Do Women With Anxiety or Depression Have Higher Rates of Myocardial Ischemia During Exercise Testing Than Men?

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Background—Women diagnosed with coronary artery disease (CAD) typically experience worse outcomes relative to men, possibly through diagnosis and treatment delays. Reasons for these delays may be influenced by mood and anxiety disorders, which are more prevalent in women and have symptoms (eg, palpitations and fatigue) that may be confounded with CAD. Our study examined sex differences in the association between mood and anxiety disorders and myocardial ischemia in patients with and without a CAD history presenting for exercise stress tests.

Methods and Results—A total of 2342 patients (women n=760) completed a single photon emission computed tomographic exercise stress test (standard Bruce Protocol) and underwent a psychiatric interview (The Primary Care Evaluation of Mental Disorders) to assess mood and anxiety disorders. Ischemia was assessed using single photon emission computed tomography, with odds ratio used to calculate the effect of sex and mood/anxiety on the presence of ischemia during stress testing by CAD history in a stratified analyses, adjusted for relevant covariates. There was a sex by anxiety interaction with ischemia in those without a CAD history (P=0.015): women with anxiety were more likely to exhibit ischemia during exercise than women without anxiety (odds ratio, 1.75; 95% confidence interval, 1.05–2.89). No significant effects were observed for men nor mood.

Conclusions—Women with anxiety and no CAD history had higher rates of ischemia than women without anxiety. Results suggest that anxiety symptoms, many of which overlap with those of CAD, might mask CAD symptoms among women (but not men) and contribute to referral and diagnostic delays. Further research is needed to confirm this hypothesis.

(*Circ Cardiovasc Qual Outcomes*. 2016;9:S53-S61. DOI: 10.1161/CIRCOUTCOMES.115.002491.)

Key Words: anxiety ■ coronary artery disease ■ depression ■ ischemia ■ myocardial ischemia

Women have been shown to have worse coronary artery disease (CAD) outcomes relative to men because more women (17%) than men (12%) die within 3 years of having their first myocardial infarction (MI),[1] and hospital mortality rates after an acute MI have been shown to be higher in women (16%) than in men (11%).[2] Suggested reasons for this sex disparity include the unique presentation of CAD in women and delays associated with diagnosis and treatment onset among women relative to men.[3–5] Sex differences are still evident when assessing laboratory-based proxies for CAD outcomes such as myocardial ischemia, with a higher prevalence in women rather than in men.[6,7] However, the extent to which sex differences in psychiatric disorders could influence both the presentation of and the ability to detect CAD has not been fully explored.

Psychiatric disorders, especially anxiety and mood disorders, seem to be more common in women than in men,[8] and there is a documented link between these disorders and worse cardiac outcomes.[9–12] In addition to more traditional physiological risk factors for CAD, having depression is now considered to be a key risk factor for CAD,[13,14] and there is emerging evidence linking anxiety to CAD development,[15,16] particularly among women.[17,18] We have recently demonstrated, in a sample of patients with premature acute coronary syndrome, that the presence of anxiety was a critical determinant of poorer access to clinical care procedures (such as ECG and fibrinolysis testing) among women, but not among men.[5] This suggests that psychiatric disorders, particularly anxiety, may be a unique risk factor for diagnostic and treatment delays among women at risk for CAD. This may be because of similarities between the presentation of symptoms of anxiety disorders and CAD, and possible misinterpretation of symptoms of CAD as symptoms of anxiety only. Patients who attend the emergency department with noncardiac chest pain are more likely to be women, and combined with a lower overall rate of acute coronary syndrome in women, these symptoms could be mistaken for anxiety-related symptoms (eg, fatigue, chest pain, and shortness of breath), rather than conducting an

Received November 16, 2015; accepted January 28, 2016.

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The Data Supplement is available at http://circoutcomes.ahajournals.org/lookup/suppl/doi:10.1161/CIRCOUTCOMES.115.002491/-/DC1.

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WHAT IS KNOWN

- Women diagnosed with coronary artery disease (CAD) typically experience worse outcomes relative to men, possibly through diagnosis and treatment delays.Reasons for these delays may be influenced by mood and anxiety disorders, which are more prevalent in women and have symptoms (eg, palpitations and fatigue) that may be confounded with CAD.

WHAT THE STUDY ADDS

- Women with anxiety and no CAD history had higher rates of ischemia than women without anxiety.
- Results suggest that anxiety symptoms, many of which overlap with those of CAD, might mask CAD symptoms among women (but not men) and contribute to referral and diagnostic delays.

urgent CAD assessment.[19] Furthermore, another study showed that in patients who presented to the emergency room with unexplained chest pains, 40% of patients were experiencing anxiety-like symptoms,[20] highlighting the potential to miss CAD symptoms that might also be apparent in these patients.

Few studies have explored sex differences in the prevalence of psychiatric disorders in patients referred for diagnostic exercise stress testing or their associations with indicators of treatment such as myocardial ischemia. Our objective was to examine the relationship between sex, psychiatric disorders, and ischemia presentation in patients referred for exercise stress single photon emission computed tomographic (SPECT) tests, including those with and without an existing history of CAD. It was hypothesized that the presence of psychiatric disorders would lead to a higher rate of ischemia during exercise stress testing and that this effect would be more pronounced in women than in men, in a stratified analysis of CAD and non-CAD patients. Based on the data from previous studies, we further expected to observe this relationship more strongly in relation to the presence of anxiety relative to mood disorders.

Methods

Participants and Recruitment

A total of 2342 participants (32.5% women) who presented to the Nuclear Medicine Department at the Montreal Heart Institute for diagnostic myocardial perfusion (SPECT) exercise stress testing participated in the study. Inclusion criteria were that patients were aged between 18 and 75 years and were fluent in English or French (to be able to complete the assessments). Only medically stable outpatients (with and without a CAD event history) who were referred for SPECT exercise (treadmill, Bruce protocol) stress testing were invited to participate. Patients were excluded if they had a documented medical condition that conferred greater risk of illness morbidity than CAD (eg, cancer and chronic obstructive pulmonary disease), if they were inpatients (hospitalized or at emergency) at the time of their stress test, if they had experienced a major cardiac event (eg, MI, percutaneous coronary intervention, and coronary artery bypass graft) in the 4 weeks before their exercise stress test, or if they were in any way unstable (eg, unstable angina and unable to exercise) at the time of their exercise test. All medication regimens were maintained for ethical reasons and to provide as much potential possible generalizability of our results. This protocol was approved by the Human Research Ethics Board of the Montreal Heart Institute and participants provided informed consent before the exercise stress test. Data collection took place between September 1998 and June 2002.

Psychiatric Assessment

The Primary Care Evaluation of Mental Disorders (PRIME-MD) was used to evaluate the prevalence of mood and anxiety disorders. The PRIME-MD[21] is a validated screening instrument designed to detect some of the most common Diagnostic and Statistical Manual of Mental Disorders disorders seen in community and medical settings.[22] The PRIME-MD evaluates 5 groups of mental disorders (mood, anxiety, somatoform, alcohol, and eating), and items were developed based on the criteria from the Diagnostic and Statistical Manual of Mental Disorders-third edition revised (DSM-III-R),[23] for which the diagnostic criteria have not changed through to Diagnostic and Statistical Manual of Mental Disorders-5.[24] Because of the high prevalence of mood and anxiety disorders in CAD populations, and their links to worse CAD outcomes, only the mood and anxiety disorder modules were administered. These modules have demonstrated good sensitivity (83%) for any psychiatric diagnosis and excellent specificity (88%) for any psychiatric disorder and across disorders (range, 88%–99%).[21] Inter-rater reliability for any psychiatric diagnosis is good (κ=0.71) and satisfactory for mood (κ=0.61) and anxiety disorders (κ=0.55).[21] The PRIME-MD was administered in computer form (Pfizer, Canada) after the exercise stress test by a licensed clinical psychologist or a PhD-level clinical psychology graduate student, who was supervised by the clinical psychologist. Comorbid presentation of mood and anxiety disorder was defined as the presentation of both any mood and any anxiety disorders. The presence of psychiatric disorders was classified as present or absent and was treated as dichotomous variables.

Ischemia Assessment

Ischemia assessment was quantified using SPECT-based myocardial ischemia and was classified dichotomously as either present or absent. The testing protocol was a 2-day rest–stress protocol, which was completed in line with standard clinical guidelines.[25] The rest day was completed first for two reasons. First, the rest day was used to obtain consent and to collect sociodemographic data. Second, to reduce the risk of remnants of ischemia from the previous day of testing being evident on the second day of imaging, the rest day was completed first to ensure that a more reliable true resting state of perfusion was obtained. The test used was a standard Bruce protocol, with ischemia being assessed at the point of peak exercise (injection of the agent), in line with standard procedures.[25,26] The image acquisition consisted of a 360° rotation of a triple-head gamma camera (Irix-3 model; Philips Inc., Cleveland, OH), with 64 views at 30-second intervals, at a frame rate of 8 frames per cycle. Specifically, to be considered ischemic patients needed to have at least a 2-point change in the stress–rest differential score, which was generated using standard software (Autoquant, Media Cybernetics, Gale Group, Farmington Hills, MI) and verified by the physician. Any borderline cases were independently re-evaluated by 2 nuclear cardiology physicians who reached a consensus on the diagnosis of ischemia.

Statistical Analysis

Demographics and Descriptive Analyses

Sociodemographic characteristics and history were obtained from questionnaires and medical records. Descriptive analyses were completed as a function of sex and CAD history. General linear models or χ^2 analyses were completed, with the demographics presented as mean (SD) or as a percentage (n). Sex was dummy coded as 0 (women) or 1 (men).

Sex Differences in Psychiatric Disorders and the Presence of Ischemia During Stress Testing

Given the dichotomous nature of our variables, sex differences in psychiatric disorders and the presence of ischemia during stress testing

Table 1. Sample Size Estimates, Based on Power of 0.8, α Probability of 0.1, and Effect

	Non-CAD Patients Only			CAD Patients Only		
	Sample Needed	Observed Effect Size	Odds Ratio (Interaction)	Sample Needed	Observed Effect Size	Odds Ratio (Interaction)
Any psychiatric disorder	237	0.50	1.35	897	0.11	0.29
Any mood disorder	233	0.52	1.41	525	0.14	0.38
Any anxiety disorder	124	0.83	2.26	880	0.15	0.41
Any comorbid disorder	171	1.20	3.26	633	0.35	0.95

CAD indicates coronary artery disease.

were assessed using a series of χ^2 analyses, with logistic regressions used to assess risk of psychiatric disorders and ischemia presentation by sex. Initial analyses examined sex differences in the presence of any psychiatric disorder, any mood disorder, any anxiety disorder, and any comorbid disorder, and in the presence of ischemia (after adjustment for covariates).

Relationship Between Sex, Psychiatric Disorders, and Ischemia in Patients With Versus Without a CAD History

Given the binary outcome of ischemia (present and absent), logistic regression models were utilized to assess the possible relationship and interactions between sex and psychiatric disorders in the presence of SPECT ischemia during exercise stress testing, which was stratified by CAD history. CAD history was determined by the presence of previous MI, percutaneous transluminal coronary angioplasty, or coronary artery bypass graft. These models were adjusted for age, smoking history, exercise performance (indexed by Metabolic Equivalents), use of anti-ischemic medication (ie, vasodilators, β-blockers, or calcium channel blocker), and number of medications. As needed, post hoc analyses were completed for each logistic regression using four groups (each given psychiatric disorder × sex) to determine the risk of the presence of ischemia during stress testing for patients with and without a history of CAD, using women without each given psychiatric disorder as a reference point. All analyses were completed using SAS 9.3 (SAS, Cary, NC), with significance set at $P<0.05$. Adjustment for multiple testing was undertaken by calculating the false-discovery rate using proc multtest (SAS 9.3). Power calculations were undertaken to determine sample size needed (Table 1). Occasional missing data are reflected in the degrees of freedom.

Results

Demographics

Sociodemographic characteristics presented as a function of sex (Table 2) and of CAD history (Table 3). Men displayed a greater prevalence of hyperlipidemia, diabetes mellitus, previous MI, history of CAD, and previous bypass surgery. Men were also more likely to have been current and previous smokers. Men displayed greater baseline diastolic blood pressure than women; women displayed greater baseline HR. There were no sex differences in baseline systolic blood pressure. More men were prescribed vasodilators, β-blockers, Ca-channel blockers, angiotensin-converting enzyme inhibitors, aspirin, and lipid-lowering medications, with the exception of diuretics which were more frequently prescribed in women.

Sex Differences in Presentation of Psychiatric Disorders and the Presence of Ischemia During Stress Testing

A series of χ^2 analyses revealed sex differences for the presentation of psychiatric disorders and ischemia and are displayed in Table 4. In contrast to men, women displayed a greater prevalence of any psychiatric disorder, any anxiety disorder, any mood disorder, and of comorbid anxiety and mood disorders. Sex differences were evident for the presence of ischemia during stress testing with men displaying a greater prevalence of ischemia. Logistic regressions were also used to examine the differences in the risk of each psychiatric disorder and the presence of ischemia during stress testing by sex and are also displayed in Table 4. Using men as a reference point, women had an elevated risk of presenting with any psychiatric disorder (odds ratio [OR], 1.76), any anxiety disorder (OR, 1.78), any mood disorder (OR, 1.62), and any comorbid anxiety and mood disorders (OR, 1.85). Using women as a reference point, men had over a 3.5-fold elevated risk of the presence of ischemia during stress testing (OR, 3.63).

Relationships Between Sex, Psychiatric Disorders, and the Presence of Ischemia During Stress Testing in Patients With Versus Without a History of CAD

Logistic regressions (with the presence of ischemia during stress testing as the outcome) were used to ascertain the relationships between sex and psychiatric status on the presence of ischemia during exercise stress testing for patients with and without a history of CAD. In patients without a history of CAD, interactions were evident for anxiety (β=−0.83; $P=0.015$ [adjusted P value for multiple testing=0.04]) and comorbid mood and anxiety (β=−1.20; $P=0.005$ [adjusted P value for multiple testing=0.032]), but not any psychiatric (β=−0.50; $P=0.10$) or mood disorder (β=−0.52; $P=0.11$). In patients with a history of CAD, no interactions were evident for any of the psychiatric disorders assessed (any psych: β=0.11, $P=0.79$; mood: β=0.14, $P=0.75$; anxiety: β=0.15, $P=0.76$; and any comorbid mood and anxiety: β=0.35, $P=0.56$).

To further examine the interaction effects present for anxiety, separate post hoc analyses in those with and without a history of CAD are displayed in Table 5. For patients without a history of CAD, in comparison with women without anxiety, men with and without anxiety had a greater risk of the presence of ischemia during stress testing (Ps<0.001). Importantly, women with anxiety had nearly a 2-fold greater risk of the presence of ischemia during stress testing than women without anxiety. This same elevated risk was not seen when directly comparing men with anxiety and men without anxiety (OR, 1.31; 95% confidence interval [CI], 0.83–2.06; $P=0.24$). In patients with a CAD history, analyses revealed that there was no elevated risk of the presence of ischemia during stress testing for women with anxiety versus women without anxiety (OR, 0.97). Men had an elevated risk of the presence of ischemia during stress testing regardless of anxiety presentation

Table 2. Participant Characteristics, Presented as a Function of Sex

Mean (SD) or % (n)	Men (n=1582)	Women (n=760)	χ^2/F	*P* Value
Sociodemographics				
Age, y	56.7	56.1	−1.68	0.09
Employed	58.1 (536)	46.6 (191)	15.1	<0.01*
Cohabitating	86.1 (795)	79.0 (323)	10.77	<0.01*
≥12 y education	61 (578)	51 (214)	12.45	0.01*
Baseline SBP, mm Hg	136.4 (20.3)	134.4 (20.4)	0.31	0.58
Baseline DBP, mm Hg	86.3 (11.0)	84.6 (12.2)	4.30	0.038*
Baseline HR, bpm	65.0 (11.4)	69.4 (12.5)	48.25	<0.01*
Medical history				
Hypertension	42.9 (619)	44.9 (318)	0.79	0.38
Hyperlipidemia	65.6 (946)	47.5 (337)	64.2	<0.01*
Diabetes mellitus	12.5 (181)	7.3 (52)	13.29	<0.01*
Previous MI	29.2 (422)	10.2 (72)	98.0	<0.01*
History of CAD	52.5 (758)	20.2 (143)	204.55	<0.01*
Previous bypass	16.0 (231)	3.3 (23)	74.25	<0.01*
Current smoker	23.0 (311)	24.2 (158)	123.22	<0.01*
Former smoker	54.6 (739)	31.4 (205)	123.22	<0.01*
Medications				
Vasodilators	33.1 (476)	27.3 (193)	7.60	<0.01*
β-blockers	40.0 (575)	28.4 (201)	27.5	<0.01*
Ca-channel blockers	19.4 (280)	17.5 (124)	1.14	0.29*
ACE inhibitors	19.2 (276)	11.7 (83)	18.73	<0.01*
Diuretics	6.66 (96)	9.62 (68)	5.88	0.02*
Lipid lowering	56.7 (817)	34.8 (246)	91.51	<0.01*
Aspirin	60.2 (866)	38.2 (270)	92.36	<0.01*
Exercise test performance				
Duration, s	426.4 (151.0)	358.1(119.5)	50.60	<0.01*
Metabolic Equivalents, 3.5 mL/kg^2 per min	8.95 (20.7)	8.25 (29.4)	0.05	0.83
% Target HR (n)	53.6 (821)	71.4 (531)	65.91	<0.01*
End SBP, mm Hg	170.2 (28.7)	165.7 (25.8)	3.42	0.06
End DBP, mm Hg	85.5 (12.7)	84.7 (11.8)	0.21	0.65
End HR, bpm	138.4 (24.2)	146.1 (21.4)	6.70	<0.01*

Medication use presented as raw percentage. Participant numbers for medical history are 1212 (men) and 685 (women) and for medication use are 1345 (men) and 639 (women). ACE indicates angiotensin-converting enzyme; CAD, coronary artery disease; DBP, diastolic blood pressure; HR, heart rate; MI, myocardial infarction; and SBP, systolic blood pressure.

*Significant *P* values.

(*P*<0.001). However, using men with anxiety as a reference point revealed no greater risk of ischemia during stress testing than men without anxiety (OR, 0.90; 95% CI, 0.59–1.37; *P*=0.61). Further adjustments for achieving target heart rate using stress testing did not alter the pattern of results; women with anxiety still were at an elevated risk of ischemia presentation in contrast to women without anxiety (OR, 1.74; 95% CI, 1.09–2.95; *P*=0.02) in patients without a history of CAD. In patients with CAD history, no effect of anxiety on the risk of ischemia was seen for women (OR, 0.99; 95% CI, 0.42–2.34; *P*=0.98). Likewise, adjustment for hypertensive, lipid-lowering, and anticoagulant medications did not change our finding that women with anxiety still were at an elevated risk of ischemia presentation in contrast to women without anxiety in patients without a history of CAD.

For illustrative purposes, the prevalence of ischemia by each group is displayed in the Figure. Post hoc examination of the interaction for any comorbid mood and anxiety and sex revealed similarities to the post hoc results for anxiety and is displayed in Table I in the Data Supplement.

Discussion

This study assessed sex differences in the associations between psychiatric disorders and the presence of exercise-induced myocardial ischemia during stress testing in a stratified analysis by CAD history. We observed an elevated risk of ischemia

Table 3. Participant Characteristics, Presented as a Function of CAD History

Mean (SD) or % (n)	No CAD History (n=1251)	CAD History (n=901)	χ^2/F	*P* Value
Sociodemographics				
Age, y	56.2	57.7	15.74	<0.01*
Sex (% women)	47.8 (685)	79.8 (566)	204.55	<0.01*
Employed	58.5 (415)	50.0 (312)	9.75	<0.01*
Cohabitating	83.8 (594)	84.1 (524)	0.03	0.87
≥12 y education	40.1 (284)	43.9 (274)	2.03	0.15
Baseline SBP, mm Hg	136.2 (20.2)	135.3 (20.9)	0.84	0.36
Baseline DBP, mm Hg	86.2 (11.6)	85.0 (11.4)	5.56	0.018*
Baseline HR, bpm	67.9 (12.6)	64.3 (10.8)	48.7	<0.01*
Medical history and risk factors				
Hypertension	39.7 (496)	49.0 (41)	18.3	<0.01*
Hyperlipidemia	79.3 (715)	45.4 (568)	250.80	<0.01*
Diabetes mellitus	8.6 (108)	13.9 (125)	14.85	<0.01*
Previous MI	0 (0)	54.8 (494)	890.3	<0.01*
Previous bypass	0 (0)	28.2 (254)	400.3	<0.01*
Current smoker	22.5 (264)	24.5 (205)	89.0	<0.01*
Former smoker	40.0 (468)	56.9 (476)	89.0	<0.01*
Medications				
Vasodilators	19.5 (243)	47.4 (426)	190.1	<0.01*
β-blockers	23.7 (296)	53.4 (480)	199.4	<0.01*
Ca-Channel blockers	14.0 (175)	25.5 (229)	45.1	<0.01*
ACE inhibitors	11.4 (142)	24.1 (217)	61.2	<0.01*
Diuretics	7.2 (90)	8.24 (74)	0.80	0.37*
Lipid lowering	31.1 (388)	75.0 (675)	403.9	<0.01*
Aspirin	33.4 (416)	80.2 (720)	459.3	<0.01*
Exercise test performance				
Duration, s	431.4 (113.7)	421.5 (109.8)	4.08	0.04*
Metabolic Equivalents, 3.5 mL/kg^2 per min	9.48 (32.2)	7.78 (1.70)	2.52	0.11
% Target HR (n)	89.5 (12.5)	80.6 (13.5)	246.1	<0.01*
End SBP, mm Hg	171.7 (27.8)	164.8 (27.8)	32.8	<0.01*
End DBP, mm Hg	85.5 (12.8)	84.7 (11.7)	1.84	0.18
End HR, bpm	147.2 (22.5)	131.7 (22.5)	245.5	<0.01*

Medication use presented as raw percentage. ACE indicates angiotensin-converting enzyme; CAD, coronary artery disease; DBP, diastolic blood pressure; HR, heart rate; MI, myocardial infarction; and SBP, systolic blood pressure.

*Significant *P* values.

in women with anxiety in contrast to women without anxiety among those without a history of CAD. This effect was not observed in women with a history of CAD or either male groups. Anxiety in women has been shown to be related to worsened CAD outcomes. In our study, women who had an anxiety disorder had increased presentation of ischemia during stress testing, and given that ischemia is related to a doubling in the risk of adverse CAD events,[27] this may, in part, explain the anxiety–CAD relationship and sex disparity in CAD outcomes.

Another possible mechanism that could underlie the sex differences in CAD outcomes is greater referral and treatment delays because of a confounding of anxiety and CAD symptoms.

Previous studies have shown that women are more likely to receive poorer care than men, with greater referral delays for key diagnostic cardiovascular tests such as ECG (eg, 21 minutes for women versus 15 minutes for men) and a higher probability of not getting appropriate treatments.[5] Consistent with this study, others have identified the presence of anxiety as a key determinant in procedural delays; women with anxiety have been shown to be less likely to receive a timely ECG than women without anxiety,[5] which could be partly because of differences in symptom presentation and complaints in contrast to men. Individuals who attend the emergency department with noncardiac chest pain are more likely to be women, and combined with a lower overall rate of acute coronary syndrome in women, these symptoms could be mistaken for anxiety-related symptoms (eg, fatigue, palpitations, and chest pain) rather than a need for an urgent CAD assessment.[19] A study of patients

Table 4. Psychiatric and Ischemia Presentation

	Men (n=1529)	Women (n=740)	χ^2 or β	*P* Value
Any psychiatric disorder				
Prevalence	31 (476)	44 (326)	χ^2=36.74	<0.001*
Odds ratio	1.00	1.76 (1.42–2.17)	β=0.56	<0.001*
Any mood disorder				
Prevalence	24 (359)	33 (244)	χ^2=23.11	<0.001*
Odds ratio	1.00	1.62 (1.29–2.04)	β=0.48	<0.001*
Any anxiety disorder				
Prevalence	17 (200)	27 (259)	χ^2=31.52	<0.001*
Odds ratio	1.00	1.78 (1.40–2.28)	β=0.58	<0.001*
Any comorbid mood and anxiety disorders				
Prevalence	9 (142)	16 (118)	χ^2=21.90	<0.001*
Odds ratio	1.00	1.85 (1.37–2.51)	β=0.62	<0.001*
Ischemia presentation†				
Prevalence	52 (797)	19 (140)	χ^2=227.60	<0.001*
Odds ratio	1.00	0.28 (0.21–0.36)	β=–1.29	<0.001*

*Significant *P* values.

†Adjusted for age, coronary artery disease history, exercise performance (Metabolic Equivalents), smoking, ischemic medication use, and number of medications. Prevalence reported as % (n); odds ratio reported as odds ratio (95% confidence interval).

who presented to the emergency room with unexplained chest pains found that 40% of patients were experiencing anxiety-like symptoms,[20] highlighting the potential to miss CAD symptoms that might be apparent in these cohorts of patients. This could be especially critical and common among women with anxiety who have no prior history of CAD.

It should also be noted that anxiety and CAD are not mutually exclusive. We have previously reported that anxiety disorders (eg, panic disorder) affect 10% to 50% of patients with CAD[28] and are associated with higher rates of panic-induced ischemia.[29] Thus, anxiety may not only mask real symptoms of CAD but also exacerbate symptoms, through psychophysiological pathways such as autonomic dysregulation,[30] that could further put anxiety disorder patients at risk.

Sex differences are evident in the autonomic nervous control of the cardiovascular system and could underlie the differences seen in the presence of ischemia in our sample. Frequent autonomic activation, indexed by increased sympathetic nervous system activity and decreased parasympathetic activity, has been linked to incident CAD.[31–36] Therefore, women with anxiety might be more likely to display a pattern of frequent autonomic activation, given that anxiety is associated with lowered peripheral nervous system control of heart rate in several different populations,[37] including individuals with CAD.[38] Furthermore, increased sympathetic activity could be responsible for an increased presence of ischemia[39] via increases in heart rate and vasoconstriction which are both controlled by sympathetic nervous system activity.[40] This phenomena of increased ischemia could be observed in women with anxiety, who may also display reduced peripheral nervous system activity. However, because it was beyond the scope of our study to assess autonomic regulation, this hypothesis remains speculative.

Our results did not demonstrate any effect of mood in the presence of ischemia in our sample, despite adjusting for sex differences in test performance (including Metabolic Equivalents and achieving target heart rate). This is surprising considering that depression has consistently been shown to be a key risk factor in predicting CAD events and outcomes,[13,41] with the dysregulation of the autonomic nervous system implicated as a mechanism linking depression to cardiac events.[42,43] The lack of an effect of mood is also surprising given the relationship between laboratory-induced ischemia and future cardiac events[44–46]; however, it should be noted that this is more commonly seen when inducing ischemia via mental stress. The choice of stressor may be important to determine the effect of depression on ischemia; mental-stress–induced ischemia is related to depressive symptoms,[47,48] whereas inconsistent evidence exists to a relationship between depression and exercise-induced ischemia.[47,48] Furthermore, as there was a trend for mood disorder to be negatively correlated with exercise duration (r=–0.04; P=0.07), it is possible that patients with mood disorder may not have performed an optimal test, making it less likely and harder to detect ischemia.[49,50] No such relationship between anxiety and exercise duration was evident (r<0.01; P=0.73).

Some limitations should be acknowledged. First, all of our study participants were referred to the Nuclear Medicine Department at the Montreal Heart Institute, which is a highly specialized cardiology hospital, so results may not generalize to general hospital or community populations. Although this population provides an excellent sample in which to examine the interactions between psychiatric disorders, sex, and ischemia, it does represent a specific population which could potentially introduce selection bias. Furthermore, the high specificity of our sample limits the interpretation of the findings to individuals that present with symptoms that warrant a stress test evaluation. Thus, our findings may be limited to this particular population and may not fully extrapolate to a wider population. Second, although all patients were referred for diagnostic testing, we do not have specific referral data, so are unable to confirm the reason for stress testing. Unfortunately,

Table 5. Post Hoc Analyses, Displaying the Odds Ratios for Ischemia Presentation, Presented by Sex and Anxiety Disorder Grouping, for Patients With and Without a History of CAD Events

	Women Without Anxiety	Women With Anxiety	Men Without Anxiety	Men With Anxiety
No CAD event history*	1.00	1.75 (1.05–2.89)	4.52 (3.10–6.69)	3.46 (2.03–5.88)
CAD event history*	1.00	0.97 (0.40–2.24)	3.59 (2.26–5.80)	4.01 (2.26–7.25)

Presented as odds ratio (95% confidence interval). CAD indicates coronary artery disease.

*Adjusted for age, smoking history, exercise performance (Metabolic Equivalents), ischemia medication usage, and number of medications. Odds ratios presented using women without anxiety as a reference point. Further statistical adjustments for target heart rate did not alter the pattern of the results.

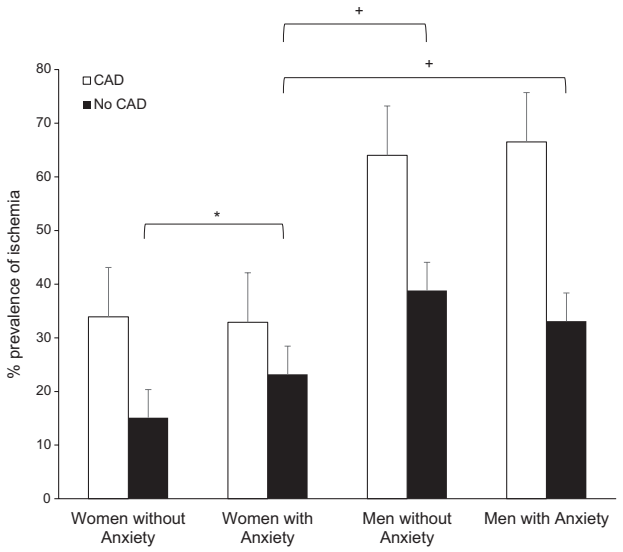

Figure. The prevalence of ischemia in men and women with and without an anxiety disorder in individuals with and without a history of coronary artery disease (CAD) events. *Significantly different from women without anxiety ($P<0.05$); +significantly different from men without anxiety ($P<0.001$).

the referral reason was not consistently stated on the SPECT requisition form, which is what the study team had access to; and when it was, it was often imprecisely or inconsistently coded, yielding unreliable data. However, we know that the range of possible indications for which patients were referred included abnormal ECG (non-SPECT treadmill test), post-MI or percutaneous transluminal coronary angioplasty, complaints of chest pain/angina, family history of ischemic heart disease, and occasionally, driver's license renewals. Although our results support the literature that suggests that women may be under-referred for stress testing, an alternative hypothesis is that men are over-referred for testing in contrast to women. Unfortunately, our study was not designed to test this question, which would require adjudication of clinical data on the entire pool of patients potentially eligible for referral for SPECT, their physicians' referral decisions, and SPECT findings. However, the proportion of men (70%) and women (30%) referred for SPECT testing in this study is generally consistent with previous reports,[51–53] suggesting that referral patterns in our sample were not distinct from previous studies. Although the literature consistently supports the notion that women are under-referred, the question of over-referral of men should be examined in greater depth. Finally, we do not yet have follow-up data on treatment and the extent to which there were sex differences in treatment as a consequence of psychiatric disorders or ischemia status after exercise. Our study was cross-sectional, and thus although we may be able to identify that women with anxiety may be at an elevated risk for ischemia in contrast to women without anxiety, we cannot ascertain the long-term impact of anxiety on cardiac outcomes. These issues could be addressed by future work.

Despite some limitations, our study also has several important strengths. It included a large, consecutive sample with a representative proportion of men and women referred for SPECT testing. In addition, our main psychiatric evaluation was the PRIME-MD which has been extensively used to screen for psychiatric disorders in primary/tertiary care. It is an interview and can generate valid and reliable diagnoses based on Diagnostic and Statistical Manual of Mental Disorders criteria, making it superior to self-report questionnaires for the classification of mood and anxiety disorders. Furthermore, physicians conducing the stress tests were blind to patients' psychiatric status as our assessment was conducted after the stress test. Moreover, <1% of patients were prescribed psychotropic medication at the time of the test, suggesting that even if physicians were aware of this, it would have affected too few patients to influence the results. The use of SPECT to quantify ischemia has higher sensitivity and specificity relative to ECG measures of ischemia and is less likely to lead to a high incidence of false positives than ECG-ischemia[49] and should be considered another strength. Finally, our sample was also well characterized, which allowed us to adjust for several potential confounders of ischemia.

In conclusion, our findings indicate a higher prevalence of psychiatric disorders among women who present for stress testing. Anxiety in women was associated with higher rates of ischemia in those without a history of CAD. Results suggest that anxiety symptoms, many of which overlap with those of CAD (eg, palpitations, chest pain, and shortness of breath) might mask those of CAD and contribute to referral and diagnostic delays among women. Psychophysiological mechanisms could be responsible; women with no CAD would not be receiving CAD treatments which could protect them from anxiety-related CAD events such as ischemia. Future studies are needed to confirm these hypotheses. Future work should also investigate the extent to which psychiatric disorders affect care trajectory and CAD outcomes among men and women and whether interventions to improve psychiatric status among those with or at risk for CAD could improve outcomes.

Sources of Funding

Project funding was supported by operating grants from the Heart and Stroke Foundation of Canada and the Canadian Institute of Health Research (CIHR: MOP 79445 and 89965). Salary support was received by Paine from le Fonds de recherché du Quebec: santé (FRQS; postdoctoral fellowship) and by Bacon and Lavoie from FRQS (chercheur boursiers) and CIHR (New Investigator Awards).

Disclosures

None.

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Circ Cardiovasc Qual Outcomes. 2016;9:S53-S61
doi: 10.1161/CIRCOUTCOMES.115.002491
Circulation: Cardiovascular Quality and Outcomes is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1941-7705. Online ISSN: 1941-7713