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

Nicola J. Paine, PhD; Simon L. Bacon, PhD; Roxanne Pelletier, PhD; André Arsenault, MD; Jean G. Diodati, MD; Kim L. Lavoie, PhD

**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.

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

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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), and hospital mortality rates after an acute MI have been shown to be higher in women (16%) than in men (11%). 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. Sex differences are still evident when assessing laboratory-based proxies for CAD outcomes such as myocardial ischemia, with a higher prevalence in women than in men. 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, and there is a documented link between these disorders and worse cardiac outcomes. In addition to more traditional physiological risk factors for CAD, having depression is now considered to be a key risk factor for CAD, and there is emerging evidence linking anxiety to CAD development, particularly among women. 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. 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...
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 (e.g., 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.10 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 (e.g., 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 (e.g., 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 (e.g., 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-MD21 is a validated screening instrument designed to detect some of the most common Diagnostic and Statistical Manual of Mental 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.21 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 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 (Autoscan, 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 χ² 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
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.

<table>
<thead>
<tr>
<th>Sample Needed</th>
<th>Observed Effect Size</th>
<th>Odds Ratio (Interaction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-CAD Patients Only</td>
<td>CAD Patients Only</td>
<td></td>
</tr>
<tr>
<td>Any psychiatric disorder</td>
<td>237</td>
<td>0.50</td>
</tr>
<tr>
<td>Any mood disorder</td>
<td>233</td>
<td>0.52</td>
</tr>
<tr>
<td>Any anxiety disorder</td>
<td>124</td>
<td>0.83</td>
</tr>
<tr>
<td>Any comorbid disorder</td>
<td>171</td>
<td>1.20</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sample Needed</th>
<th>Observed Effect Size</th>
<th>Odds Ratio (Interaction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-CAD Patients Only</td>
<td>CAD Patients Only</td>
<td></td>
</tr>
<tr>
<td>Any psychiatric disorder</td>
<td>897</td>
<td>0.11</td>
</tr>
<tr>
<td>Any mood disorder</td>
<td>525</td>
<td>0.14</td>
</tr>
<tr>
<td>Any anxiety disorder</td>
<td>880</td>
<td>0.15</td>
</tr>
<tr>
<td>Any comorbid disorder</td>
<td>633</td>
<td>0.35</td>
</tr>
</tbody>
</table>

**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 evidence for anxiety (\( \beta=-0.83; P=0.015 \) [adjusted \( P \) value for multiple testing=0.04]) and comorbid mood and anxiety (\( \beta=-1.20; P=0.005 \) [adjusted \( P \) value for multiple testing=0.032]), but not any psychiatric (\( \beta=-0.50; P=0.10 \)) or mood disorder (\( \beta=-0.52; P=0.11 \)). In patients with a history of CAD, no interactions were evident for any of the psychiatric disorders assessed (any psych: \( \beta=0.11, P=0.79 \); mood: \( \beta=0.14, P=0.75 \); anxiety: \( \beta=0.15, P=0.76 \); and any comorbid mood and anxiety: \( \beta=0.35, P=0.56 \)).

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 (\( P<0.001 \). 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.
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 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 presentation in contrast to women without anxiety in patients without a history of CAD.
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, 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. 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, 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.

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

<table>
<thead>
<tr>
<th>Mean (SD) or % (n)</th>
<th>No CAD History (n=1251)</th>
<th>CAD History (n=901)</th>
<th>χ²/F</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sociodemographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>56.2</td>
<td>57.7</td>
<td>15.74</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Sex (% women)</td>
<td>47.8 (685)</td>
<td>79.8 (566)</td>
<td>204.55</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Employed</td>
<td>58.5 (415)</td>
<td>50.0 (312)</td>
<td>9.75</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Cohabitating</td>
<td>83.8 (594)</td>
<td>84.1 (524)</td>
<td>0.03</td>
<td>0.87</td>
</tr>
<tr>
<td>≥12 y education</td>
<td>40.1 (284)</td>
<td>43.9 (274)</td>
<td>2.03</td>
<td>0.15</td>
</tr>
<tr>
<td>Baseline SBP, mm Hg</td>
<td>136.2 (20.2)</td>
<td>135.3 (20.9)</td>
<td>0.84</td>
<td>0.36</td>
</tr>
<tr>
<td>Baseline DBP, mm Hg</td>
<td>86.2 (11.6)</td>
<td>85.0 (11.4)</td>
<td>5.56</td>
<td>0.018*</td>
</tr>
<tr>
<td>Baseline HR, bpm</td>
<td>67.9 (12.6)</td>
<td>64.3 (10.8)</td>
<td>48.7</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td><strong>Medical history and risk factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>39.7 (496)</td>
<td>49.0 (41)</td>
<td>18.3</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>79.3 (715)</td>
<td>45.4 (568)</td>
<td>250.80</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>8.6 (108)</td>
<td>13.9 (125)</td>
<td>14.85</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Previous MI</td>
<td>0 (0)</td>
<td>54.8 (949)</td>
<td>890.3</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Previous bypass</td>
<td>0 (0)</td>
<td>28.2 (254)</td>
<td>400.3</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Current smoker</td>
<td>22.5 (264)</td>
<td>24.5 (205)</td>
<td>89.0</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Former smoker</td>
<td>40.0 (468)</td>
<td>56.9 (476)</td>
<td>89.0</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td><strong>Medications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasodilators</td>
<td>19.5 (243)</td>
<td>47.4 (426)</td>
<td>190.1</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>β-blockers</td>
<td>23.7 (296)</td>
<td>53.4 (480)</td>
<td>199.4</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Ca-Channel blockers</td>
<td>14.0 (175)</td>
<td>25.5 (229)</td>
<td>45.1</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>11.4 (142)</td>
<td>24.1 (217)</td>
<td>61.2</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Diuretics</td>
<td>7.2 (90)</td>
<td>8.24 (74)</td>
<td>0.80</td>
<td>0.37*</td>
</tr>
<tr>
<td>Lipid lowering</td>
<td>31.1 (388)</td>
<td>75.0 (675)</td>
<td>403.9</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Aspirin</td>
<td>33.4 (416)</td>
<td>80.2 (720)</td>
<td>459.3</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td><strong>Exercise test performance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration, s</td>
<td>431.4 (113.7)</td>
<td>421.5 (109.8)</td>
<td>4.08</td>
<td>0.04*</td>
</tr>
<tr>
<td>Metabolic Equivalents, 3.5 mL/kg² per min</td>
<td>9.48 (32.2)</td>
<td>7.78 (1.70)</td>
<td>2.52</td>
<td>0.11</td>
</tr>
<tr>
<td>% Target HR (n)</td>
<td>89.5 (12.5)</td>
<td>80.6 (13.5)</td>
<td>246.1</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>End SBP, mm Hg</td>
<td>171.7 (27.8)</td>
<td>164.8 (27.8)</td>
<td>32.8</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>End DBP, mm Hg</td>
<td>85.5 (12.8)</td>
<td>84.7 (11.7)</td>
<td>1.84</td>
<td>0.18</td>
</tr>
<tr>
<td>End HR, bpm</td>
<td>147.2 (22.5)</td>
<td>131.7 (22.5)</td>
<td>245.5</td>
<td>&lt;0.01*</td>
</tr>
</tbody>
</table>

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.
CAD28 and are associated with higher rates of panic-induced
orders (eg, panic disorder) affect 10% to 50% of patients with
anxiety who have no prior history of CAD.

It should also be noted that anxiety and CAD are not mutu-
ally exclusive. We have previously reported that anxiety dis-
orders (eg, panic disorder) affect 10% to 50% of patients with
CAD but also exacerbate symptoms, through psychophysi-
ological pathways such as autonomic dysregulation,30 that
could be especially critical and common among women with
symptoms that might be apparent in these cohorts of patients. This
results in predicting CAD events and outcomes,13,41 with the dysregu-
lation 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 labora-
tory-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 impor-
tant 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.49,50 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 evi-
dent (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 exam-
ine 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 find-
ings 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 4. Psychiatric and Ischemia Presentation

<table>
<thead>
<tr>
<th>Psychiatric Disorder</th>
<th>Men (n=1529)</th>
<th>Women (n=740)</th>
<th>χ² or β</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any psychiatric disorder</td>
<td>Prevalence 31 (476)</td>
<td>44 (326)</td>
<td>χ²=36.74</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Odds ratio</td>
<td>1.00</td>
<td>1.76 (1.42–2.17)</td>
<td>β=0.56</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Any mood disorder</td>
<td>Prevalence 24 (359)</td>
<td>33 (244)</td>
<td>χ²=23.11</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Odds ratio</td>
<td>1.00</td>
<td>1.62 (1.29–2.04)</td>
<td>β=0.48</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Any anxiety disorder</td>
<td>Prevalence 17 (200)</td>
<td>27 (259)</td>
<td>χ²=31.52</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Odds ratio</td>
<td>1.00</td>
<td>1.78 (1.40–2.28)</td>
<td>β=0.58</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Any comorbid mood and anxiety disorders</td>
<td>Prevalence 9 (142)</td>
<td>16 (118)</td>
<td>χ²=21.90</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Odds ratio</td>
<td>1.00</td>
<td>1.85 (1.37–2.51)</td>
<td>β=0.62</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Ischemia presentation†</td>
<td>Prevalence 52 (797)</td>
<td>19 (140)</td>
<td>χ²=227.60</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Odds ratio</td>
<td>1.00</td>
<td>0.28 (0.21–0.36)</td>
<td>β=−1.29</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

*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,39 highlighting the potential to miss CAD symp-
oms in the presence of ischemia in our sample. Frequent
autonomic activation, indexed by increased 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 regula-
tion, 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 dif-
fferences 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 dysregula-
tion 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 labora-
tory-induced ischemia and future cardiac events,46, however, it
should be noted that this is more commonly seen when inducing
ischemia via mental stress. The choice of stressor may be impor-
tant 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.49,50 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 evi-
dent (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 exam-
ine 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 find-
ings 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

<table>
<thead>
<tr>
<th>Ischemia Presentation†</th>
<th>Women Without Anxiety</th>
<th>Women With Anxiety</th>
<th>Men Without Anxiety</th>
<th>Men With Anxiety</th>
</tr>
</thead>
<tbody>
<tr>
<td>No CAD event history*</td>
<td>1.00</td>
<td>1.75 (1.05–2.89)</td>
<td>4.52 (3.10–6.69)</td>
<td>3.46 (2.03–5.88)</td>
</tr>
<tr>
<td>CAD event history†</td>
<td>1.00</td>
<td>0.97 (0.40–2.24)</td>
<td>3.59 (2.26–5.80)</td>
<td>4.01 (2.26–7.25)</td>
</tr>
</tbody>
</table>

*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.
A representative proportion of men and women referred for outcomes. These issues could be addressed by future work. We cannot ascertain the long-term impact of anxiety on cardiac risk for ischemia in contrast to women without anxiety, we yet have follow-up data on treatment and the extent to which women are under-referred, the question of over-referral of women is that men are over-referred for testing in contrast to women. Although the literature consistently supports the notion that patterns in our sample were not distinct from previous studies. Consistent with previous reports, suggesting that referral (30%) referred for SPECT testing in this study is generally the entire pool of patients potentially eligible for referral. 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 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.

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Disclosures
None.

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Do Women With Anxiety or Depression Have Higher Rates of Myocardial Ischemia During Exercise Testing Than Men?
Nicola J. Paine, Simon L. Bacon, Roxanne Pelletier, André Arsenault, Jean G. Diodati and Kim L. Lavoie

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