ORIGINAL ARTICLE

Panic Attacks and Risk of Incident Cardiovascular Events Among Postmenopausal Women in the Women's Health Initiative Observational Study

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Context: Previous studies have documented an association of depression and phobic anxiety with cardiovascular morbidity and mortality, but little is known about the cardiovascular sequelae of panic anxiety.

Objective: To determine whether panic attacks are associated with risk of cardiovascular morbidity and mortality in postmenopausal women.

Design: Prospective cohort survey.

Setting: Ten clinical centers of the 40-center Women's Health Initiative.

Participants: A total of 3369 community-dwelling, generally healthy postmenopausal women (aged 51-83 years) enrolled between 1997 and 2000 in the Myocardial Ischemia and Migraine Study who completed a questionnaire about occurrence of panic attacks in the previous 6 months.

Main Outcome Measures: Cardiovascular/cerebrovascular outcomes (fatal and nonfatal myocardial infarction and stroke) and all-cause mortality were ascertained after a mean of 5.3 years of follow-up.

Results: A 6-month history of full-blown panic attacks, endorsed by 10% of postmenopausal women in this cohort, was associated with both coronary heart disease (hazard ratio, 4.20; 95% confidence interval, 1.76-9.99) and the combined end point of coronary heart disease or stroke (hazard ratio, 3.08; 95% confidence interval, 1.60-5.94) after controlling for multiple potential confounders. The hazard ratio for all-cause mortality, excluding those with a history of cardiovascular/cerebrovascular events, was 1.75 (95% confidence interval, 1.04-2.94).

Conclusion: Panic attacks are relatively common among postmenopausal women and appear to be an independent risk factor for cardiovascular morbidity and mortality in older women.

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While it has been consistently reported that depression is a risk factor for cardiac events,[1-3] there have been relatively few outcome studies of the role of anxiety in incident cardiovascular disease outcomes, particularly among women. A study of 34 000 male health professionals aged 42 to 77 years indicated that men with high levels on the Crown-Crisp index of phobic anxiety had a 6-fold increase in sudden deaths (hazard ratio [HR], 6.08; 95% confidence interval [CI], 2.35-15.73), which was unchanged after controlling for other risk factors.[4] There was no association between phobic anxiety and nonfatal myocardial infarction (MI). More recently, the Nurses' Health Study found that among women (mean age, 54 years) with no history of cardiovascular disease, high levels of phobic anxiety were associated with increased risk of fatal coronary heart disease (CHD) after 12 years of follow-up.[5]

Phobic anxiety (as measured by the Crown-Crisp index) assesses unreasonable fear of situations such as enclosed spaces, incurable illness, heights, crowds, being alone, and travel. Panic attacks, in contrast, involve sudden episodes of fear, anxiety, or extreme discomfort accompanied by 4 or more associated (cognitive or autonomic) symptoms. Panic attacks may occur sporadically[6] or as a feature of several anxiety disorders, including panic disorder, social anxiety disorder, and specific phobias.[7]

Recent evidence suggests that panic attacks are more common among postmenopausal women than previously suspected.[8] In the Myocardial Ischemia and Migraine Study (MIMS), which included 3369 women, 18% reported full-blown or limited-symptom panic attacks in the past 6 months.[8] Another report from this study[9]

indicated that a 6-month history of full-blown panic attacks, reported by 10% of postmenopausal women, was associated with both ischemic and nonischemic chest pain on 24-hour ambulatory electrocardiogram (ECG) monitoring, although there was no effect of panic attacks on silent ischemia.[9] Women with full-blown panic attacks were 79% more likely to report chest pain during monitoring than women with a history of recent panic (HR, 1.79; 95% CI, 1.24-2.59). Although panic attacks are associated with prevalent CHD and thus may be a consequence of CHD, the relationship of a history of panic attacks to incident cardiac events is unknown. The objective of this study was to examine prospectively the relationship of panic attacks to fatal plus nonfatal MI, to stroke, and to all-cause mortality among postmenopausal women.

METHODS

The study population consisted of 3369 community-dwelling postmenopausal women enrolled between 1997 and 2000 in MIMS who completed a panic questionnaire at enrollment. The objective of MIMS was to investigate the relationships among migraine, ischemia as measured on a 24-hour ambulatory ECG Holter monitor, and panic symptoms. The MIMS was conducted in 10 clinical centers selected from among the 40 centers of the Women's Health Initiative (WHI) Observational Study. The WHI Observational Study is an ongoing multicenter prospective study of risk factors for heart disease, cancer, fractures, and other causes of morbidity and mortality among 93 676 postmenopausal women. A detailed description of the WHI study design and the baseline characteristics have been reported elsewhere.[10,11] The WHI Observational Study participants, after giving written informed consent approved by each of the participating institutions' institutional review board, completed questionnaires at baseline and annually, had a physical examination, and provided blood samples at baseline and again 3 years later. The MIMS participants could join concomitantly with the WHI baseline visit (which took place between 1993 and 1998), at the WHI third-year visit, or between these 2 visits; in several cases, they joined after the third-year WHI visit.

Participants enrolled in the WHI clinical trials of hormone therapy or dietary modification were ineligible for the WHI Observational Study and, thus, for MIMS. On the basis of self-report responses to screening questionnaires asking about long-term illness, heart failure, or liver disease, which triggered clinical practitioner evaluations of the selected conditions, participants were deemed ineligible if their survival was expected to be less than 3 years because of the illness. Clinical practitioner judgment, with guidance from the clinical center principal investigator, was used to determine the ineligibility of participants who self-reported depression, drug use, or excessive alcohol intake that would prevent them from active study participation and adherence to protocol.

Participants in MIMS completed a questionnaire about occurrence of panic attacks in the previous 6 months and about migraine headaches before being fitted with the Holter monitor. Participant age at WHI enrollment was 50 to 79 years; age at MIMS enrollment was 51 to 83 years, and mean ± SD age was 65.9 ± 7.16 years.

DEFINITION OF VARIABLES

Panic episodes were defined on the basis of responses to a questionnaire adapted from the *DSM-IV* Panic Disorder Field Trial.[12] As described previously,[8] participants were asked to complete a self-report "Anxiety Questionnaire," which begins with 2 screening questions referring to the past 6 months adapted from those used to screen primary care patients in the *DSM-IV* Panic Disorder Field Trial.[12] The first question asks whether the participant has experienced a sudden attack of feeling frightened, anxious, or extremely uncomfortable; the second asks whether she has experienced a sudden episode of rapid or irregular heartbeats. The first question was modified from that used in the field trial[12] by referring to "a sudden attack" rather than labeling it a "panic attack." If the answer to either of the screening questions was yes, the participant was asked which panic attack symptoms occurred during the last bad episode. Because of a clerical error, the panic symptom of sweating was inadvertently omitted from this symptom list, so that the panic symptom checklist included 12 rather than 13 panic attack symptoms. A full-blown panic attack was therefore conservatively defined by a positive response to the anxiety attack stem question and 4 associated symptoms not including sweating.

This questionnaire was administered at the clinic visit during which ambulatory ECG monitoring was initiated and before the start of recording. *Full-blown panic attack* was defined as an attack of sudden fear, anxiety, or extreme discomfort during the past 6 months accompanied by 4 or more panic attack symptoms from a 12-symptom checklist (n = 330). *Limited-symptom panic attack* was defined as above except that 1 to 3 panic symptoms were endorsed (n = 273). Women were considered to have *indeterminate panic attack* if they endorsed only the second screening question (an episode of sudden or irregular heartbeats in the past 6 months but not an attack of fear, anxiety, or extreme discomfort) along with 4 or more panic symptoms. This last group of women (n = 126) likely included a mixture of women with and without true panic attacks, and thus were excluded from the analytic cohort. The definition of full-blown or limited-symptom panic does not specify whether these attacks were spontaneous, isolated, or part of panic disorder. The comparison group was women classified as having *neither full-blown nor limited-symptom panic attacks* in the past 6 months (n = 2640). Further details on panic definitions were provided in a previous publication.[8]

Depression, as described in more detail elsewhere,[1] was measured by means of an 8-item screening instrument developed for the Medical Outcomes Study[13] that incorporates 6 items about depressive symptoms in the past week from the Center for Epidemiologic Studies Depression Scale (CES-D)[14] and 2 items about sad or depressed mood within the past 2 years from the Diagnostic Interview Schedule.[15] These latter 2 items were (1) "In the past year, have you had 2 weeks or more during which you felt sad, blue, or depressed or lost pleasure in things that you usually cared about or enjoyed?" and (2) "Have you had 2 years or more in your life when you felt depressed or sad most days, even if you felt okay sometimes?" and (if yes) "Have you felt depressed or sad much of the time in the past year?" A logistic regression prediction equation based on these 8 items was used to assign a scale score based on a weighted combination of item responses. This screening instrument has been widely used (including in other large-scale studies of postmenopausal women[16]) and has demonstrated good sensitivity and positive predictive value for detecting depressive disorder in the past month in both primary care and mental health user populations,[13] using a cutoff point of 0.06; this cutoff point was therefore used to define a positive depression screen in our sample.

History of CHD before the MIMS was defined as self-report of MI, coronary artery bypass graft surgery, or angioplasty before WHI baseline or one of these outcomes after WHI baseline but before enrollment into MIMS and the administration of the panic questionnaire. History of cardiovascular/cerebrovascular disease before MIMS was defined as history of CHD or stroke before enrollment into MIMS. Hypertension sta-

tus was based on self-report as follows: *no hypertension* meant that the participant had never been told by a physician that she had high blood pressure; *treated hypertension*, the participant had a medical diagnosis of hypertension and was taking medication for hypertension; and *untreated hypertension*, the participant had a medical diagnosis of hypertension and was not taking medication for hypertension. The WHI definitions of diabetes mellitus and high cholesterol are incomplete and rely on self-report of taking insulin or oral drugs for diabetes and self-report of having high cholesterol level requiring medication; serum glucose and cholesterol measurements were not available. Thus, models including these 2 variables likely underestimate their effects.

Outcomes of interest were cardiovascular events occurring after the panic questionnaire was administered and include CHD (defined as MI or CHD death), stroke, the combined end point of CHD or stroke, and all-cause mortality. These end points were ascertained from Medical History Update Questionnaires mailed annually to participants or by direct report to staff from participants or third parties between annual questionnaires. Such reported hospitalizations or potential events of interest triggered a telephone interview with the participant or with the proxy the participant had identified when joining the WHI to obtain further details. Medical records, laboratory and other diagnostic results, and, when necessary, death certificates were obtained. Trained physician adjudicators at each site evaluated the complete information and made the decision on cause of event. Coronary heart disease events were documented by ECG and laboratory test results and, where appropriate, death certificate information and autopsy reports. For participants not responding to the mailed questionnaires or to follow-up telephone calls, proxy respondents identified for each participant at baseline were contacted. In addition, the National Death Index was searched and death certificates were obtained to determine cause of death. Stroke diagnosis was based on rapid onset of a neurologic deficit attributable to an obstruction or rupture of the arterial system. The deficit was not known to be secondary to brain trauma, tumor, infection, or other cause, and must have lasted more than 24 hours unless death supervened or there was a demonstrable lesion compatible with acute stroke on computed tomography or magnetic resonance imaging. Follow-up data were missing for only 1 participant in MIMS, and that participant was in the no-panic group.

The mean±SD duration of follow-up after enrollment in MIMS was 5.30±0.81 years (range, 0.41-7.32 years).

STATISTICAL METHODS

Baseline characteristics of women with a history of full-blown panic attacks and those with no panic were compared by χ^2 test for categorical variables or Fisher exact test where appropriate. Continuous variables were compared by 2-tailed *t* test or analysis of variance if there were more than 2 categories. The HRs were obtained from Cox proportional hazards regressions to evaluate the association between 6-month history of full-blown panic attacks vs no panic attacks and the outcomes of interest; HRs are presented for unadjusted regressions, as well as with adjustment for age (continuous), race/ethnicity (black, Hispanic, or other vs white as the reference group), and family income (<$20 000 and $20 000-$50 000 vs >$50 000) and with adjustment for multiple variables. The fully adjusted models included baseline variables that were significantly different between the full-blown panic attack and no-panic attack groups: age, race, income, and body mass index as continuous variables; history of diabetes treatment (yes or no); history of smoking (current or past vs never); history of depression (yes or no); history of atrial fibrillation (yes or no); and history of MI, coronary artery bypass graft surgery, angioplasty, or stroke (yes or no). Each of these variables has been associated in the literature with cardiovascular end points. Additional variables previously shown to be related to risk of cardiovascular events were also included: hormone use (current and past vs never), high cholesterol level requiring medication (yes or no), hypertension status (controlled hypertension and uncontrolled hypertension vs not hypertensive), and physical activity (number of episodes per week of moderate or strenuous exercise of >20 minutes' duration). Collinearity was considered by examining the correlations among variables in the model. Almost all such correlations were less than 0.10, and no correlation was above 0.19. For participants with no events of interest, time to censoring was the minimum of days to the last contact form or days to death. All analyses were conducted with SAS statistical software (SAS Institute Inc, Cary, North Carolina).

RESULTS

Postmenopausal women who experienced at least 1 panic attack in the preceding 6-month period differed on demographic characteristics and were more likely to have cardiovascular risk factors of smoking, higher body mass index, diabetes mellitus, hypertension, and depressive symptoms, as well as a history of cardiovascular morbidities (**Table 1**), as previously reported.[8]

As shown in **Table 2**, there were 41 CHD events (fatal or nonfatal MI), 40 strokes, and 147 deaths from all causes after an average of 5.3 years of follow-up.

Recent history of full-blown panic attacks was associated with excess risk of the combined end point of CHD or stroke and with all-cause mortality in unadjusted analyses (**Table 3**). In the fully adjusted model, controlling for age, race, income, body mass index, alcohol intake, smoking, hormone use, high cholesterol level requiring medication, hypertension, physical activity, depression, history of diabetes, atrial fibrillation, and history of cardiovascular disease, full-blown panic attacks appeared to be an independent risk factor for both CHD (HR, 4.20; 95% CI, 1.76-9.99) and the combined end point of CHD or stroke (HR, 3.08; 95% CI, 1.60-5.94), as well as all-cause mortality (HR, 1.75; 95% CI, 1.04-2.94). Although we adjusted for history of cardiovascular disease in these models, we also ran the analyses excluding the 149 women who had such a history before the assessment of panic attacks. The HRs in these analyses were similar: CHD: HR, 3.5; 95% CI, 1.29-9.54; combined CHD or stroke: HR, 2.77; 95% CI, 1.37-5.59; and all-cause mortality: HR, 1.98; 95% CI,1.15-3.41. In the fully adjusted model that included panic attacks, depression was not significantly related to death (HR, 1.08; 95% CI, 0.61-1.94) or to the combined end point of CHD or stroke (HR, 0.89; 95% CI, 0.39-2.03). Thus, the finding that panic attacks were significantly associated with cardiovascular events after controlling for depression but that depression was not significantly associated with cardiovascular events after controlling for panic attacks, suggests that panic attacks are a risk factor for cardiovascular events independent of depression.

Hazard ratios for limited-symptom panic attacks compared with no panic attacks showed similar, although weaker, associations with outcomes. The risk associated with limited-symptom panic attacks for the combined end point of CHD or stroke in the fully adjusted

Table 1. Baseline Characteristics

	No. (%)			
	No Panic Attack[a] (n = 2640)	Limited-Symptom Panic Attack (n = 273)	Full-Blown Panic Attack (n = 330)	*P* Value
Demographics				
Age at WHI screening visit, y				
50-59	859 (32.5)	90 (33.0)	161 (48.8)	<.001
60-69	1221 (46.3)	126 (46.2)	116 (35.2)	
70-79	560 (21.2)	57 (20.9)	53 (16.1)	
Race				
White	1919 (72.7)	212 (77.7)	250 (75.8)	<.001
Asian/PI	464 (17.6)	33 (12.1)	31 (9.4)	
Black	135 (5.1)	16 (5.9)	26 (7.9)	
Hispanic	56 (2.1)	7 (2.6)	13 (3.9)	
Other	66 (2.5)	5 (1.8)	10 (3.0)	
Education				
No school to some high school	106 (4.0)	7 (2.6)	20 (6.1)	<.001
High school diploma	405 (15.4)	46 (17.0)	41 (12.5)	
School after high school	862 (32.8)	108 (39.9)	143 (43.5)	
College degree or higher	1253 (47.7)	110 (40.6)	125 (38.0)	
Income, $				
< 10 000	61 (2.5)	10 (3.9)	23 (7.3)	<.001
10 000-19 999	212 (8.5)	31 (12.1)	38 (12.0)	
20 000-34 999	567 (22.7)	44 (17.1)	62 (19.6)	
35 000-49 999	468 (18.8)	52 (20.2)	68 (21.5)	
50 000-74 999	539 (21.6)	61 (23.7)	65 (20.6)	
≥ 75 000	647 (25.9)	59 (23.0)	60 (19.0)	
CVD Risk Factors and Lifestyle Variables				
Smoking				
Never	1507 (57.5)	142 (52.2)	181 (54.9)	<.002
Past	990 (37.8)	115 (42.3)	117 (35.5)	
Current	125 (4.8)	15 (5.5)	32 (9.7)	
Alcohol				
Nondrinker	435 (16.5)	39 (14.3)	44 (13.4)	.02
Past drinker	484 (18.4)	39 (14.3)	84 (25.5)	
< 1 Drink/mo	324 (12.3)	35 (12.9)	36 (10.9)	
< 1 Drink/wk	472 (17.9)	57 (21.0)	69 (21.0)	
1 to < 7 Drinks/wk	608 (23.1)	64 (23.5)	58 (17.6)	
≥ 7 Drinks/wk	308 (11.7)	38 (14.0)	38 (11.6)	
Hormone use				
Never	624 (23.9)	56 (20.7)	75 (22.9)	.36
Past	463 (17.7)	60 (22.2)	65 (19.9)	
Current	1524 (58.4)	154 (57.0)	187 (57.2)	

(continued)

model was an HR of 2.05 (95% CI, 0.99-4.23) and was nonsignificant for either end point separately and for all-cause mortality.

COMMENT

We found that postmenopausal women aged 51 to 83 years who reported at least 1 panic attack in the previous 6 months were at increased risk of subsequent cardiovascular events during a follow-up period of 5.3 years. After adjustment for multiple potential confounders and known cardiovascular risk factors, recent history of full-blown panic attack was independently associated with a nearly 4-fold increased risk of fatal or nonfatal MI and a nearly 3-fold increased risk of the combined end point of CHD or stroke. The HR for stroke alone, while elevated, did not show statistical significance; thus, the association with panic attacks may be stronger for CHD than for cerebrovascular disease. Limited-symptom panic attacks, which have previously been associated with levels of impairment similar to that seen with full-blown attacks,[8,17] were associated with nonsignificant increases in risk of cardiovascular morbidity and mortality. The risks in the limited-symptom group were intermediate between those of the no-panic attack and full-blown panic attack groups.

To our knowledge, ours is the largest study to examine prospectively the association between panic anxiety attacks and cardiovascular morbidity and mortality. Previous studies examining the association between panic disorder and coronary artery disease have primarily involved clinical samples of patients with chest pain in emergency department or cardiology settings (see Katerndahl[18] for review). In contrast to our study, most of these

Table 1. Baseline Characteristics (cont)

	No. (%)			
	No Panic Attack[a] (n = 2640)	Limited-Symptom Panic Attack (n = 273)	Full-Blown Panic Attack (n = 330)	*P* Value
BMI				
< 25	1253 (47.9)	114 (42.2)	142 (43.4)	<.001
25-30	887 (33.9)	94 (34.8)	91 (27.8)	
> 30	478 (18.3)	62 (23.0)	94 (28.8)	
Physical activity[b]				
None	293 (11.1)	26 (9.5)	43 (13.0)	.69
Some	994 (37.7)	112 (41.0)	126 (38.2)	
2-4	529 (20.1)	54 (19.8)	70 (21.2)	
> 4	819 (31.1)	81 (29.7)	91 (27.6)	
Hypertension				
Never had hypertension	1815 (69.1)	198 (72.5)	210 (63.6)	.10
Untreated hypertension	197 (7.5)	13 (4.8)	30 (9.1)	
Treated hypertension	615 (23.4)	62 (22.7)	90 (27.3)	
High cholesterol level requiring medication	386 (14.8)	32 (11.9)	55 (16.7)	.25
Diabetes mellitus being treated	83 (3.2)	13 (4.8)	18 (5.5)	.02
Coffee use	1797 (68.3)	192 (70.3)	212 (64.4)	.26
Depression	191 (7.3)	28 (10.3)	101 (30.9)	<.001
History of Cardiovascular Morbidities Before MIMS Baseline				
Any history of CHD[c]	74 (2.8)	11 (4.0)	25 (7.6)	<.001
Any history of stroke[d]	36 (1.4)	3 (1.1)	8.0 (2.4)	.28
Any history of CHD or stroke	106 (4.0)	13 (4.8)	30 (9.1)	<.001
History of atrial fibrillation	76 (2.9)	14 (5.2)	21 (6.5)	<.001

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CHD, coronary heart disease; CVD, cardiovascular disease; MIMS, Myocardial Ischemia and Migraine Study; PI, Pacific Islander; WHI, Women's Health Initiative.
[a] The missing values for all variables were less than 1% except for income, which had 5.4% missing values.
[b] Episodes per week of moderate or strenuous activity for longer than 20 minutes.
[c] Self-reported history of myocardial infarction, coronary bypass graft surgery, or percutaneous transluminal coronary angioplasty at WHI baseline or occurring after WHI baseline but before administration of the panic questionnaire.
[d] Stroke history at WHI baseline or occurring after WHI baseline but before administration of the panic questionnaire.

studies examined clinician-diagnosed panic disorder. While summary estimates from these studies have not established an association between panic disorder and coronary artery disease,[18] a few studies have suggested that panic attacks or panic disorder may be associated with ischemia or increased mortality.[19-22] Two small early studies suggested that men with panic disorder have an increased risk of cardiovascular death.[19,20] A subsequent study of 5034 individuals from the Epidemiologic Catchment Area's New Haven cohort found an elevated risk of self-reported heart attack and stroke among 60 individuals with panic disorder compared with 3778 individuals with no psychiatric disorder.[23]

Our study adds panic attacks to the list of emotional states and psychiatric symptoms that have been linked to excess risk of cardiovascular disease and death in nonclinical samples. Numerous large-scale prospective studies have documented an association between depression or depressive symptoms and ischemic heart disease.[24] In a prospective study of the full WHI cohort (N=93 676), postmenopausal women completed a baseline shortened 6-item CES-D questionnaire asking about depressive symptoms in the past week; those scoring above a cutoff point of 5, which corresponds to the cutoff point of 16 generally used to classify people as depressed on the full 20-item CES-D questionnaire, had a 50% higher risk of death from cardiovascular disease during 4.1 years of follow-up than those scoring below this cutoff point even after controlling for major cardiac risk factors. Women who reported a history of depressive symptoms

Table 2. CVD Events After Panic Attack Assessment

		No. (%)		
	Total	No Panic Attack (n = 2640)	Limited-Symptom Panic Attack (n = 273)	Full-Blown Panic Attack (n = 330)
CHD[a] or stroke	81	58 (2.2)	9 (3.3)	14 (4.2)
CHD	41	29 (1.1)	4 (1.5)	8 (2.4)
Stroke	40	29 (1.1)	5 (1.8)	6 (1.8)
All-cause mortality	147	110 (4.2)	15 (5.5)	22 (6.7)
Cardiovascular death[b]	38	30 (1.1)	4 (1.5)	4 (1.2)
Cancer	74	57 (2.2)	6 (2.2)	11 (3.3)
Other or unknown	35	23 (0.9)	5 (1.8)	7 (2.1)

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease.
[a] Fatal or nonfatal myocardial infarction or death classified as being due to atherosclerotic heart disease or possible CHD.
[b] Death due to atherosclerotic cardiac disease or possible CHD, other CHD, pulmonary embolism, other unknown CHD, or stroke.

Table 3. Hazard Ratios Associated With Panic Attacks

	Hazard Ratio (95% CI)		
	Unadjusted	Adjusted for Age, Race, and Income	Fully Adjusted[a]
Full-Blown Panic Attack vs No Panic Attack			
CHD[b] or stroke	1.96 (1.09-3.51)	2.80 (1.53-5.11)	3.08 (1.60-5.94)
CHD[b]	2.07 (0.95-4.50)	1.92 (1.20-3.07)	4.20 (1.76-9.99)
Stroke (fatal or nonfatal)	1.66 (0.69-4.02)	2.18 (0.88-5.41)	1.98 (0.75-5.24)
All-cause mortality	1.60 (1.01-2.53)	1.92 (1.20-3.07)	1.75 (1.04-2.94)
Limited-Symptom Panic Attack vs No Panic Attack			
CHD[b] or stroke	1.49 (0.74-3.01)	1.83 (0.90-3.72)	2.05 (0.99-4.23)
CHD[b]	1.23 (0.43-3.48)	1.42 (0.82-2.45)	1.65 (0.56-4.82)
Stroke (fatal or nonfatal)	1.66 (0.64-4.29)	2.00 (0.76-5.26)	2.29 (0.86-6.07)
All-cause mortality	1.30 (0.76-2.23)	1.42 (0.82-2.45)	1.34 (0.77-2.34)

Abbreviations: CHD, coronary heart disease; CI, confidence interval.

[a] Adjusted for age, race, income, body mass index, alcohol, hormone use, high cholesterol level requiring medication, history of diabetes mellitus treatment, smoking, depression, history of atrial fibrillation before Women's Health Initiative baseline, hypertension status, moderate to strenuous activity for longer than 20 minutes 3 or more times a week, and history of myocardial infarction, coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, or stroke before administration of the panic questionnaire.

[b] Nonfatal or fatal myocardial infarction or CHD death, with CHD death defined as death classified as being due to atherosclerotic heart disease or possible CHD.

during the past 2 years had similar results.[1] The present study demonstrates that panic attack is a predictor of hard cardiovascular end points, independent of depression. Phobic anxiety, measured on the Crown-Crisp index, has been shown to predict sudden cardiac death in studies of both men[4,25] and women.[5] Albert and colleagues[5] found an association between self-rated phobic anxiety and both fatal CHD and sudden cardiac death (but not nonfatal MI) in a cohort of 72 359 women (mean age, 54 years) from the Nurses' Health Study during 12 years of follow-up. Chronic worry has also been associated with excess risk of nonfatal MI and CHD in a prospective study of men.[26] Several studies have also documented an association between anger or hostility and risk of MI.[27] Although we were not able to control for hostility or phobic anxiety, we did find that panic attacks were associated with cardiovascular outcomes independent of depression in our analyses.

If panic anxiety is associated with cardiovascular morbidity and mortality, what might be the mechanism? One possibility is that the relationship is mediated through an association of panic attacks with other cardiovascular risk factors, such as hypertension.[28] This does not appear to be the case in our study because the association with CHD and CHD or stroke persisted after controlling for major cardiovascular risk factors and history of cardiovascular disease, and also among those who had no earlier history of cardiovascular disease or stroke. A second possibility is that anxiety itself has adverse cardiovascular effects.[29] Several studies have suggested that episodes of anger, anxiety, or depressed mood may trigger acute coronary ischemia,[30,31] and negative emotional states may be associated with heightened platelet activation and altered hemodynamic reactivity.[27] Panic attacks have been associated with increased sympathetic outflow and coronary vasospasm,[32] which might trigger ischemia. In a recent study of 65 patients with coronary artery disease, Fleet et al[21] found that panic attacks induced by carbon dioxide inhalation were associated with reversible myocardial perfusion defects. In a previous study of the MIMS cohort, our group observed an elevated risk of ischemic chest pain (but not silent ischemia) during 24-hour ambulatory ECG monitoring among postmenopausal women with a 6-month history of panic attack (odds ratio, 4.94; 95% CI, 1.41-17.30).[9] Alterations in cardiac vagal tone may provide another pathophysiologic link between panic and risk for increased cardiac morbidity and mortality. Several studies have documented a relationship between reduced heart rate variability, an index of autonomic dysregulation, and panic disorder.[33-35] Studies documenting an association between phobic anxiety and risk of sudden cardiac death among men[4,25] and women[5] have invoked proarrhythmic effects of anxiety as a mediating cause, and reduced heart rate variability has been documented among men with high levels of phobic anxiety.[36]

Our results should be viewed in light of several limitations. First, our panic attack questionnaire was a cross-sectional measure assessing the presence of at least 1 panic episode during a 6-month period. Thus, we cannot distinguish cardiovascular outcomes among women who may have had multiple recurrent attacks (or who may have met criteria for panic disorder) from those who may have had infrequent or sporadic attacks. Second, the use of a self-report measure may have led to underreporting or overreporting of panic attacks relative to what might have been seen with direct interview methods. Of note, however, previous research has shown that a self-report measure comprising simply the 2 screening questions of our measure had excellent negative predictive value (0.94-1.00) but low positive predictive value (0.18-0.40) for detecting panic disorder when compared with a diagnostic interview in samples of primary care patients.[37] Because panic was assessed before the cardiovascular outcomes, misclassification would likely bias results toward the null. Third, it is possible that panic attacks reported by women who went on to develop adverse cardiovascular outcomes were in fact episodes of cardiac abnormality (eg, ischemia or arrhythmia). If so, self-reported panic attacks might represent a marker of underlying cardiovascular disease that may presage MI or stroke.

Finally, although we found a similar pattern of results for limited-symptom panic, they did not reach statistical significance; because of the smaller number of women reporting these attacks, we cannot rule out the possibility of type II error.

In summary, we found that postmenopausal women who had experienced panic attacks in the previous 6 months had a 3-fold higher risk of heart attack or stroke during a 5-year follow-up period than those who did not experience such attacks, after controlling for standard cardiovascular risk factors and concurrent depression. These results suggest that panic anxiety is a marker for increased risk of cardiovascular morbidity and mortality among postmenopausal women. Future studies are needed to clarify the causal connection, if any, between panic attacks and cardiovascular events. Our results imply, however, that older women with a recent history of panic attacks represent a subgroup at elevated risk of MI and stroke in whom careful monitoring and cardiovascular risk reduction may be particularly important.

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