we examined the relationship between MSIMI and CAD severity and whether there are sex differences in this association. We hypothesized that the association between CAD severity with MSIMI would be stronger in men than in women. For both women and men, we contrasted the results of MSIMI with

those of ischemia induced by a conventional stress test (exercise or pharmacological stress test).

METHODS

Participants

Study participants for the Myocardial Infarction and Mental Stress 2 study included early-onset MI cases and community controls without a history of CAD. The study was conducted between May 1, 2012, and April 30, 2017; further details were previously published (17). Briefly, patients who survived an MI in the previous 8 months and who were 18 to 60 years old at the time of screening, were recruited from the pool of patients admitted with a documented history of MI, either an ST-segment elevation MI (STEMI) or non-STEMI, at the Emory-affiliated hospitals in Atlanta, Georgia. The diagnosis of MI was verified by medical record review based on standard criteria of a troponin level increase and symptoms of ischemia and/or ECG changes or other evidence of myocardial necrosis; presence of obstructive CAD was not a criterion for inclusion (21). We only considered type 1 MI for this study because we wanted to focus on a primary coronary event, whereas type 2 MI includes a variety of etiologies, which would increase the heterogeneity of the sample and make the interpretation of our results difficult.

Participants were excluded if they had a severe comorbid medical or psychiatric disorder that could interfere with the study results, such as cancer, renal failure, severe uncontrolled hypertension, current alcohol or substance abuse, or schizophrenia; if they were pregnant or breastfeeding; or if they were currently using immunosuppressant or psychotropic medications other than antidepressants. Patients with MI were also excluded if they had unstable angina, acute MI, or decompensated heart failure within the previous week; if they weighed over 450 lbs (due to weight bearing limits of the nuclear stress test equipment); and if it was deemed to be unsafe by study cardiologists to withhold anti-ischemic medications for 24 hours before the testing.

Patients underwent mental stress testing and conventional stress testing (exercise or pharmacological stress) in conjunction with single-photon emission computed tomography (SPECT) as described hereinafter and according to the published methodology (22). Sociodemographic and psychosocial data were collected at the first visit before cardiac testing. At the end of the study protocol, medical records were abstracted for clinical information, including catheterization data. Participants without angiographic data in conjunction with MI were excluded from the current analysis ($n = 37$). The Emory University Institutional Review Board approved the protocol, and all participants provided written informed consent.

Mental Stress Procedure

After resting for 30 minutes in a quiet, dimly lit, temperature-controlled room, mental stress was induced by a standardized public speaking task as previously described (15,16,22). Patients were asked to imagine a real-life stressful situation, in which a close relative was mistreated in a nursing home, and were asked to make up a realistic story around this

scenario. They were given 2 minutes to prepare a statement and then 3 minutes to present it in front of a video camera and an audience wearing white coats. Participants were told that their speech would be evaluated by the laboratory staff for content, quality, and duration. We recorded blood pressure and heart rate at 5-minute intervals during the resting phase and at 1-minute intervals during the mental stress task and calculated the rate-pressure product as peak systolic blood pressure multiplied by peak heart rate.

Myocardial Perfusion Imaging

Study participants underwent three SPECT myocardial perfusion imaging scans after injection of Sestamibi radio labeled with Technetium-99 m (^{99m}Tc) at rest, during mental stress, and during conventional stress, at the dose of 10–14 mCi for rest imaging and 30–40 mCi for stress imaging, based on weight. Testing was carried out in two separate days up to 1 week apart on a dedicated SPECT camera (Philips Cardio MD) without attenuation correction. Participants were fasting overnight except for water and had their anti-ischemic medications withheld for 24 hours before testing. On the mental stress day, ^{99m}Tc Sestamibi was injected 1 minute after the onset of the public speech task. On the conventional stress day, participants underwent a standard Bruce protocol or (if unable to exercise) a pharmacological stress test with Regadenoson (Abbott, Chicago, IL). The radioisotope injection was given at peak exertion or immediately after the Regadenoson injection.

An experienced nuclear cardiologist (P.R.) performed visual interpretation blinded to stress test type and clinical data. MSIMI and CSIMI were defined as a new or worsening impairment in myocardial perfusion using a 17-segment model. Each myocardial segment was scored from 0 to 4, with 0 being normal, 1 possibly normal, 2 definitely abnormal, 3 severely abnormal, and 4 no perfusion. Ischemia was defined as a new impairment with a score of 2 or higher in any segment, or as worsening of a pre-existing impairment by at least 2 points if in a single segment, or by at least 1 point if in two or more contiguous segments (23). Summed perfusion defect scores were also calculated at rest and with stress in a conventional manner, and their difference (inducible ischemia) was calculated (23).

CAD Severity Assessment

Angiographic data were obtained from the coronary angiogram performed in conjunction with the index MI. CAD severity was quantified using the Gensini semiquantitative angiographic scoring system (GS) (24), which takes into account the potential functional significance of the coronary lesion with a multiplier for specific coronary tree locations, and was log transformed (lnGS). We also examined the Sullivan Stenosis Score (SSS), which places more emphasis on the degree of stenotic CAD burden irrespective of location, and is based on eight vessel segments scored on a scale of 1 to 4, where 1 is assigned for 1% to 49% reduction in lumen diameter, 2 for 50% to 74%, 3 for 75% to 99%, and 4 for total occlusion (25). The lnGS was our main CAD severity variable of interest given that it is one of the most widely used and is a valid measure of coronary plaque burden (26).

A total of 224 participants (82%) had a revascularization procedure after coronary angiography at the time of their MI. Given that myocardial ischemia is predictive of

outcomes irrespective of revascularization (27) and that PCI in stable patients with CAD does not improve symptoms and functioning compared with placebo (28), our main analysis focused on native CAD burden (before revascularization). However, we also evaluated a “postrevascularization” CAD severity definition where vessels that were successfully revascularized were considered disease free before calculating the lnGS and the SSS.

Other Measurements

A detailed medical history including medication use was obtained by a research nurse. Height and weight were objectively measured during the clinical examination and used to calculate body mass index (BMI, kilogram per square meter). Blood samples were drawn for the measurements of glucose and a lipid profile after an overnight fast.

Behavioral, social, and mental health information was obtained using psychometric instruments with established reliability and validity. Depressive symptoms were assessed with the Beck Depression Inventory II (29), a reliable and valid measure of depressive symptoms, which has been widely used in cardiac populations and has a high internal consistency, with α coefficients of 0.86 and 0.81 for psychiatric and nonpsychiatric populations, respectively (30).

We also assessed symptoms of posttraumatic stress disorder (PTSD) using the PTSD Symptom Checklist, Civilian Version, which has an α co-efficients of 0.94 (31). Finally, we administered the Cohen’s Perceived Stress Scale, a 10-item measure of general stress validated in multiethnic populations, which has shown α coefficients of greater than 0.8 (32).

Statistical Analysis

We used the two-tailed unpaired t test for comparison of normally distributed continuous variables, the Wilcoxon rank-sum test for nonnormally distributed variables, and the χ^2 test or Fisher’s exact tests for categorical variables when appropriate. Univariate and multivariable logistic regression models were used to examine the association between indicators of CAD severity and the binary outcome ischemia. Because the distribution of the GS was highly skewed, it was log transformed in the analysis. Covariates were selected on the basis of a previous theory, including demographic factors (age as a continuous variable, sex, race [African America versus other], education, life-style), CVrisk factors (current smoking, BMI, hypertension, hyperlipidemia, diabetes mellitus), and medication use (aspirin, p-blockers, clopidogrel, statins, calcium channel blockers, and angiotensin-converting enzyme [ACE] inhibitors). Because of concerns of overfitting the model, we evaluated a reduced model that included only the most plausible predictor for each domain selected a priori, i.e., race for demographics, smoking status for CAD risk factors, depression for psychological factors, and also including rate-pressure product for hemodynamic reactivity, and left ventricular ejection fraction for cardiac function. Effect modification by sex was tested by including interaction terms between sex and each indicator of CAD severity (GS or SSS). p values of less than .05 were considered significant for main effects, whereas p values of less than .10 were considered significant for interaction terms. Analyses were performed with SAS 9.4 (SAS, Inc, Cary, NC).

RESULTS

Study Sample and Baseline Characteristics

Of 313 patients with MI included in the Myocardial Infarction and Mental Stress 2 study, 276 (88%), 141 men and 135 women, had angiographic data and completed the mental stress protocol. Of these, 269 also completed the conventional stress protocol. The mean (SD) age was 51 (6) years and was similar in women and men (50.9 and 51.4, respectively). A total of 48 patients (17%) developed MSIMI, and 70 (26%) developed CSIMI. Only 27 patients (10%) had both MSIMI and CSIMI. The median (interquartile range [IQR]) GS was 32 (10–59), and the median SSS was 7 (4–9).

Table 1 compares patients with and without MSIMI and those with and without CSIMI. Overall, there were only minor differences in terms of demographic factors, medication use, clinical and lifestyle factors, indicators of MI severity, and psychosocial factors. However, patients with MSIMI (compared with those without) were more likely to have had an STEMI as their index MI, whereas patients with CSIMI were more likely to have had an anterior wall MI. The MSIMI group also had a slightly lower average ejection fraction than those without MSIMI. Both the MSIMI and CSIMI groups had higher SPECT summed rest scores (and, as expected, higher summed difference scores) than those without ischemia.

Both the MSIMI and CSIMI groups were more likely to have obstructive CAD (luminal stenosis of >70%) in the left anterior descending territory than those without ischemia. CSIMI were also more likely to have obstructive CAD in the left circumflex territory. MSIMI status was not associated with differences in hemodynamics (rate-pressure product) at rest or during mental stress. As expected given the Bruce protocol staging for exercise stress testing, CSIMI was associated with a lower incremental RPP response during conventional stress.

These results were overall consistent after stratification by sex, except that women who developed ischemia with either condition more often had had an MI before the index MI as compared with men, and men who developed MSIMI had a lower ejection fraction than men without MSIMI (Supplementary Table 1, Supplemental Digital Content 1, <http://links.lww.com/PSYMED/A514>, and Supplementary Table 2, Supplemental Digital Content 2, <http://links.lww.com/PSYMED/A515>).

Association Between Angiographic Severity of CAD and MSIMI/CSIMI

Overall, the GS (IQR) tended to be higher among patients with MSIMI (median [IQR] = 46.5 [17.5–79.5]) compared with patients without MSIMI (median [IQR] = 26.8 [8.5–54.8], $p = .017$). After stratifying by sex (Figure 1A), the GS was higher among men with MSIMI (median = 65.0) compared with men without MSIMI (median = 32.0). However, the GS was not significantly different in women with or without MSIMI (median = 28.5 versus 20.5, $p = .37$). In contrast, the median GS was higher in both men (51.0 versus 32.0) and women (32.3 versus 18.8) with CSIMI compared with their counterparts without CSIMI (Figure 1B).

The results pertaining to the SSS were similar (Figure 2). After stratifying by sex, the SSS was higher among men with MSIMI compared with men without MSIMI, whereas it was not significantly different in women. In contrast, the SSS was higher in both men with CSIMI compared with their counterparts without CSIMI.

After adjusting for demographic factors, CV risk factors, and use of aspirin, β -blockers, and clopidogrel, the results remained consistent (Table 2, Figure 3). The GS was associated with increased odds of MSIMI among men, but not among women. More specifically, a 1-unit increase in lnGS was associated with an odds ratio (OR) of 1.95 (95% CI, 1.13–3.36) among men, whereas the corresponding OR in women was 1.02 (95% CI, 0.74–1.42); the inter-action between sex and lnGS was significant ($p = .042$). In contrast, the GS was associated with CSIMI in both men and women (Table 2, Figure 3). Results were not sensitive to change when adjusting for psychosocial factors, including symptoms of depression, perceived stress, and PTSD (Model 3 in Table 2) and further adjusting for additional CV medications, including statins, calcium channel blockers, and ACE inhibitors (data not shown). When using the alternative measures of CAD burden, (the SSS) results remained consistent (Table 2, Figure 3). We also evaluated a reduced model with fewer covariates selected a priori including race, smoking status, and depression and including rate-pressure product for hemodynamic reactivity and left ventricular ejection fraction for cardiac function, and results were materially unchanged.

When we examined postrevascularization CAD severity, i.e., a CAD severity definition that classified revascularized vessels as normal vessels, the association of CAD severity with both types of ischemia was attenuated. Postrevascularization CAD severity was not associated with MSIMI among men (OR = 0.99, 95% CI, 0.76–1.42, for each unit of lnGS, and OR = 1.02, 95% CI, 0.90–1.20, for each unit of SSS) or women (OR = 0.82, 95% CI, 0.61–1.13, for each unit of lnGS, and OR = 0.99, 95% CI, 0.86–1.15, for each unit of SSS). After adjustment for demographic factors, CV risk factors and use of aspirin, β -blockers, and clopidogrel, results remained consistent. In contrast, postrevascularization CAD severity was associated with CSIMI, primarily among men (Table 3). After adjustment for the previously mentioned covariates, the association was attenuated. When we used similar reduced models as described previously, results remained essentially the same.

DISCUSSION

Among young patients with post-MI, we found that when men and women are pooled together, MSIMI seems weakly related to angiographic CAD severity. These results, however, differ by sex. Whereas in men MSIMI shows a robust association with CAD severity, in women this relationship is absent. In contrast, CSIMI is associated with CAD severity in both men and women. These results suggest that MSIMI and CSIMI are driven by different mechanisms, especially among women, despite having relatively similar prognostic significance.

Although it was previously observed that mental stress can induce myocardial ischemia in participants with negative conventional stress results (33), former studies have not been consistent about the relationship between MSIMI and CAD. Although several investigators

have reported no association between MSIMI and atherosclerotic CAD burden (5,8,11–14,34–37), others have reached opposite conclusions (14,38). For example, Modena et al. (38) reported that in a group of 56 patients with chest pain, there was a higher likelihood of MSIMI among those with multivessel disease compared with those with single-vessel disease or no disease. Furthermore, Kuroda et al. (14) reported that patients with three-vessel disease had a greater decrease in ejection fraction during mental stress as compared with patients with single- and two-vessel disease. However, these studies were limited by a sample of primarily male participants with broadly defined CAD. Furthermore, in most previous research, there was a large variation in the time between the last coronary angiogram and mental stress testing, which may have biased the results; for example, there was a median of 3-year interval in the study by Ramadan et al. (11). In our study, which was based on a sample of patients with post-MI, all younger than 61 years and with their index MI and coronary angiogram within 8 months, we demonstrated that there is a clear distinction between MSIMI and CSIMI in terms of their association with CAD severity, especially among women. Whereas among men CAD severity was associated with both MSIMI and CSIMI in a similar fashion, among women CAD severity was only associated with CSIMI. Women with and without MSIMI had a similar severity of CAD. These data support previous suggestions of a different pathophysiology for MSIMI and CSIMI, for example, the fact that MSIMI occurs at a lower rate-pressure product than CSIMI (4,39–41). Thus, other mechanisms must be implicated in the pathophysiology of MSIMI and, potentially, its associated adverse outcomes (19,37,42). However, these differences in pathophysiology may apply to women more than to men. Our finding that among men, but not women, MSIMI was associated with lower ejection fraction is consistent with a role of CAD severity in MSIMI in men only and agrees with previous studies in predominantly male patient populations (43).

We have previously shown that there is an interaction between age and sex for MSIMI and that younger women are more likely to develop MSIMI than men of similar age (15,16). We also found that women and men differ in their pathophysiological mechanisms for MSIMI in that peripheral vasoconstriction during mental stress is a stronger predictor of MSIMI in women, whereas the rate-pressure product response to mental stress is a stronger predictor of MSIMI in men (44). Consistent with previous data (45,46), our current findings support the notion that men and women have distinct mechanisms for MSIMI, and, specifically, that vasomotor tone, rather than flow-limiting lesions, may be implicated in MSIMI among women more than among men.

Our results fit with current perspectives on sex differences in the pathophysiology of ischemic heart disease. Microcirculatory dysfunction is a potential mechanism in the pathogenesis of ischemic heart disease in women with patent epicardial coronary arteries. Interestingly, previous studies have shown that female patients with patent epicardial coronary arteries who experience myocardial ischemia are more likely to have abnormal brachial flow-mediated dilatation (37). Moreover, Pepine et al. (47) demonstrated that among women with suspected myocardial ischemia, abnormal coronary microvascular reactivity provided prognostic information over and above angiographic CAD burden. Thus, MSIMI in women could predominantly be an expression of coronary microvascular

dysfunction and may represent an important mechanism of risk and a novel prognostic indicator for women with CAD (7).

In this study, we also found that native CAD severity, before revascularization, was a better predictor of CSIMI than CAD severity after accounting for revascularization. Although our study did not evaluate presence of persistent ischemia in the same territory after revascularization, these findings may indicate that restoration of coronary flow may not be associated with reduction in total myocardial ischemic burden (48–51). The persistence of ischemia despite revascularization in the same territory has been attributed to microvascular obstruction and coronary endothelial dysfunction (49,50) and is associated with higher mortality and adverse CV outcomes (52–55). Our findings support the notion that CAD burden before revascularization remains a strong correlate of myocardial ischemia.

A limitation of our study is the relatively modest incidence of MSIMI. Despite having a relatively large sample of patients with a substantial representation of women, the interaction between sex and CAD severity was borderline significant for InGS and did not reach statistical significance for SSS. In addition to the modest incidence of MSIMI, this may be due to the fact that although there was variability in CAD severity in this post-MI sample, virtually all patients, both women and men, had some degree of coronary obstruction. However, our study still shows a clear demarcation of results between men and women that should not be dismissed. In addition, being conducted in Atlanta, our study included a large proportion of African Americans. Although this may decrease the generalizability of this study to other geographic locations, the high representation of understudied minorities is an advantage of our study. We also did not have data on gender role measures, which have been associated with CV risk factors, mental health, and physiological dysregulations independent of biological sex (56,57). Another limitation is the lack of long-term outcome data. Previous literature shows that MSIMI carries an adverse prognosis to a similar extent as CSIMI, even though the mechanism may differ (7). Our work, as a whole, suggests that such mechanisms may diverge especially among women. This is a group for whom the prognostic significance of MSIMI requires further study, because previous outcome studies have included mostly men.

We believe that these limitations are offset by several strengths of this study. Our sample of young and middle-aged patients with post-MI was well defined and relatively homogenous, limiting possible confounding by disease duration or severity. We enrolled a high proportion of women, which allowed us to examine sex differences in the relationship between CAD severity and MSIMI. Furthermore, we used myocardial perfusion imaging, which is considered the criterion standard for the assessment of ischemia, and we tested ischemia with both mental stress and conventional stress to gain insight into differential pathophysiology between these two ischemic processes.

In conclusion, we found that overall, MSIMI is weakly associated with atherosclerotic CAD burden, but this relationship differs by sex. Whereas in men CAD severity is robustly associated with ischemia with both mental and conventional stress, among women CAD is not related to MSIMI. These results suggest that MSIMI must be driven by alternative mechanisms especially among women and provide motivation for further research to

understand sex-specific mechanisms for the effects of mental stress on myocardial ischemia and long-term outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Source of Funding and Conflicts of Interest: This work was supported by the National Institute of Health (R01 HL109413, R01 HL109413-02S1, R01 HL125246, R01 HL136205, P01 HL101398, KL2TR000455, K24HL077506, K24 MH076955, K23HL127251, and T32HL130025 and K12HD085850). The sponsors of this study had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the article. Ernest V. Garcia receives royalties from the sale of the Emory Cardiac Toolbox, used for some analyses in this study.

Glossary

ACE	angiotensin-converting enzyme
BMI	body mass index
CAD	coronary artery disease
CSIMI	conventional stress-induced myocardial ischemia
IQR	interquartile range
lnGS	natural log-transformed Gensini Score
MI	myocardial infarction
MSIMI	mental stress-induced myocardial ischemia
OR	odds ratio
SD	standard deviation
SPECT	single-photon emission computed tomography
SSS	Sullivan Stenosis Score

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FIGURE 1.

Angiographic burden of coronary artery disease assessed with the Gensini score by sex and ischemia status. *P* Values compare the median Gensini score between groups with and without ischemia using the nonparametric Wilcoxon rank-sum median two-sample test. The first graph in each panel includes the whole sample and the second graph shows sex-stratified results. MSIMI indicates mental stress-induced myocardial ischemia; CSIMI, conventional stress-induced myocardial ischemia.

FIGURE 2.

Angiographic burden of CAD assessed with the SSS by sex and ischemia status. *P* Values compare the mean Sullivan score between groups with and without ischemia using nonparametric Wilcoxon rank-sum median two-sample test. The first graph in each panel includes the whole sample and the second graph shows sex-stratified results. MSIMI, mental stress-induced myocardial ischemia; CSIMI, conventional stress-induced myocardial ischemia.

FIGURE 3.

Associations of indicators of CAD severity with ischemia with mental stress (MSIMI) and conventional stress (CSIMI). Odds ratios are adjusted for age (continuous), sex, African American race, income below poverty level, smoking status, BMI (continuous), hypertension, hyperlipidemia, diabetes, and medication use (aspirin, β -blockers, and clopidogrel). Sex-specific ORs were obtained by including in the model an interaction term between sex and CAD severity scores (Gensini or Sullivan, respectively). Error bars represent 95% CIs. Color image is available only in online version (www.psychosomaticmedicine.org).

TABLE 1.

Characteristics of Study Population by MSIMI and CSIMI Status

	MSIMI –	MSIMI +	P	CSIMI –	CSIMI +	P
Total number	228	48		199	70	
Demographic factors						
Age, M (SD), y	51.2 (6.1)	50.9 (6.8)	.75	51.3 (6.0)	51.3 (6.6)	.96
Female, <i>n</i> (%)	108 (47.4)	27 (56.3)	.26	92 (46.2)	40 (57.1)	.12
African American, <i>n</i> (%)	145 (63.6)	32 (66.7)	.69	126 (63.3)	46 (65.7)	.72
Income below poverty status (\$20,000)	62 (30.2)	14 (33.3)	.69	53 (28.8)	22 (36.1)	.29
High school education or less	34 (15.2)	7 (14.9)	.96	29 (14.7)	12 (17.7)	.55
Clinical history and life-style factors						
BMI, M (SD), kg/m ²	30.8 (6.3)	30.6 (9.3)	.88	31.3 (6.8)	28.9 (6.2)	.009
Current smoker, <i>n</i> (%)	53 (23.9)	11 (23.4)	.95	50 (25.3)	14 (21.2)	.51
Diabetes, <i>n</i> (%)	69 (30.3)	19 (39.6)	.21	60 (30.2)	27 (38.6)	.20
Hypertension, <i>n</i> (%)	178 (78.1)	41 (85.4)	.25	162 (81.4)	53 (75.7)	.31
High blood cholesterol, <i>n</i> (%)	182 (79.8)	39 (81.3)	.82	160 (80.4)	56 (80.0)	.94
History of MI before index MI, <i>n</i> (%)	41 (18.0)	14 (29.2)	.078	37 (18.6)	16 (22.9)	.44
Revascularization, <i>n</i> (%)	184 (80.7)	43 (89.6)	.21	157 (78.9)	67 (95.7)	.001
MI severity indicators						
Left ventricular ejection fraction, M (SD)	52.0 (10.8)	46.5 (13.8)	.011	51.8 (11.5)	49.4 (11.4)	.13
Type of MI (STEMI), <i>n</i> (%)	64 (28.1)	24 (50.0)	.003	58 (29.2)	27 (38.6)	.14
Anterior MI, <i>n</i> (%)	75 (33.0)	20 (41.7)	.25	60 (30.3)	32 (45.7)	.020
Maximum troponin, M (SD)	24.8 (47.8)	43.7 (60.7)	.060	25.2 (47.5)	34.3 (53.2)	.20
Presence of obstructive (70% stenosis) LAD disease, <i>n</i> (%)	102 (44.7)	33 (68.8)	.003	86 (43.2)	45 (64.3)	.002
Presence of obstructive (70% stenosis) LCX disease, <i>n</i> (%)	104 (45.6)	20 (41.7)	.62	82 (41.2)	40 (57.1)	.021
Presence of obstructive (70% stenosis) RCA disease, <i>n</i> (%)	105 (46.1)	19 (39.6)	.41	89 (44.7)	34 (48.6)	.58
SPECT summed rest score, M (SD) ^a	3.3 (2.5)	6.3 (4.4)	.003	3.0 (6.0)	5.5 (5.8)	.002
SPECT summed difference score during mental stress, M (SD) ^a	0.15 (0.72)	4.4 (2.4)	<.001	0.6 (1.8)	1.8 (2.4)	<.001
SPECT summed difference score during physical stress, M (SD) ^a	1.4 (2.6)	3.3 (3.8)	.002	0.3 (0.2)	5.6 (4.9)	<.001
Psychosocial factors, M (SD)						

	MSIMI –	MSIMI +	P	CSIMI –	CSIMI +	P
Beck Depression Inventory	11.9 (10.3)	13.5 (9.5)	.30	11.7 (10.2)	13.1 (10.1)	.34
PTSD Symptom Checklist	30.7 (14.1)	34.3 (14.7)	.077	31.1 (14.7)	30.8 (10.7)	.83
Perceived Stress Scale	15.8 (8.2)	18.3 (8.8)	.056	15.8 (8.5)	17.2 (7.9)	.22
Medications, <i>n</i> (%)						
Aspirin	186 (81.9)	43 (89.6)	.20	164 (82.4)	59 (84.3)	.72
β-Blocker	191 (84.1)	44 (91.7)	.20	169 (84.9)	62 (88.6)	.45
Clopidogrel	166 (73.1)	36 (75.0)	.79	144 (72.4)	54 (77.1)	.44
ACE inhibitor	98 (43.2)	28 (58.3)	.056	89 (44.7)	35 (50.0)	.45
Antidepressant	38 (16.7)	8 (16.7)	.99	35 (17.6)	9 (12.9)	.36
Statin	195 (85.9)	42 (87.5)	.77	169 (84.9)	63 (90.0)	.29
Hemodynamics, mental stress testing, M (SD)						
RPP at rest stress, beat × mm Hg/min per 1000	8.6 (2.2)	8.6 (2.2)	.96	8.8 (2.2)	8.2 (2.2)	.055
RPP response during stress, beat × mm Hg/min per 1000 ^b	6.3 (3.1)	6.5 (3.2)	.62	6.4 (3.1)	6.1 (3.0)	.56
Hemodynamics, conventional stress testing						
RPP at rest, beat × mm Hg/min per 1000	8.6 (2.1)	8.7 (2.1)	.82	8.8 (2.1)	8.1 (2.1)	.015
RPP response during stress, beat × mm Hg/min per 1000 ^b	15.8 (6.1)	14.3 (6.1)	.11	16.0 (6.0)	14.2 (6.3)	.050

MSIMI = mental stress-induced myocardial ischemia; CSIMI = conventional stress-induced myocardial ischemia; SD = standard deviation; STEMI = ST-segment elevation myocardial infarction; MI = myocardial infarction; SPECT = single-photon emission computed tomography; BMI = body mass index; PTSD = posttraumatic stress disorder; ACE = angiotensin-converting enzyme; CAD = coronary artery disease; LAD = left anterior descending artery; RCA = right coronary artery; LCX = circumflex branch of left coronary artery; RPP = rate-pressure product.

Statistical tests: categorical variables: χ^2 and Fisher's exact tests when appropriate. Continuous variables: Student's *t* test.

^aHigher SPECT perfusion scores indicate greater perfusion deficit.

^bDifference between maximum value during stress and minimum value during rest.

TABLE 2.
Overall and Sex-Specific Associations of Myocardial Ischemia and Indicators of CAD Severity

	Total Population			Women			Men		
	OR ^a (95% CI)	p		OR ^a (95% CI)	p		OR ^a (95% CI)	p	p Value of Sex Interaction
MSIMI									
Ln Gensini Score									
Model 1	1.27 (1.00–1.61)	.055		1.11 (0.83–1.50)	.48		1.77(1.08–2.90)	.023	.11
Model 2	1.27 (0.97–1.67)	.087		1.02 (0.74–1.42)	.90		1.95 (1.13–3.36)	.016	.042
Model 3	1.39 (1.03–1.87)	.030		1.13 (0.79–1.62)	.49		1.96(1.15–3.34)	.013	.084
SSS									
Model 1	1.06 (0.98–1.15)	.14		1.03 (0.92–1.15)	.62		1.13 (1.00–1.28)	.049	.25
Model 2	1.07 (0.97–1.17)	.17		1.0 (0.89–1.15)	.83		1.13(1.00–1.29)	.068	.22
Model 3	2.03 (0.99–4.19)	.055		1.03 (0.90–1.17)	.65		1.14(1.00–1.31)	.053	.25
CSIMI									
Ln Gensini Score									
Model 1	1.53 (1.20–1.93)	.001		1.50(1.10–2.04)	.010		1.78(1.17–2.78)	.007	.56
Model 2	1.49 (1.14–1.95)	.003		1.40 (1.00–1.96)	.050		1.56(1.01–2.41)	.043	.79
Model 3	1.59 (1.19–2.11)	.002		1.53 (1.06–2.22)	.023		1.56(1.01–2.43)	.047	.93
SSS									
Model 1	1.12 (1.04–1.20)	.003		1.11 (1.00–1.23)	.046		1.16(1.04–1.30)	.009	.54
Model 2	1.12 (1.04–1.24)	.005		1.12 (1.00–1.26)	.068		1.16(1.02–1.32)	.019	.66
Model 3	1.15 (1.05–1.26)	.004		1.13 (1.00–1.28)	.044		5.38(1.41–20.50)	.020	.75

OR = odds ratio; CI = confidence interval; MSIMI = mental stress-induced myocardial ischemia; SSS = Sullivan Stenosis Score; CSIMI = conventional stress-induced myocardial ischemia.

Model 1: CAD severity index in main effects model; CAD severity index and CAD severity index *sex in sex-specific models.

Model 2: model 1 covariates + age, sex, African American race, education, smoking status, BMI (continuous), hypertension, hyperlipidemia, diabetes, aspirin use, β -blocker use, and clopidogrel use.

Model 3: model 2 covariates + symptoms of depression, perceived stress, and PTSD.

Statistical tests: logistic regression models with and without interaction.

^aPer 1-unit increment in CAD severity scores.

TABLE 3.

Overall and Sex-Specific Associations of Myocardial Ischemia and Indicators of CAD Severity after accounting for revascularization

Main Effect Estimates			Interaction Effect Estimates		
	Total		Women	Men	
	OR ^a (95% CI)	p	OR ^a (95% CI)	OR ^a (95% CI)	p Value of Sex Interaction
MSIMI					
Ln Gensini Score					
Model 1	0.92 (0.74–1.15)	.47	0.83 (0.61–1.13)	1.04 (0.76–1.42)	.82 .31
Model 2	0.90(0.71–1.12)	.34	0.82 (0.60–1.12)	0.99 (0.72–1.38)	.97 .40
Model 3	0.89 (0.71–1.13)	.34	0.83 (0.59–1.15)	0.97 (0.70–1.35)	.86 .50
SSS					
Model 1	1.01 (0.92 1.12)	.78	0.99 (0.86–1.15)	1.04 (0.90–1.20)	.57 .64
Model 2	1.01 (0.90–1.12)	.91	0.99 (0.85–1.16)	1.02 (0.88–1.18)	.79 .79
Model 3	1.00 (0.89–1.11)	.92	0.98(0.83–1.15)	1.01 (0.87–1.17)	.91 .78
CSIMI					
Ln Gensini Score					
Model 1	1.25 (1.04–1.50)	.018	1.17(0.91–1.50)	1.35 (1.03–1.78)	.031 .44
Model 2	1.18 (0.97–1.44)	.093	1.14(0.88–1.48)	1.24 (0.92–1.66)	.16 .69
Model 3	1.19 (0.98–1.46)	.087	1.1 7 (0.90–1.53)	1.22 (0.90–1.65)	.19 .84
SSS					
Model 1	1.10(1.01–1.20)	.033	1.09 (0.96–1.23)	1.12 (0.90–2.50)	.063 .71
Model 2	1.09 (0.99–1.20)	.091	1.07 (0.94–1.23)	1.10 (0.96–1.25)	.16 .82
Model 3	1.08 (0.98–1.19)	.11	1.07 (0.93–1.23)	1.09 (0.95–1.25)	.20 .87

OR = odds ratio; CI = confidence interval; MSIMI = mental stress-induced myocardial ischemia; SSS = Sullivan Stenosis Score; CSIMI = conventional stress-induced myocardial ischemia. Model 1: CAD severity index in main effects model; CAD severity index and CAD severity index *sex in sex-specific models.

Model 2: model 1 covariates + age, sex, African American race, education, smoking status, BMI (continuous), hypertension, hyperlipidemia, diabetes, aspirin use, β -blocker use, and clopidogrel use.

Model 3: model 2 covariates + symptoms of depression, perceived stress, and PTSD.

Statistical tests: logistic regression models with and without interaction.

^aPer 1-unit increment in CAD severity scores.