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ORIGINAL RESEARCH

Sex Differences in Psychosocial Factors and Angina in Patients With Chronic Coronary Disease

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BACKGROUND: Women with chronic coronary disease have more frequent angina and worse health status than men, despite having less coronary artery disease (CAD). We examined whether perceived stress and depressive symptoms mediate sex differences in angina, and whether this relationship differs in the setting of obstructive CAD or ischemia with no obstructive coronary artery disease (INOCA).

METHODS: We analyzed the association between sex, stress (Perceived Stress Scale-4) and depressive symptoms (Patient Health Questionnaire-8) on angina-related health status (Seattle Angina Questionnaire [SAQ]) at enrollment in the ISCHEMIA (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches) trial and CIAO-ISCHEMIA (Changes in Ischemia and Angina Over 1 Year Among ISCHEMIA Trial Screen Failures With No Obstructive CAD on Coronary CT [Computed Tomography] Angiography) ancillary study.

RESULTS: Scores for the SAQ, Perceived Stress Scale-4, and Patient Health Questionnaire-8 were available in 1626 participants (N=1439 CAD and N=187 INOCA). Women had lower (worse) SAQ-7 summary scores than men in both CAD and INOCA cohorts (CAD: median 76 [25th, 75th percentiles 60, 90] versus 83 [70, 96], $P<0.001$; INOCA: 80 [64,89] versus 85 [75, 93], $P=0.012$). Higher stress and depressive symptoms were associated with worse angina in both cohorts. Female sex, Perceived Stress Scale-4 score, and Patient Health Questionnaire-8 score were each independently associated with lower SAQ summary score, but CAD versus INOCA cohort was not. There was no interaction between sex and stress (−0.39 [95% CI, −1.01 to 0.23]) or sex and depression (−0.00 [95% CI, −0.53 to 0.53]) on SAQ summary score.

CONCLUSIONS: High stress and depressive symptoms were independently associated with worse angina and poorer health status, without interaction with sex with or without obstructive CAD. Factors other than stress or depression contribute to worse health status in women with obstructive CAD or INOCA.

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Key Words: angina ■ chronic coronary disease ■ depression ■ ischemia ■ stress

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CLINICAL PERSPECTIVE

What Is New?

- In this analysis including coronary artery disease (CAD) and ischemia with no obstructive CAD, selected using the same clinical and stress test entry criteria, female sex, stress and depressive symptoms were each independently associated with worse angina-related health status, and patients with CAD and ischemia with no obstructive CAD had similar health status based on ISCHEMIA (International Study of Comparative Health Effectiveness wWith Medical and Invasive Approaches) entry criteria including moderate or severe ischemia and medically controlled angina.
- There were no significant interactions between female sex and CAD versus ischemia with no obstructive CAD status, stress, or depressive symptoms on angina in pooled analyses including participants with CAD and ischemia with no obstructive CAD.

What Are the Clinical Implications?

- Clinicians should apply multimodal approaches toward angina relief, particularly in women, who may be more severely affected by angina than men.

Nonstandard Abbreviations and Acronyms

CCD	chronic coronary disease
CIAO-ISCHEMIA	Changes in Ischemia and Angina Over One Year Among ISCHEMIA Trial Screen Failures With No Obstructive Coronary Artery Disease on Coronary CT [Computed Tomography] Angiography
INOCA	ischemia with no obstructive coronary artery disease
ISCHEMIA	International Study of Comparative Health Effectiveness With Medical and Invasive Approaches
PSS	Perceived Stress Scale
PHQ	Patient Health Questionnaire
SAQ	Seattle Angina Questionnaire

Angina is a common symptom of chronic coronary disease (CCD), resulting in significant morbidity and reduced quality of life.[1] There is little correlation between extent of coronary artery disease (CAD), severity of ischemia, and angina-related health status.[2] Sex differences in angina frequency and health status have been previously described in the ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial, in which women had a higher burden of angina despite less ischemia and less extensive CAD.[3] Identifying factors other than disease severity is needed to improve treatment of women and to minimize sex-based disparities.

Psychosocial factors, such as perceived stress and depression, have been associated with increased angina burden.[2] Stress and depression result in lower quality of life and predict mortality and morbidity among patients with ischemic heart disease.[4–6] Mechanisms linking acute and chronic stress to symptoms of angina have been previously described, including provocation of ischemia via autonomic imbalance, and stress-induced endothelial dysfunction and coronary vasospasm.[7] Women are more likely than men to suffer stress, anxiety, and depression[8–12] and are also more likely to have mental stress-induced ischemia than men.[13,14] Women are also more likely to have ischemia with no obstructive coronary artery disease (INOCA), which is considered a type of CCD in contemporary guidelines. Whether perceived stress and depression mediate sex differences in angina severity and whether this relationship differs patients with CAD or INOCA are unknown.

Severity of anxiety and depression in patients with INOCA is similar to patients with obstructive CAD.[15] Among women with INOCA in the WISE (Women's Ischemia Syndrome Evaluation) and WISE-CVD (WISE-Coronary Vascular Dysfunction) cohorts, higher levels of home, work, and financial stress were associated with cardiac symptoms, functional impairment, poorer self-rated health, depression, and CAD risk factors.[16] As in the case of patients with obstructive CAD, women with INOCA have more severe and persistent symptoms, and poorer quality of life, as compared with men.[17–19] It is not known whether the association between psychosocial factors and angina differs between patients with INOCA and obstructive CAD.

We previously investigated stress and depression in women presenting with myocardial infarction and found that stress was higher among women with CAD than with no obstructive CAD, whereas depressive symptoms were similar by CAD status.[20] In the current study, we explored whether perceived stress and depressive symptoms mediate sex differences in angina severity among patients with CCD, and whether this

relationship differs between patients with obstructive CAD or INOCA.

METHODS

Deidentified ISCHEMIA trial data can be shared with researchers through the National Heart, Lung, and Blood Institute BioLINCC repository (https://biolincc.nhlbi.nih.gov/). Additional data related to this study are available from the corresponding author upon reasonable request. This is a secondary analysis of the ISCHEMIA trial and the CIAO-ISCHEMIA (Changes in Ischemia and Angina Over One Year in ISCHEMIA Trial Screen Failures With No Obstructive Coronary Artery Disease on Coronary CT [Computed Tomography] Angiography) study. ISCHEMIA was a large National Heart, Lung, and Blood Institute-funded multisite randomized clinical trial comparing a routine initial invasive management strategy to a conservative management strategy among patients with CCD, moderate or severe myocardial ischemia on stress testing and obstructive CAD on coronary CT angiography.[21] CIAO-ISCHEMIA was a prospective National Heart, Lung, and Blood Institute-funded ancillary study of ISCHEMIA that enrolled patients who were not eligible for randomization in the main trial due to the absence of obstructive CAD on coronary CT angiography.[19] Thus, the CIAO-ISCHEMIA participants represent a cohort with INOCA.

Eligibility criteria for both studies have been previously published.[19,21] As previously reported, in the ISCHEMIA trial, all randomized participants completed the Seattle Angina Questionnaire (SAQ-7) at baseline. More comprehensive quality of life and psychosocial assessment was completed in a substudy that included participants randomized in the United States and Canada plus 11 other countries that agreed to participate.[22] In CIAO-ISCHEMIA, all participants were asked to complete SAQ-7 and psychosocial questionnaires.[19] In this analysis we included participants from ISCHEMIA and CIAO-ISCHEMIA with available coronary CT angiography data, who completed psychosocial questionnaires and questionnaires on angina-related health status and quality of life at baseline.

Psychosocial questionnaires included the Perceived Stress Scale (PSS-4), and the Patient Health Questionnaire (PHQ-8). The PSS-4 is a 4-item validated survey that measures the degree to which an individual appraises situations in their life as overwhelming, uncontrollable, and unpredictable over the past month.[23,24] Items are rated on a 5-point scale with the total PSS-4 score ranging from 0 to 16; higher scores indicate greater perceived stress. Consistent with prior studies, high stress was considered to be a score of ≥6, which has been associated with mortality and poorer health status post myocardial infarction.[6] The PHQ-8 is an 8-item measure of depressive symptoms over the past 2 weeks based on diagnostic criteria for major depressive disorder.[25] Items are rated on a 4-point scale, resulting in range of 0 to 24, with higher total scores indicating greater depressive symptoms. Moderate to severe depressive symptoms are represented by a score of ≥10.[26] A clinically meaningful difference in PHQ score is ≥5.

Angina-related health status was assessed using the SAQ-7. This is a validated, reproducible instrument assessing disease-related health status among patients with ischemic heart disease.[27] The SAQ-7 includes questions on physical limitation, quality of life, and angina frequency and produces 3 subscales and a summary score (average of the 3). A higher score corresponds to better health status and lower symptom burden.[27] A clinically meaningful difference in SAQ-7 summary score is considered ≥5 points. A clinically meaningful difference in angina frequency, quality of life, and physical limitation score is ≥10 points.[28]

The study was approved by the New York University Grossman School of Medicine Institutional Review Board and by the local institutional review board of each site. All participants signed informed consent.

Statistical Analysis

Baseline demographics, clinical factors and psychosocial variables were compared between participants with obstructive CAD (hereafter referred to as CAD) and INOCA. Categorical variables were compared via chi-square or Fisher's exact test, and continuous variables were compared using the Mann–Whitney *U* test. Proportions of high stress and depressive symptoms by sex in each group were compared using the chi-square test. We used linear regression models with SAQ summary score or subscale scores as dependent variables, with sex×stress or sex×depression as interaction terms, stratified by CAD status (CAD or INOCA), controlling for age and diabetes. A pooled analysis of participants with CAD and INOCA was performed using linear regression models with SAQ summary score and subscales as dependent variables, with sex×stress/sex×depression and sex×CAD as interaction terms. All analyses were performed using R version 4.3.3. A 2-sided $P<0.05$ was considered to be statistically significant. *P* values and 95% CIs presented in this report have not been adjusted for multiplicity.

RESULTS

Sample Characteristics

Of 3956 ISCHEMIA and CIAO-ISCHEMIA participants with available coronary CT angiography data, 1626 participants (N=1439 CAD and N=187 INOCA) had available SAQ-7 and psychosocial questionnaires (PSS-4 or PHQ-8; Figure 1). Participants with CAD were older (67 [25th–75th percentile

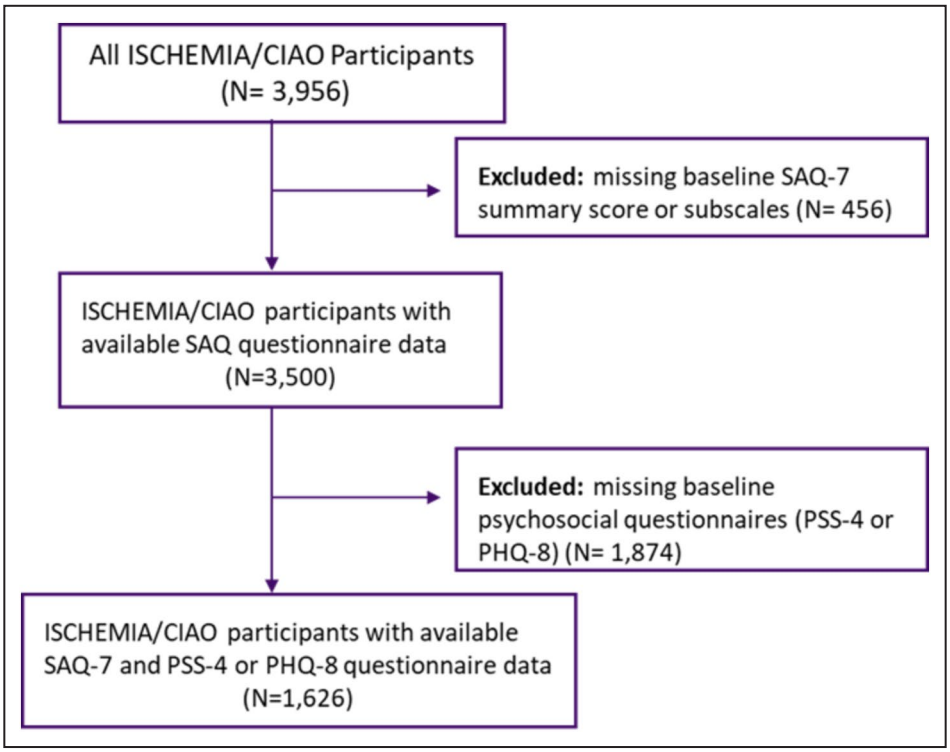

Figure 1. Flow diagram.
CIAO indicates Changes in Ischemia and Angina Over One Year Among ISCHEMIA Trial Screen Failures With No Obstructive Coronary Artery Disease on Coronary CT [Computed Tomography] Angiography; ISCHEMIA, International Study of Comparative Health Effectiveness With Medical and Invasive Approaches; PHQ, Patient Health Questionnaire; PSS, Perceived Stress Scale; and SAQ, Seattle Angina Questionnaire.

61, 72] years versus 62 [56, 70]), less likely to be female (17% versus 64%), and less likely to report Hispanic ethnicity (18% versus 29%) than participants with INOCA. Participants with CAD had a greater burden of underlying cardiovascular risk factors (Table 1).

Sex Differences in Angina-Related Health Status, Stress, and Depression

Women had lower SAQ-7 summary scores, indicating worse angina-related health status, compared with men in both cohorts with CAD and INOCA (CAD: median 76 [25th, 75th percentiles 60, 90] versus 83 [70, 96], $P<0.001$; INOCA: 80 [64, 89] versus 85 [75, 93], $P=0.012$; Table 2). Women with CAD had more frequent angina than men with CAD. There was more frequent angina among women with INOCA than men with INOCA but this was not statistically significant likely due to low sample size. Women also had more angina-related physical limitations and worse angina-related quality of life than men in both the groups with CAD and INOCA.

There were no sex differences in continuous PSS-4 scores in either participants with CAD or INOCA. In pooled analysis, there was a trend toward a higher proportion of participants categorized as having high perceived stress (PSS-4 ≥6) among women than men (45% versus 39%, $P=0.067$, Figure 2). Women with CAD had higher continuous PHQ-8 scores than men with CAD (3 [1, 8] versus 2 [0, 5], $P<0.001$). In pooled analysis, women were also more likely to report higher scores for depressive symptoms (PHQ-8 ≥10) than men (16% versus 11%, $P=0.01$, Figure 2).

Associations Between Angina and Stress/Depression

High stress was associated with lower (worse) SAQ-7 summary score in both cohorts with INOCA and CAD (CAD: 77 [61, 89] versus 85 [73, 96], $P<0.001$, INOCA: 74 [59, 88] versus 85 [78, 92], $P<0.001$). Similarly, depressive symptoms (PHQ-8 ≥10) were associated with lower SAQ-7 summary score in both cohorts with INOCA and CAD cohorts (CAD: 63 [47, 80] versus 83 [71, 96], $P<0.001$, INOCA: 60 [42, 75] versus 83 [72, 92], $P<0.001$; Figure 3).

Differential Effects of Stress and Depression on Angina-Related Health Status in Relation to Sex and CAD Status

Figure 4 shows the relationship between sex and angina-related health status in subgroups defined by

Table 1. Baseline Characteristics

	All participants (N=1626)	CAD (N=1439)	INOCA (N=187)
Age at enrollment, y, median (Q1, Q3)	67 (60–72)	67 (61–72)	62 (56–70)
Sex			
Female	369/1626 (23%)	249/1439 (17%)	120/187 (64%)
Race			
White	1369/1614 (85%)	1205/1428 (84%)	164/186 (88%)
Black	110/1614 (7%)	100/1428 (7%)	10/186 (5%)
Asian	116/1614 (7%)	106/1428 (7%)	10/186 (5%)
Other*	19/1614 (1%)	17/1428 (1%)	2/186 (1%)
Ethnicity			
Hispanic/Latino	300/1543 (19%)	247/1363 (18%)	53/180 (29%)
Not Hispanic/Latino	1243/1543 (81%)	1116/1363 (82%)	127/180 (71%)
Cigarette smoking			
Current smoker	221/1602 (14%)	203/1439 (14%)	18/163 (11%)
Former smoker	794/1602 (50%)	743/1439 (52%)	51/163 (31%)
Never smoked	587/1602 (37%)	493/1439 (34%)	94/163 (58%)
Diabetes	604/1626 (37%)	567/1439 (39%)	37/187 (20%)
Hypertension	1228/1623 (76%)	1107/1437 (77%)	121/186 (65%)
Prior myocardial infarction	253/1620 (16%)	249/1433 (17%)	4/187 (2%)
History of peripheral artery disease	70/1620 (4%)	68/1433 (5%)	2/187 (1%)

CAD indicates coronary artery disease; and INOCA, ischemia with no obstructive coronary arteries.

*Other includes participants who identify as any race other than White, Asian or Black including American Indian or Alaskan Native, Native Hawaiian or other Pacific Islander, or multiple races.

CAD or INOCA with stress and depressive symptoms considered as high versus low. There was an interaction between sex and depressive symptoms for SAQ-7 physical limitations score in patients with INOCA in both unadjusted and adjusted models whereby high depressive symptoms were more strongly associated with lower (worse) physical limitation scores in men than in women (regression coefficient, 1.30 [95% CI, 0.15–2.45]; $P_{\text{interaction adjusted}}$=0.027). There were no other significant interactions between sex and stress or sex and depression for SAQ-7 physical limitations score in patients with CAD or SAQ-7 summary score, SAQ-7 angina frequency score, or SAQ-7 quality-of-life score in either patients with CAD or INOCA (Figure 4). In pooled analyses examining continuous PSS-4 and PHQ-8 scores, female sex remained strongly associated with worse angina-related health status even after adjustment for stress, depressive symptoms, and CAD status (SAQ-7 summary score regression coefficient –5.12 [95% CI, –7.32 to –2.92], Table 3). This remained true in models adjusting for stress and depression scores separately (Table S1). There was no statistically significant interaction between sex and stress (–0.39 [95% CI –1.01 to 0.23]) or sex and depressive symptoms (–0.00 [95% CI –0.53 to 0.53]) on SAQ-7 summary score or any subscale score (Tables 3 and 4). The *P* value for interaction between sex and CAD status for SAQ-7 summary score was 0.186; however, the point estimate suggested the potential for a larger sex difference favoring men in the subgroup with CAD than in the subgroup with INOCA (3.04 [95% CI –1.47 to 7.55]) and there was uncertainty with a relatively wide CI around the estimate based in part on the small sample size of participants with INOCA. Results were similar for the angina frequency and physical limitation subscale scores. There was an interaction between female sex and CAD status on the quality-of-life subscale score such that the average difference in the score between CAD and INOCA was 2.67 [95% CI, –2.72 to 8.06] units larger in women than this difference was in men, after adjusting for other variables; the *P* value for this interaction was 0.045.

DISCUSSION

Given known disparities in the health status of women versus men with CCD, it is important to improve understanding of factors that may contribute to these differences in outcomes. In the context of the known greater burden of stress and depression in women, we hypothesized that stress and depression might contribute to the worse health status in women than men. In our large cohort of participants with CCD, including both CAD and INOCA, the prevalence of stress and depressive symptoms were relatively similar between women and men. However, female sex, stress, and

Table 2. Angina, Stress, and Depression by Sex in Patients With CAD and INOCA

	CAD (N=1439)	Female sex (N=249)	Male sex (N=1190)	*P* value	INOCA (N=187)	Female sex (N=120)	Male sex (N=67)	*P* value
SAQ-7 summary score, median (Q1, Q3)	83 (67–94)	76 (60–90)	83 (70–96)	<0.001	82 (66–91)	80 (64–89)	85 (75–93)	0.012
SAQ-7 angina frequency score, median (Q1, Q3)	90 (70–100)	90 (70–100)	90 (80–100)	<0.001	90 (80–100)	80 (70–100)	90 (80–100)	0.051
SAQ-7 physical limitation score, median (Q1, Q3)	92 (75–100)	83 (58–100)	100 (75–100)	<0.001	88 (69–100)	83 (64–95)	95 (75–100)	0.010
SAQ-7 quality-of-life score, median (Q1, Q3)	75 (50–88)	63 (50–88)	75 (50–88)	0.007	75 (50–83)	67 (50–83)	75 (62–92)	0.027
PHQ-8, median (Q1, Q3)	2 (0–6)	3 (1–8)	2 (0–5)	<0.001	2 (0–7)	3 (1–7)	1 (0–6)	0.109
High depressive symptoms PHQ-8 ≥10, N (%)	159/1384 (11%)	39/240 (16%)	120/1144 (10%)	0.015	31/186 (17%)	19/119 (16%)	12/67 (18%)	0.891
PSS-4, median (Q1, Q3)	4 (1–7)	5 (1–8)	4 (1–7)	0.185	5 (2–8)	5 (2–7)	6 (2–8)	0.395
High stress PSS-4 ≥10, N (%)	549/1402 (39%)	104/241 (43%)	445/1161 (38%)	0.186	89/183 (49%)	56/118 (47%)	33/65 (51%)	0.784

CAD indicates coronary artery disease; INOCA, ischemia with no obstructive coronary arteries; PHQ, Patient Health Questionnaire; PSS, Perceived Stress Scale; and SAQ, Seattle Angina Questionnaire.

depressive symptoms were each independently associated with worse angina-related health status. Results were similar in direction for patients with CAD and INOCA. In a pooled analysis including patients with CAD and INOCA there were no significant interactions between sex and stress or sex and depressive symptoms on overall health status outcomes.

Depression, anxiety, and stress have each been associated with more angina but no prior study, to our knowledge, has addressed both CAD and INOCA and both stress and depression.[6,16,29] Proposed mechanisms for this association may include the effects of stress and depression on neurologic pain processing pathways. For example, mental stress-induced ischemia and depressive symptoms were associated with greater odds of being in a higher angina frequency category, whereas extent of CAD and extent of ischemia on exercise or pharmacological stress tests were not associated with angina frequency in a prior study.[30] Among patients with CAD, activation of the inferior frontal lobe and other brain regions associated with pain processing in response to acute mental stress is associated with increased severity of angina.[31] Cortical activation is also different in silent versus painful ischemia.[32] This suggests a link between neurologic processing of stress and depressive symptoms and angina perception.

The relationship between psychosocial factors and angina is likely bidirectional. For example, facial expression during ischemia reveals more sadness and less happiness than without ischemia.[33] New onset depression and anxiety are increased among patients with low physical functioning at baseline, and physical functioning is worse among patients with diagnosed depression or anxiety.[34] The reasons behind this bidirectional relationship remain understudied, and longitudinal studies of stress and depression in relation to angina are lacking. Interestingly, patient misconceptions related to angina (eg, "angina is a small heart attack") were previously shown to be associated with higher levels of anxiety, depression, and lower physical functioning but not with higher angina frequency.[35] This suggests that stress and depressive symptoms may have a unique impact on physical functioning, potentially related in some patients to misperceptions of how physical activity may affect the heart.

We found that women had poorer angina-related health status than men regardless of CAD status. This is consistent with prior studies in patients with CAD and with INOCA.[36] Our findings support the idea that perceived stress and depressive symptoms cannot fully explain this sex difference. A prior study of 3979 patients with CAD showed that women reported more angina, lower physical functioning, and poorer angina-related quality of life.[36] Women also reported more depressive symptoms and lower social support. However, despite adjustment for depression and social support, sex remained an independent predictor of angina-related health status.[36] Together with the findings of the current study, these data support the need for future research seeking alternate mediators of sex differences in angina severity and angina-related quality of life other than perceived stress and depression.

Our results are counter to the hypothesis that mechanisms of ischemia and severity of CAD are important determinants of angina severity and health status. Despite a substantial female predominance in the group with INOCA and male predominance in the group with obstructive CAD, we found that there was overall no clinically significant difference in angina scores between women with CAD and with INOCA.

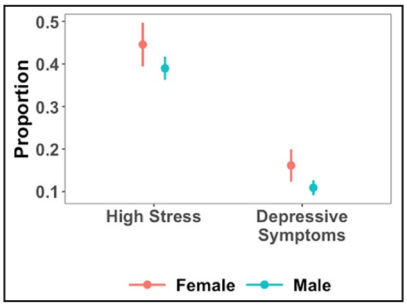

Figure 2. Bar graph of high stress (PSS-4 ≥6) and high depressive symptoms (PHQ-8 ≥10) proportion in women vs men in the entire cohort (pooled data).
PHQ indicates Patient Health Questionnaire; and PSS, Perceived Stress Scale.

There was an interaction between female sex and CAD status whereby the difference in scores between women and men was larger in the subgroup with CAD than the subgroup with INOCA for the quality-of-life subscale score. There was uncertainty about the potential for this interaction when considering the summary score and other subscale scores. Still, our results indicate that regardless of the underlying pathophysiology of ischemia, women experience worse symptoms than men. This effect may be even greater for women with CAD than INOCA. Mechanisms of ischemia in INOCA include coronary microvascular dysfunction, epicardial or microvascular coronary spasm, or a combination, and these mechanisms can also contribute to symptoms and ischemia in patients with significant atherosclerotic disease. Our results confirm findings of prior studies demonstrating that patients with INOCA have similar or worse levels of angina and angina-related health status when compared with patients with CAD.[37–39] We have previously shown in ISCHEMIA that women with obstructive CAD reported more angina than men despite less extensive CAD.[3] The primary results from the CIAO-ISCHEMIA study demonstrated no relationship between change in ischemia on stress testing and change in angina severity over 1 year.[19] Thus, neither CAD severity nor ischemia severity seems to be the driver of worse angina-related health status among women.

The greatest impact of female sex on angina-related health status was observed in the physical functioning domain. Prior studies have also demonstrated greater impact of psychosocial factors on physical functioning among women than men with angina.[40–42] Lower social support and lower self-efficacy are each associated with less physical activity among patients with angina.[43] Longer disease duration and a less favorable impression of the local environment were also associated with poorer physical functioning among women but not among men.[43] Longer disease duration has been correlated with lower physical functioning in more than 1 study, suggesting that interventions are needed to bolster activity levels among women, for example, cardiac rehabilitation.[44] Women typically shoulder more responsibility for household tasks and are often unable to perform these tasks due to heart disease.[45] The extent to which this may shape perception of differences in physical limitation by sex is not known. Women achieve lower peak oxygen consumption than men in both cohorts with CAD and healthy cohorts; thus, it is possible that women are less able to tolerate a decrement in physical functioning than men,

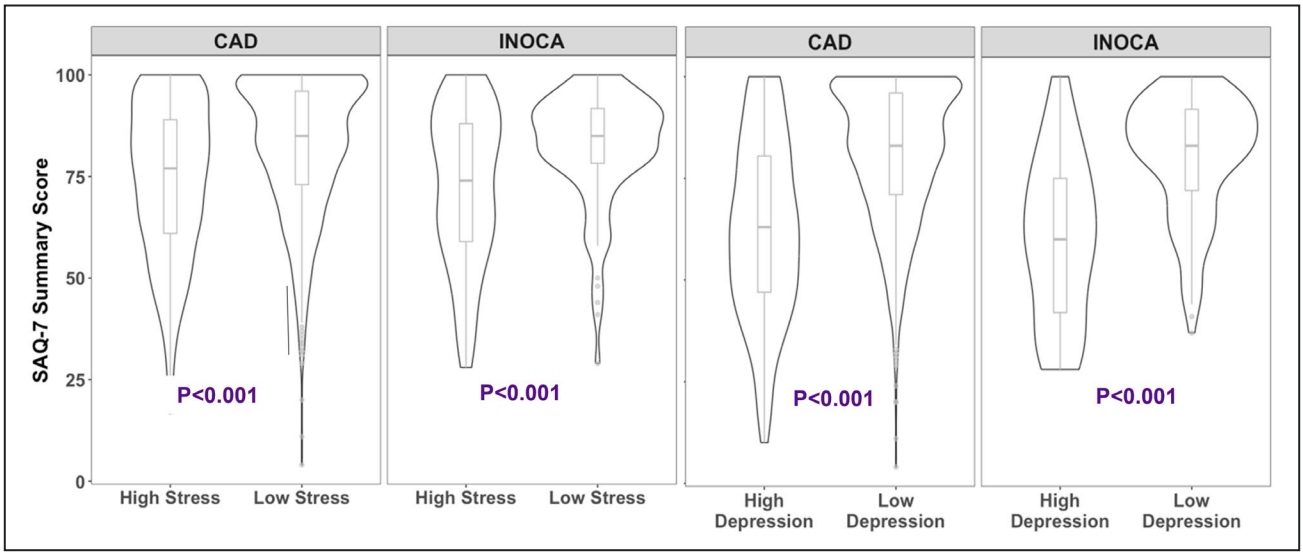

Figure 3. Association between SAQ-7 summary score and high vs low stress and depression stratified by CAD status.
CAD indicates coronary artery disease; INOCA, ischemia with no obstructive coronary artery disease; and SAQ, Seattle Angina Questionnaire.

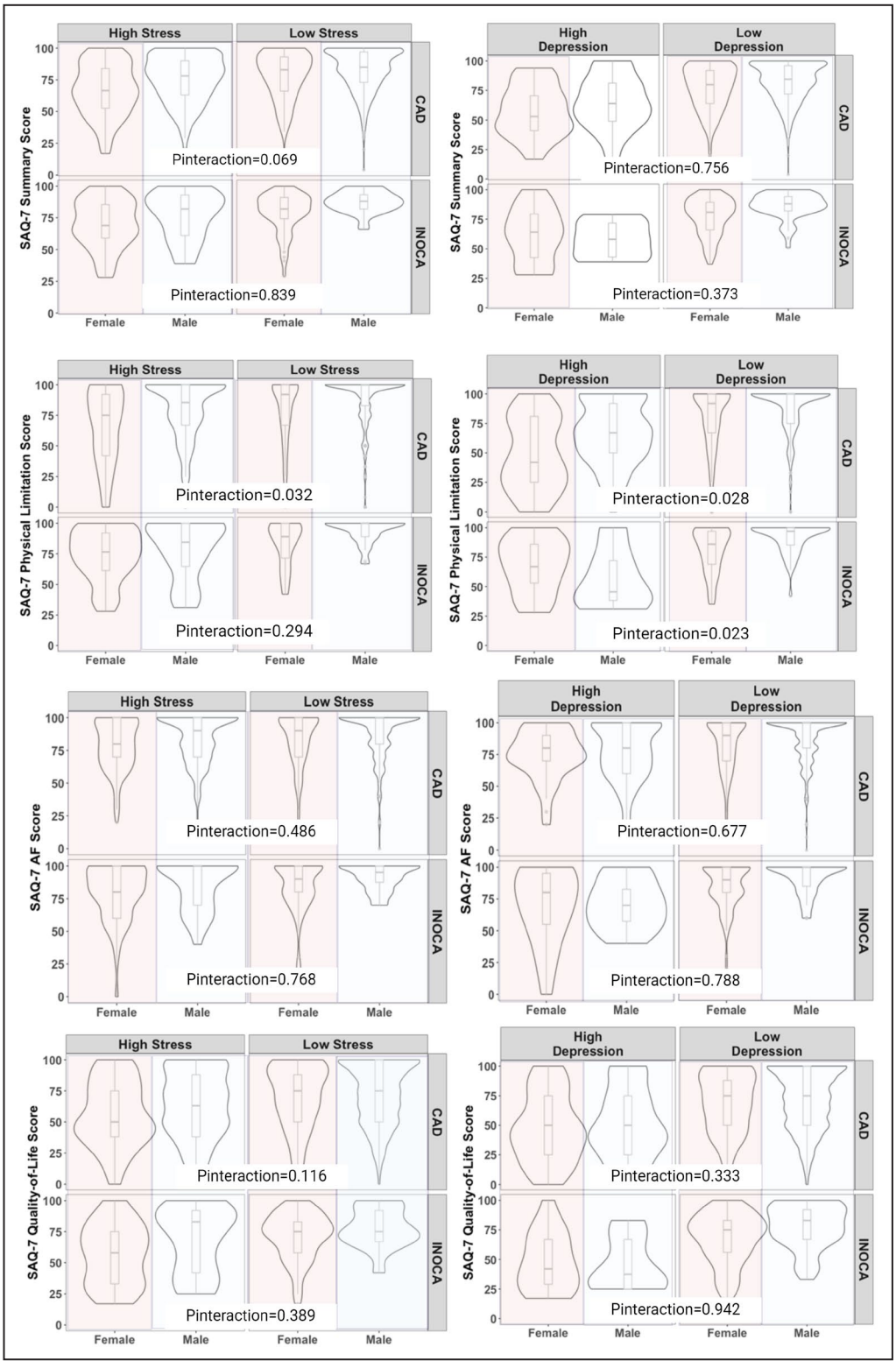

Figure 4. Association between angina and perceived stress or depressive symptoms by sex and CAD status.

*All *P* values were obtained from models that included adjustment for age and diabetes. Interaction *P* values assess the interaction between sex and the psychosocial variable (stress or depression) on the quality-of-life outcome within each CAD or INOCA stratum. High stress, PSS-4 ≥6; high depressive symptoms, PHQ-8 ≥10. AF indicates angina frequency; CAD, coronary artery disease; INOCA, ischemia with no obstructive coronary artery disease; PHQ, Patient Health Questionnaire; PSS, Perceived Stress Scale; and SAQ, Seattle Angina Questionnaire.

Table 3. SAQ Scores, Adjusted for Age and Diabetes, Before and After Including Perceived Stress and Depressive Symptoms in the Model

SAQ scores adjusted for sex, CAD, perceived stress, and depressive symptoms					
	Variable	Unadjusted	*P* value	Adjusted	*P* value
SAQ-7 summary score	Intercept	82.70 (79.86 to 85.54)	0.001	81.77 (79.40 to 84.14)	0.001
	Female sex	−7.09 (−9.54 to −4.64)	0.001	−5.12 (−7.32 to −2.92)	0.001
	CAD	−1.92 (−4.80 to 0.97)	0.193	−1.97 (−4.38 to 0.45)	0.110
	PSS-4			−0.78 (−1.06 to −0.50)	0.001
	PHQ-8			−1.38 (−1.62 to −1.14)	0.001
Physical limitations score	Intercept	88.12 (84.39 to 91.86)	0.001	87.05 (83.87 to 90.22)	0.001
	Female sex	−9.81 (−13.22 to −6.39)	0.001	−7.55 (−10.57 to −4.53)	0.001
	CAD	−1.21 (−4.96 to 2.54)	0.526	−1.42 (−4.61 to 1.76)	0.380
	PSS-4			−0.82 (−1.18 to −0.46)	0.001
	PHQ-8			−1.82 (−2.12 to −1.52)	0.001
Angina frequency score	Intercept	87.96 (85.00 to 90.92)	0.001	87.42 (84.61 to 90.23)	0.001
	Female sex	−5.51 (−7.90 to −3.12)	0.001	−4.41 (−6.75 to −2.06)	0.001
	CAD	−1.96 (−4.97 to 1.05)	0.202	−1.95 (−4.79 to 0.89)	0.179
	PSS-4			−0.29 (−0.59 to 0.02)	0.063
	PHQ-8			−0.80 (−1.05 to −0.55)	0.001
Quality of life score	Intercept	72.60 (68.72 to 76.48)	0.001	71.48 (68.06 to 74.90)	0.001
	Female sex	−6.30 (−9.60 to −3.00)	0.001	−3.84 (−6.87 to −0.81)	0.013
	CAD	−2.92 (−6.81 to 0.98)	0.142	−3.07 (−6.50 to 0.37)	0.080
	PSS-4			−1.19 (−1.60 to −0.78)	0.001
	PHQ-8			−1.67 (−2.00 to −1.34)	0.001

CAD indicates coronary artery disease; PHQ, Patient Health Questionnaire; PSS, Perceived Stress Scale; and SAQ, Seattle Angina Questionnaire.

perhaps contributing to greater perception and reporting of physical limitation among women.[46,47]

limitations and Strengths

The current study should be interpreted in view of the following potential limitations. Based on an administrative decision, the full battery of questionnaires included here was collected only in a subset of the ISCHEMIA cohort based on country of enrollment, limiting our sample size. The number of participants in the cohort with INOCA was smaller compared with the cohort with CAD, and there were important differences in demographics and clinical characteristics between the groups, limiting power to detect interactions between sex, perceived stress or depression categories, and

Table 4. Interaction Table

	Interaction variables	Effect size (CI)	*P* value
SAQ-7 summary score	Female sex×PSS-4	−0.39 (−1.01 to 0.23)	0.221
	Female sex×PHQ-8	−0.00 (−0.53 to 0.53)	0.992
	Female sex×CAD	3.04 (−1.47 to 7.55)	0.186
Physical limitations score	Female sex×PSS-4	−0.71 (−1.53 to 0.11)	0.091
	Female sex×PHQ-8	−0.38 (−1.07 to 0.31)	0.277
	Female sex×CAD	−0.08 (−6.15 to 5.98)	0.978
Angina frequency score	Female sex×PSS-4	−0.11 (−0.76 to 0.54)	0.743
	Female sex×PHQ-8	−0.15 (−0.68 to 0.39)	0.585
	Female sex×CAD	2.67 (−2.72 to 8.06)	0.331
Quality of life score	Female sex×PSS-4	−0.59 (−1.44 to 0.26)	0.176
	Female sex×PHQ-8	0.18 (−0.54 to 0.90)	0.617
	Female sex×CAD	6.70 (0.15 to 13.26)	0.045

SAQ scores, adjusted for age and diabetes. Interactions between Perceived Stress Scale×sex, Patient Health Questionnaire×sex and CAD status×sex. CAD indicates coronary artery disease; and SAQ, Seattle Angina Questionnaire.

CAD status. In addition, the methods for ischemia testing were different between groups. CIAO included only participants who underwent stress echocardiograms whereas ISCHEMIA included participants who underwent various ischemia testing modalities. This may have resulted in bias in our INOCA sample. Our analysis on psychosocial factors was limited to perceived stress and depressive symptoms. Symptoms of anxiety were not assessed. Our analysis of perceived stress and depressive symptoms in relation to angina was cross-sectional, and further analysis of the longitudinal effects of these factors over time is needed. Overall levels of depressive symptoms in both cohorts were low, limiting power for these analyses. The potential role of sex differences in physician advice about activity and angina management in general in our findings is unknown. The participants were predominantly Non-Hispanic White, so results may not be generalizable to other racial or ethnic groups. Despite these limitations, these analyses have several strengths, including a large number of participants and a diverse cohort enrolled from multiple countries, with well-defined coronary anatomy. Our study is unique in that patients with CAD and INOCA were selected using the same clinical and ischemia-based entry criteria.

CONCLUSIONS

Our results demonstrate that worse angina-related health status among women compared with men cannot be fully explained by perceived stress or depression levels or extent of CAD. Perceived stress and depression were each independent contributors to poorer health status in our study, without interaction with sex. The relationship between female sex and angina-related health status thus warrants further study with a focus on alternate mediators. Future research should explore sex differences in neurobiological and pain processing mechanisms that may contribute to symptoms of angina.

ARTICLE INFORMATION

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Supplemental Material

Data S1–S2
Table S1

REFERENCES

1. Joshi PH, de Lemos JA. Diagnosis and Management of Stable Angina: a review. *Jama*. 2021;325:1765–1778. doi: 10.1001/jama.2021.1527
2. Arnold SV, Spertus JA, Ciechanowski PS, Soine LA, Jordan-Keith K, Caldwell JH, Sullivan MD. Psychosocial modulators of angina response to myocardial ischemia. *Circulation*. 2009;120:126–133. doi: 10.1161/CIRCULATIONAHA.108.806034

3. Reynolds HR, Shaw LJ, Min JK, Spertus JA, Chaitman BR, Berman DS, Picard MH, Kwong RY, Bairey-Merz CN, Cyr DD, et al. Association of sex with Severity of coronary artery disease, ischemia, and symptom burden in patients with moderate or severe ischemia: secondary analysis of the ISCHEMIA randomized clinical trial. *JAMA Cardiol*. 2020;5:773–786. doi: 10.1001/jamacardio.2020.0822
4. Vaccarino V, Badimon L, Bremner JD, Cenko E, Cubedo J, Dorobantu M, Duncker DJ, Koller A, Manfrini O, Milicic D, et al. Depression and coronary heart disease: 2018 position paper of the ESC working group on coronary pathophysiology and microcirculation. *Eur Heart J*. 2020;41:1687–1696. doi: 10.1093/eurheartj/ehy913
5. Richardson S, Shaffer JA, Falzon L, Krupka D, Davidson KW, Edmondson D. Meta-analysis of perceived stress and its association with incident coronary heart disease. *Am J Cardiol*. 2012;110:1711–1716. doi: 10.1016/j.amjcard.2012.08.004
6. Arnold SV, Smolderen KG, Buchanan DM, Li Y, Spertus JA. Perceived stress in myocardial infarction: long-term mortality and health status outcomes. *J Am Coll Cardiol*. 2012;60:1756–1763. doi: 10.1016/j.jacc.2012.06.044
7. Mehta PK, Sharma A, Bremner JD, Vaccarino V. Mental stress-induced myocardial ischemia. *Curr Cardiol Rep*. 2022;24:2109–2120. doi: 10.1007/s11886-022-01821-2
8. Mehta LS, Beckie TM, DeVon HA, Grines CL, Krumholz HM, Johnson MN, Lindley KJ, Vaccarino V, Wang TY, Watson KE, et al. Acute myocardial infarction in women: a scientific statement from the American Heart Association. *Circulation*. 2016;133:916–947. doi: 10.1161/CIR.0000000000000351
9. Smolderen KG, Strait KM, Dreyer RP, D'Onofrio G, Zhou S, Lichtman JH, Geda M, Bueno H, Beltrame J, Safdar B, et al. Depressive symptoms in younger women and men with acute myocardial infarction: insights from the VIRGO study. *J Am Heart Assoc*. 2015;4:4. doi: 10.1161/JAHA.114.001424
10. Altemus M, Sarvaiya N, Epperson CN. Sex differences in anxiety and depression clinical perspectives. *Front Neuroendocrinol*. 2014;35:320–330. doi: 10.1016/j.yfrne.2014.05.004
11. Gradus JL. Prevalence and prognosis of stress disorders: a review of the epidemiologic literature. *Clini Epidemiol*. 2017;9:251–260. doi: 10.2147/CLEP.S106250
12. Kessler RC, Petukhova M, Sampson NA, Zaslavsky AM, Wittchen HU. Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. *Intern J Methods Psychiatric Res*. 2012;21:169–184. doi: 10.1002/mpr.1359
13. Vaccarino V, Wilmot K, Mheid IA, Ramadan R, Pimple P, Shah AJ, Garcia EV, Nye J, Ward L, Hammadah M. Sex differences in mental stress-induced myocardial ischemia in patients with coronary heart disease. *J Am Heart Assoc*. 2016;5:e003630. doi: 10.1161/JAHA.116.003630
14. Sullivan S, Hammadah M, Al Mheid I, Wilmot K, Ramadan R, Alkhoder A, Isakadze N, Shah A, Levantsevych O, Pimple PM. Sex differences in hemodynamic and microvascular mechanisms of myocardial ischemia induced by mental stress. *Arterioscl Thromb Vascu Biol*. 2018;38:473–480. doi: 10.1161/ATVBAHA.117.309535
15. Konst RE, Elias-Smale SE, Lier A, Bode C, Maas AH. Different cardiovascular risk factors and psychosocial burden in symptomatic women with and without obstructive coronary artery disease. *Eur J Preven Cardiol*. 2019;26:657–659. doi: 10.1177/2047487318814298
16. Gomez MA, Merz NB, Eastwood JA, Pepine CJ, Handberg EM, Bittner V, Mehta PK, Krantz DS, Vaccarino V, Eteiba W. Psychological stress, cardiac symptoms, and cardiovascular risk in women with suspected ischaemia but no obstructive coronary disease. *Stress Health*. 2020;36:264–273. doi: 10.1002/smi.2928
17. Kothawade K, Merz CNB. Microvascular coronary dysfunction in women—pathophysiology, diagnosis, and management. *Curr Probl Cardiol*. 2011;36:291–318. doi: 10.1016/j.cpcardiol.2011.05.002
18. Sedlak TL, Lee M, Izadnegahdar M, Merz CNB, Gao M, Humphries KH. Sex differences in clinical outcomes in patients with stable angina and no obstructive coronary artery disease. *Am Heart J*. 2013;166:38–44. doi: 10.1016/j.ahj.2013.03.015
19. Reynolds HR, Picard MH, Spertus JA, Peteiro J, Lopez Sendon JL, Senior R, El-Hajjar MC, Celutkiene J, Shapiro MD, Pellikka PA. Natural history of patients with ischemia and no obstructive coronary artery disease: the CIAO-ISCHEMIA study. *Circulation*. 2021;144:1008–1023. doi: 10.1161/CIRCULATIONAHA.120.046791
20. Hausvater A, Spruill TM, Xia Y, Smilowitz NR, Arabadjian M, Shah B, Park K, Giesler C, Marzo K, Thomas D. Psychosocial factors of women presenting with myocardial infarction with or without obstructive coronary arteries. *J Am Coll Cardiol*. 2023;82:1649–1658. doi: 10.1016/j.jacc.2023.08.028
21. Maron DJ, Hochman JS, O'Brien SM, Reynolds HR, Boden WE, Stone GW, Bangalore S, Spertus JA, Mark DB, Alexander KP. International study of comparative health effectiveness with medical and invasive approaches (ISCHEMIA) trial: rationale and design. *Am Heart J*. 2018;201:124–135. doi: 10.1016/j.ahj.2018.04.011
22. Ford ND, Cox S, Ko JY, Ouyang LJ, Romero L, Colarusso T, Ferre CD, Kroelinger CD, Hayes DK, Barfield WD. Hypertensive disorders in pregnancy and mortality at delivery hospitalization - United States, 2017–2019. *MMWR*. 2022;71:585–591. doi: 10.15585/mmwr.mm7117a1
23. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Soc Behav*. 1983;24:385–396. doi: 10.2307/2136404
24. Cohen S, Williamson GM. Perceived stress in a probability sample of the United-States. *Soc Psych Health*. 1988;31–67.
25. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9 - validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16:606–613. doi: 10.1046/j.1525-1497.2001.016009606.x
26. Kroenke K, Strine TW, Spitzer RL, Williams JB, Berry JT, Mokdad AH. The PHQ-8 as a measure of current depression in the general population. *J Affect Disord*. 2009;114:163–173. doi: 10.1016/j.jad.2008.06.026
27. Chan PS, Jones PG, Arnold SA, Spertus JA. Development and validation of a short version of the Seattle angina questionnaire. *Circ Cardiovasc Qual Outcomes*. 2014;7:640–647. doi: 10.1161/circoutcomes.114.000967
28. Thomas M, Jones PG, Arnold SV, Spertus JA. Interpretation of the Seattle angina questionnaire as an outcome measure in clinical trials and clinical care: a review. *JAMA Cardiol*. 2021;6:593–599. doi: 10.1001/jamacardio.2020.7478
29. Ruo B, Rumsfeld JS, Hlatky MA, Liu H, Browner WS, Whooley MA. Depressive symptoms and health-related quality of life: the Heart and Soul tudy. *Jama*. 2003;290:215–221. doi: 10.1001/jama.290.2.215
30. Pimple P, Shah AJ, Rooks C, Bremner JD, Nye J, Ibeanu I, Raggi P, Vaccarino V. Angina and mental stress-induced myocardial ischemia. *J Psychosom Res*. 2015;78:433–437. doi: 10.1016/j.jpsychores.2015.02.007
31. Moazzami K, Wittbrodt MT, Alkhalaf M, Lima BB, Nye JA, Mehta PK, Quyyumi AA, Vaccarino V, Bremner JD, Shah AJ. Association between mental stress-induced inferior frontal cortex activation and angina in coronary artery disease. *Circulation. Cardiovasc Imag*. 2020;13:e010710. doi: 10.1161/CIRCIMAGING.120.010710
32. Rosen SD, Paulesu E, Nihoyannopoulos P, Tousoulis D, Frackowiak RSJ, Frith CD, Jones T, Camici PG. Silent ischemia as a central problem: regional brain activation compared in silent and painful myocardial ischemia. *Ann Intern Med*. 1996;124:939–949. doi: 10.7326/0003-4819-124-11-199606010-00001
33. Bekendam MT, Kop WJ, Vermeltfoort IAC, Widdershoven JW, Mommersteeg PMC. Facial expressions of emotions during pharmacological and exercise stress testing: the role of myocardial ischemia and cardiac symptoms. *Int J Behav Med*. 2021;28:692–704. doi: 10.1007/s12529-021-09963-3
34. Stegenga BT, Nazareth I, Torres-González F, Xavier M, Švab I, Geerlings MI, Bottomley C, Marston L, King M. Depression, anxiety and physical function: exploring the strength of causality. *J Epidemiol Community Health*. 2012;66:e25. doi: 10.1136/jech.2010.128371
35. Furze G, Lewin RJ, Murberg T, Bull P, Thompson DR. Does it matter what patients think? The relationship between changes in patients' beliefs about angina and their psychological and functional status. *JPsychosomatic Res*. 2005;59:323–329. doi: 10.1016/j.jpsychores.2005.06.071
36. Norris CM, Spertus JA, Jensen L, Johnson J, Hegadoren KM, Ghali WA. Sex and gender discrepancies in health-related quality of life outcomes among patients with established coronary artery disease. *Circ Cardiovasc Qual Outcomes*. 2008;1:123–130. doi: 10.1161/CIRCOUTCOMES.108.793448
37. Tavella R, Cutri N, Tucker G, Adams R, Spertus J, Beltrame JF. Natural history of patients with insignificant coronary artery disease. *Eur Heart J Qual Care Clin Outcomes*. 2016;2:117–124. doi: 10.1093/ehjqcco/qcv034
38. Ford TJ, Stanley B, Good R, Rocchiccioli P, McEntegart M, Watkins S, Eteiba H, Shaukat A, Lindsay M, Robertson K, et al. Stratified medical therapy using invasive coronary function testing in angina: the CorMicA trial. *J Am Coll Cardiol*. 2018;72:2841–2855. doi: 10.1016/j.jacc.2018.09.006

39. Jespersen L, Abildstrøm SZ, Hvelplund A, Prescott E. Persistent angina: highly prevalent and associated with long-term anxiety, depression, low physical functioning, and quality of life in stable angina pectoris. *Clin Res Cardiol*. 2013;102:571–581. doi: 10.1007/s00392-013-0568-z
40. Richardson J. Gender differences associated with physical functioning in older persons with angina. *Disabil Rehabil*. 2003;25:973–983. doi: 10.1080/0963828031000122294
41. Barsky L, Speier W, Fuller G, Cheng S, Kim A, Joung S, Arnold C, Dhawan S, Lopez M, Mastali M, et al. Sex-based differences in remote monitoring of biometric, psychometric and biomarker indices in stable ischemic heart disease. *Biol Sex Differ*. 2022;13:15. doi: 10.1186/s13293-022-00423-5
42. Dreyer R, Arstall M, Tavella R, Morgan C, Weekes A, Beltrame J. Gender differences in patients with stable angina attending primary care practices. *Heart Lung Circ*. 2011;20:452–459. doi: 10.1016/j.hlc.2011.02.005
43. Huang WT, Liu CY, Hung HF, Hsu SP, Chiou AF. Gender differences in factors associated with physical activity in patients with coronary artery disease. *J Cardiovasc Nurs*. 2022;37:368–377. doi: 10.1097/JCN.0000000000000804
44. Kimble LP, McGuire DB, Dunbar SB, Fazio S, De A, Weintraub WS, Strickland OS. Gender differences in pain characteristics of chronic stable angina and perceived physical limitation in patients with coronary artery disease. *Pain*. 2003;101:45–53. doi: 10.1016/s0304-3959(02)00319-6
45. Kimble LP. Impact of cardiac symptoms on self-reported household task performance in women with coronary artery disease. *J Cardpulm Rehabil*. 2001;21:18–23. doi: 10.1097/00008483-200101000-00005
46. Ades PA, Savage PD, Brawner CA, Lyon CE, Ehrman JK, Bunn JY, Keteyian SJ. Aerobic capacity in patients entering cardiac rehabilitation. *Circulation*. 2006;113:2706–2712. doi: 10.1161/CIRCULATIONAHA.105.606624
47. Santisteban KJ, Lovering AT, Halliwill JR, Minson CT. Sex differences in VO(2max) and the impact on endurance-exercise performance. *Int J Environ Res Public Health*. 2022;19:4946. doi: 10.3390/ijerph19094946