ORIGINAL RESEARCH

Depressive Symptoms in Younger Women and Men With Acute Myocardial Infarction: Insights From the VIRGO Study

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***Background*—**Depression was recently recognized as a risk factor for adverse medical outcomes in patients with acute myocardial infarction (AMI). The degree to which depression is present among younger patients with an AMI, the patient profile associated with being a young AMI patient with depressive symptoms, and whether relevant sex differences exist are currently unknown.

***Methods and Results*—**The Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients (VIRGO) study enrolled 3572 patients with AMI (67.1% women; 2:1 ratio for women to men) between 2008 and 2012 (at 103 hospitals in the United States, 24 in Spain, and 3 in Australia). Information about lifetime history of depression and depressive symptoms experienced over the past 2 weeks (Patient Health Questionnaire; a cutoff score $\geq$10 was used for depression screening) was collected during index AMI admission. Information on demographics, socioeconomic status, cardiovascular risk, AMI severity, perceived stress (14-item Perceived Stress Scale), and health status (Seattle Angina Questionnaire, EuroQoL 5D) was obtained through interviews and chart abstraction. Nearly half (48%) of the women reported a lifetime history of depression versus 1 in 4 in men (24%; $P<0.0001$). At the time of admission for AMI, more women than men experienced depressive symptoms (39% versus 22%, $P<0.0001$; adjusted odds ratio 1.64; 95% CI 1.36 to 1.98). Patients with more depressive symptoms had higher levels of stress and worse quality of life ($P<0.001$). Depressive symptoms were more prevalent among patients with lower socioeconomic profiles (eg, lower education, uninsured) and with more cardiovascular risk factors (eg, diabetes, smoking).

***Conclusions*—**A high rate of lifetime history of depression and depressive symptoms at the time of an AMI was observed among younger women compared with men. Depressive symptoms affected those with more vulnerable socioeconomic and clinical profiles. **(*J Am Heart Assoc*. 2015;4:e001424 doi: 10.1161/JAHA.114.001424)**

Key Words: acute myocardial infarction • depression • sex differences

Young women aged <60 years who present with an acute myocardial infarction (AMI) have an elevated risk of mortality compared with men of that age group.[1,2] A potential mediator of their poor outcomes might be depressive symptoms, which occur in ≈1 of every 3 patients with AMI[3] and have been shown to be associated with detrimental long-term outcomes.[4–6] Although the nature and causality of the mechanisms that might explain the association between depressive symptoms and adverse prognosis in cardiac disease have not been established, both biological (eg, increased inflammation, inflammatory imbalance, increased platelet reactivity) and behavioral (eg, smoking, obesity, poor medication adherence) mechanisms have been proposed.[7] Among depressed patients with AMI, some subpopulations

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Accompanying Tables S1 through S5 are available at http://jaha.ahajournals.org/content/4/3/e001424/suppl/DC1

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may be particularly vulnerable to adverse outcomes.[4,8] Prior studies have suggested that demographic characteristics can identify higher risk patients (eg, depressive symptoms are present in 40% of women aged ≤60 years, whereas 1 in 5 men in that age group report having depressive symptoms).[4,8] The need for further work to confirm and extend the existing literature on the most vulnerable patients (eg, young women)[4] is underscored by the latest scientific statement issued by the American Heart Association, which elevated depression to the status of an official risk factor in cardiac disease.[6] A significant gap remains in the knowledge about prevalence and correlates of significant depressive symptoms among young patients presenting with an AMI. Identifying subtypes and characteristics of depression among young patients with AMI can lay the foundation for developing novel targeted treatments for depression in this group of patients.

The Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients (VIRGO) study was designed to examine the risk factors and outcomes for young patients recovering from an AMI.[9] The goals of this study were (1) to evaluate the degree to which depressive symptom burden (lifetime history and depressive symptoms assessed during AMI admission) is present among younger patients with AMI; (2) to examine the demographic, socioeconomic, and clinical patient profiles associated with being a young AMI patient and having concomitant depressive symptoms; and (3) to examine the association between sex and depressive symptoms in AMI patients, independent of other risk factors. Being able to address these goals could inform a more actionable approach in risk-stratifying young men and women with AMI who are at risk of experiencing depressive symptoms. We hypothesized that female patients and those with more unfavorable socioeconomic and clinical profiles would suffer from a higher depression burden. Being able to address these aims would allow us to identify key areas of focus for younger AMI patients in designing plans for better prevention, identification, and treatment of their depressive symptoms. In addition, this study may also identify important characteristics that differ by sex that might confound sex-based differences between outcomes in younger patients with AMI.

Methods

Participants

Patients 18 to 55 years old with AMI were recruited into the VIRGO study between August 21, 2008, and January 5, 2012, from 103 hospitals in the United States, 24 in Spain, and 3 in Australia using a 2:1 ratio of women to men for enrollment. The methods of VIRGO have been described previously.[9] In brief, patients were eligible for the study if they had increased cardiac biomarkers (ie, myocardial necrosis needed to be present or at least 1 of the following markers needed to be elevated: troponin I or T level >99th percentile of the upper reference limit or creatine kinase level greater than twice the upper reference limit with creatine kinase–MB activity level >10% total) and at least 1 of the following conditions: symptoms of ischemia or electrocardiographic changes indicative of new ischemia (new ST-T changes, new or presumably new left bundle branch block, or the development of pathological Q waves). Only patients who presented directly or who were transferred to the enrolling site within the first 24 hours of presentation were eligible. Patients who were incarcerated; who did not speak English or Spanish; who were unable to provide informed consent or to be contacted for follow-up; or who developed elevated cardiac markers as a result of elective coronary revascularization, physical trauma, or surgery were excluded. An overview of the actual reasons for exclusion is provided in Table S1. Institutional review board approval was obtained at each participating center, and all patients provided informed consent for their study participation.

Data Collection and Variables

Baseline hospitalization data were collected by medical chart abstraction, and standardized in-person interviews were administered by trained personnel during admission for AMI or shortly thereafter (92% were performed in the hospital, 8% were conducted within 3 days of discharge) (Table S2). Depressive symptoms and health status data were collected through the baseline interview.

Information about depression consisted of self-reported lifetime history of depression collected at the time of the in-person interview ("Have you ever in your life been told you have depression or been treated for depression by a doctor or other health care provider?" [yes or no]) and current symptoms of depression assessed with the 9-item version of the Patient Health Questionnaire (PHQ-9),[10] a standardized and validated instrument that has been used widely among cardiac populations.[4,11,12] The PHQ-9 quantifies the frequency of depressive symptoms experienced in the past 2 weeks based on the 9 criteria for a major depressive disorder described in the *Diagnostic and Statistical Manual of Mental Disorders* (fourth edition; DSM).[13] Each item is answered along a 4-point Likert scale with responses ranging from 0 (not at all) to 3 (nearly every day); a sum score between 0 and 27 points is derived by adding all responses. A PHQ-9 score ≥10 is commonly used as a screening criterion that has 88% sensitivity and specificity to detect a major depressive disorder.[10] Depressive symptoms can further be classified according to severity: none (scores 0 to 4), mild (scores 5 to 9), moderate (scores 10 to 14), moderately severe (15 to 19), and severe (scores ≥20).

Disease-specific health status was assessed with the Seattle Angina Questionnaire (SAQ; physical limitations, angina frequency, and quality of life domains were analyzed) during the in-person interview at study enrollment. This instrument asks patients to reflect on the health status that they experienced in the 4 weeks prior to the assessment. This widely used instrument has been validated and used in a variety of coronary artery disease populations, including AMI.[14–18] Scores on each subscale range from 0 to 100, with higher scores indicating better health status (ie, fewer physical limitations, less angina, and better quality of life).

Generic health status at the time of patients' AMI admission was measured with the visual analog scale of the standardized EuroQoL 5D instrument, which asks patients to rate their current health on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state).[19,20]

Perceived stress levels that patients experienced over the past month were assessed with the 14-item Perceived Stress Scale (PSS).[21] Items are answered along a 5-point Likert scale, and scores on this instrument range from 0 to 56, with higher scores referring to higher stress levels. The PSS has been used previously in AMI populations.[22]

Sociodemographic factors considered in this study were age and self-identified race (black, white, other [used as reference category in our multivariable models]). For US patients, an additional ethnicity variable was included (Hispanic versus not). Ethnicity is a different variable than race, for example, patients can be Hispanic and black at the same time. Race and ethnicity categories were captured using the revised 1997 Office of Management and Budget definitions.[23]

Socioeconomic status was quantified by defining patients' marital status, highest education, working status, health insurance, and practice of avoiding health care because of cost. All of this information was obtained through patient interviews.

Medical history and clinical characteristics at AMI presentation were abstracted for prior coronary symptoms. Coronary disease included AMI, percutaneous coronary intervention or coronary artery bypass grafting, congestive heart failure, and angina. Other cardiac risk factors and comorbidities included hypertension, current smoking (within past 30 days), obesity (body mass index $\geq$30 kg/m^2), prior stroke or transient ischemic attack, peripheral arterial disease, renal dysfunction, cancer, and chronic lung disease. Clinical severity of patients' AMI presentations was assessed by Killip class, peak troponin level, hemodynamic instability, final AMI diagnosis (ST-elevation AMI), and ejection fraction <40%. Cardiac symptoms included typical versus atypical chest pain, back pain, abdominal pain, nausea, other pain, shortness of breath, fatigue, other cardiac symptoms, and other acute noncardiac conditions at arrival (eg, stroke, acute kidney failure, sepsis), a variable previously shown to be highly prognostic of mortality.[24] The number of cardiac symptoms experienced by a patient were counted and recorded as a continuous variable.

Finally, information about antidepressants at discharge and newly prescribed antidepressants was abstracted from patients' medical records.

Study Sample

Of the 5585 patients meeting eligibility criteria, 3572 (64%) were enrolled (2985 from the United States, 516 from Spain, 71 from Australia). The most common reasons for not enrolling were refusal of informed consent and discharge occurring prior to contact by the site study coordinator. Because our primary objective was to look at the association between depressive symptoms and patient characteristics in women and men with an AMI, we restricted our depression analyses to those who had PHQ-9 scores available. Depressive symptom scores were uncommonly missing ($\leq$4%; n=148) without differences by sex (Table S3).

Statistical Analysis

To provide an overview of the patient characteristics for the overall sample and by sex, frequencies and percentages were used to summarize categorical variables, and medians, means, standard deviations, and interquartile ranges were reported to summarize continuous variables. Chi-square tests for categorical variables and Wilcoxon rank-sum tests for continuous variables were used to assess statistical significance. A P value <0.05 was considered statistically significant. In addition, Cohen's d effect sizes were calculated for continuous variables for which mean and standard deviations were provided.[25]

To describe the burden of depressive symptoms by sex, we used the same descriptive approach: We summarized data on the history of depression and current symptoms of depression for the overall sample and by sex. Similarly, we described the demographic, socioeconomic, and clinical profiles of patients with AMI by sex and depression status.

Next, logistic regression models were used to assess the independent relationship between sex and PHQ-9 scores $\geq$10. Sociodemographic, socioeconomic, medical history, and health status variables were added sequentially to identify the association of sex with depressive symptoms. The first model included only sex; age and race were added next, and the third step included socioeconomic variables (marital status, education level, working status). The fourth step added medical history information, including congestive heart failure; prior AMI, percutaneous coronary intervention, or coronary artery bypass grafting; prior stroke or transient ischemic attack; peripheral arterial disease; history of

diabetes; final AMI diagnosis; smoking in the past 30 days; obesity; and chronic lung disease. In the final step, health status information was added (SAQ subscales for angina frequency, physical limitation, and quality of life). All analyses were performed using SAS 9.3 (SAS Institute Inc). Figures were created in R 2.15.1 (R Foundation for Statistical Computing).

Results

Patient Characteristics for the Overall Population and by Sex

There were 1175 men and 2397 women. Most characteristics were similar between men and women (Table 1); however, lower proportions of women were white and married. Women presented with higher rates of diabetes and obesity but had lower rates of hypercholesterolemia compared with men. Women had also had higher rates of cancer and chronic lung disease.

Mean SAQ physical limitation scores in patients who recently had an AMI were lower in women compared with men (Cohen's d=0.33). About half of patients reported angina symptoms in the 4 weeks leading up to their AMI, with lower SAQ angina frequency and SAQ quality of life scores in women compared with men (Cohen's d=0.20 and 0.21, respectively). The same pattern was observed for generic health status (Cohen's d=0.19). As compared with men, perceived stress levels were highest among women (Cohen's d=0.40).

Depressive Symptoms by Sex

Significantly more women than men reported having had a diagnosis of depression in the past (48% versus 24%; P<0.0001). At the time of their AMI, more women than men had significant depressive symptoms (PHQ-9 scores ≥10 in 39% of women versus 22% of men; P<0.0001). Of those who had a history of depression, more than twice as many women (26%) presented with PHQ-9 scores ≥10 as men (10%; P<0.0001). Women also scored higher for the overall PHQ-9 (mean score of 9±7 versus 6±6 in men; Cohen's d=0.46; P<0.0001) (Table 2). Women were more likely to have PHQ-9 scores ≥10 in all 3 countries (Table S4).

Demographic, Socioeconomic, and Clinical Profiles of Patients With AMI by Sex and by Depression Status

Both women and men had different demographic and socioeconomic patient profiles based on the level of their PHQ-9 scores. Among patients who had PHQ-9 scores ≥10, fewer married patients were noted, and fewer patients had a full- or part-time job compared with women who had lower depressive symptom scores. In addition, patients with PHQ-9 scores ≥10 had lower rates of completing high school or higher levels of education and lower rates of health insurance compared with those who had lower depressive symptom scores, and more reported that they were avoiding getting health care because of cost (Table 3).

With regards to their clinical profile, both women and men with scores ≥10 on the PHQ-9 presented with higher rates of cardiovascular comorbidity and risk factors (prior AMI, percutaneous coronary intervention, or coronary artery bypass grafting; congestive heart failure; hypertension; diabetes; hypercholesterolemia; smoking in the past 30 days; prior stroke or transient ischemic attack; obesity; higher Killip class), chronic lung disease, and more AMI symptoms compared with those having lower depressive symptom scores. Patients with PHQ-9 scores ≥10 experienced worse health status and more stress compared with those who had lower scores. Finally, antidepressants at discharge and newly prescribed antidepressants were more common among women and men with PHQ-9 scores ≥10 compared with patients who had lower PHQ-9 scores. (Table 3).

Independent Association Between Sex and Depressive Symptoms

Women had 2.28 greater odds of presenting with depressive symptoms at the time of AMI compared with men (95% CI 1.94 to 2.69). After adjustment for demographic, socioeconomic, clinical, and health status variables, the association between female sex and significant depressive symptoms persisted (odds ratio 1.64; 95% CI 1.36 to 1.98) (Table 4). Other characteristics associated with having depressive symptoms included history of cardiac disease, nonmarried status, and being unemployed (Figure shows adjusted model results, and Table S5 shows the fully adjusted model). Sensitivity analyses were run to verify whether our findings were different if each participating country's data were individually excluded to verify whether findings were robust across these international settings, and results remained essentially unchanged (data not shown).

Discussion

Although depression was recently recognized as a risk factor for adverse medical outcomes in patients with AMI,[6] many basic questions remain with regard to the extent to which this risk factor is prevalent among younger patients with AMI. We found a much greater prevalence of prior depression and concurrent depressive symptoms among young women with

Table 1. Patient Characteristics for the Overall Sample and by Sex

	Overall (N=3572, 100%)	Men (n=1175, 32.9%)	Women (n=2397, 67.1%)
	n (%)	n (%)	n (%)
Sociodemographic characteristics			
Age, range, y	18 to 55	23 to 55	18 to 55
Age, median (IQR), y	48 (44 to 52)	48 (43 to 52)	48 (44 to 52)
Race			
White	2800 (78)	980 (84)	1820 (76)
Black	554 (16)	114 (10)	440 (18)
Other	212 (6)	79 (7)	133 (6)
Hispanic	269 (8)	92 (8)	177 (7)
Married	1827 (51)	678 (58)	1149 (48)
Socioeconomic characteristics			
Education			
Less than high school	185 (5)	47 (4)	138 (6)
High school	1459 (42)	489 (43)	970 (41)
More than high school	1860 (53)	612 (53)	1248 (53)
Work full or part time	2204 (62)	856 (73)	1348 (57)
Health insurance	2870 (80)	920 (78)	1950 (81)
Avoid getting health care because of cost	1070 (30)	333 (28)	737 (31)
Medical history			
Prior AMI, PCI, or CABG	682 (19)	241 (21)	441 (18)
Angina	966 (27)	307 (26)	659 (28)
Congestive heart failure	141 (4)	24 (2)	117 (5)
Hypertension	2260 (63)	730 (62)	1530 (64)
Diabetes	1246 (35)	317 (27)	929 (39)
Hypercholesterolemia	3062 (86)	1080 (92)	1982 (83)
Smoked within past 30 days	2133 (60)	697 (59)	1436 (60)
Obesity (BMI $\geq$30 kg/m^2)	1745 (49)	524 (45)	1221 (51)
Prior stroke/TIA	147 (4)	27 (2)	120 (5)
Peripheral arterial disease	80 (2)	23 (2)	57 (2)
Renal dysfunction	367 (10)	91 (8)	276 (12)
Cancer	119 (3)	23 (2)	96 (4)
Chronic lung disease	363 (10)	65 (6)	298 (12)
Health status			
SAQ physical limitation score, mean (SD)	81 (25)	87 (21)	79 (27)
SAQ angina frequency score, mean (SD)	84 (20)	87 (18)	83 (21)
SAQ angina frequency categories			
Daily (0 to 30)	96 (3)	16 (1)	80 (3)
Weekly (31 to 60)	566 (16)	158 (14)	408 (17)
Monthly (61 to 99)	1235 (35)	414 (35)	821 (34)
None (100)	1656 (46)	583 (50)	1073 (45)
SAQ quality of life score, mean (SD)	57 (24)	60 (22)	55 (25)

Continued

Table 1. Continued

	Overall (N=3572, 100%)	Men (n=1175, 32.9%)	Women (n=2397, 67.1%)
	n (%)	n (%)	n (%)
EuroQoL 5D VAS, mean (SD)	64 (22)	67 (20)	63 (22)
PSS-14, mean (SD)	26 (10)	23 (10)	27 (10)
Clinical characteristics at AMI presentation			
Killip class			
I, no heart failure	3242 (92)	1083 (93)	2159 (91)
II, heart failure	110 (3)	26 (2)	84 (4)
III, pulmonary edema	26 (1)	4 (1)	22 (1)
IV, cardiogenic shock	21 (1)	5 (1)	16 (1)
Peak troponin level, median (IQR), ng/mL	6.9 (1.5 to 28.0)	9.6 (2.0 to 37.5)	5.8 (1.4 to 23.1)
Hemodynamic instability	309 (9)	97 (8)	212 (9)
Final AMI diagnosis: STEMI	1860 (52)	705 (60)	1155 (48)
Ejection fraction <40%	370 (11)	127 (11)	243 (11)
Experienced typical chest pain	2835 (79)	980 (83)	1855 (77)
Experienced atypical chest pain	634 (18)	164 (14)	470 (20)
Experienced back pain	514 (14)	118 (10)	396 (17)
Experienced abdominal pain	158 (4)	42 (4)	116 (5)
Experienced nausea	1477 (41)	409 (35)	1068 (45)
Experienced other type of pain	729 (20)	237 (20)	492 (21)
Experienced shortness of breath	1577 (44)	512 (44)	1065 (44)
Experienced fatigue	387 (11)	116 (10)	271 (11)
Experienced other symptoms	2284 (64)	739 (63)	1545 (64)
Had other acute noncardiac conditions at arrival	173 (5)	41 (4)	132 (6)
Number of symptoms, median (IQR)	3 (2 to 4)	3 (2 to 4)	3 (2 to 4)

AMI indicates acute myocardial infarction; BMI, body mass index; CABG, coronary artery bypass grafting; IQR, interquartile range; PCI, percutaneous coronary intervention; PSS-14, 14-item Perceived Stress Scale; SAQ, Seattle Angina Questionnaire; STEMI, ST-elevation myocardial infarction; TIA, transient ischemic attack; VAS, visual analog scale.

Table 2. Descriptive Overview of Comorbid Depression Rates (History and Current Symptoms) for the Overall Sample and by Sex

	Overall (N=3572, 100%)	Men (n=1175, 32.9%)	Women (n=2397, 67.1%)	*P* Value
	n (%)	n (%)	n (%)	
History of depression	1421 (40)	280 (24)	1141 (48)	<0.0001
PHQ-9 overall score, mean (SD)*	8 (6)	6 (6)	9 (7)	<0.0001
PHQ-9 ≥10	1131 (33)	245 (22)	886 (39)	<0.0001
PHQ-9 depression levels				
No depression (score 0 to 4)	1333 (39)	577 (51)	756 (33)	<0.0001
Mild depression (score 5 to 9)	960 (28)	310 (27)	650 (28)	
Moderate depression (score 10 to 14)	552 (16)	141 (12)	411 (18)	
Moderately severe depression (score 15 to 19)	364 (11)	68 (6)	296 (13)	
Severe depression (score ≥20)	215 (6)	36 (3)	179 (8)	
PHQ-9 ≥10 and history of depression	710 (21)	114 (10)	596 (26)	<0.0001

PHQ-9 indicates 9-item Patient Heath Questionnaire.
*Only 3424 subjects had PHQ-9 overall scores (n=1132 for men, and n=2292 for women).

Table 3. Descriptive Overview of Patient Characteristics Presented by Sex and Depression Status (PHQ-9<10 PHQ-9≥10)

	Men			Women		
	PHQ-9 <10 n=887, 78.4%	PHQ-9 ≥10 n=245, 21.6%	*P* value	PHQ-9 <10 n=1406, 61.3%	PHQ-9 ≥10 n=886, 38.7%	*P* value
Sociodemographic characteristics						
Age, median (IQR), years	48 (43 to 52)	48 (44 to 51)	0.76	48 (44 to 52)	48 (44 to 52)	0.52
Race			0.61			0.06
White	736 (83)	209 (85)		1056 (75)	694 (79)	
Black	87 (10)	23 (10)		261 (19)	153 (17)	
Other	62 (7)	13 (5)		88 (6)	37 (4)	
Hispanic	57 (6)	31 (13)	0.012	106 (8)	62 (7)	0.55
Married	536 (61)	118 (48)	0.0005	721 (51)	374 (42)	<0.0001
Education			0.0013			0.0021
Less than high school	34 (4)	10 (4)		76 (5)	56 (6)	
High school	342 (39)	126 (52)		532 (38)	392 (45)	
More than high school	491 (57)	105 (44)		778 (56)	423 (49)	
Work full or part time	685 (78)	144 (59)	<0.0001	901 (64)	394 (45)	<0.0001
Health insurance	724 (82)	171 (70)	<0.0001	1176 (84)	689 (78)	0.0003
Avoid getting health care because of cost	210 (24)	107 (44)	<0.0001	349 (25)	361 (41)	<0.0001
Medical history						
Prior AMI, PCI, or CABG	166 (19)	68 (28)	0.0020	234 (17)	189 (21)	0.0051
Congestive heart failure	10 (1)	12 (5)	0.0002	57 (4)	58 (7)	0.0078
Hypertension	529 (60)	176 (72)	0.0005	836 (59)	624 (70)	<0.0001
Diabetes	211 (24)	95 (39)	<0.0001	492 (35)	394 (44)	<0.0001
Hypercholesterolemia	805 (91)	235 (96)	0.0088	1131 (80)	759 (86)	0.0014
Smoked within past 30 days	493 (56)	176 (72)	<0.0001	762 (54)	603 (68)	<0.0001
Obesity (BMI ≥30 kg/m^2)	384 (43)	121 (49)	0.0920	667 (48)	492 (56)	0.0002
Prior stroke/TIA	17 (2)	10 (4)	0.0497	65 (5)	48 (5)	0.39
Peripheral arterial disease	13 (1)	8 (3)	0.0670	31 (2)	25 (3)	0.36
Renal dysfunction	69 (8)	19 (8)	0.9945	148 (11)	114 (13)	0.08
Cancer	16 (2)	7 (3)	0.3009	54 (4)	37 (4)	0.69
Chronic lung disease	40 (5)	21 (9)	0.0128	116 (8)	170 (19)	<0.0001
Health status						
SAQ physical limitation score, mean (SD)	91 (17)	74 (26)	<0.0001	86 (22)	67 (31)	<0.0001
SAQ quality of life score, mean (SD)	63 (21)	50 (22)	<0.0001	61 (22)	45 (25)	<0.0001
PSS-14, mean (SD)	21 (8)	32 (8)	<0.0001	23 (8)	34 (8)	<0.0001
Clinical characteristics at presentation						
Killip class			0.0173			0.37
I, no heart failure	825 (94)	217 (89)		1273 (92)	793 (91)	
II, heart failure	14 (2)	12 (5)		42 (3)	38 (4)	
III, pulmonary edema	2 (1)	2 (1)		13 (1)	9 (1)	
IV, cardiogenic shock	4 (1)	1 (1)		7 (1)	8 (1)	

Continued

Table 3. Continued

	Men			Women		
	PHQ-9 <10 n=887, 78.4%	PHQ-9 ≥10 n=245, 21.6%	*P* value	PHQ-9 <10 n=1406, 61.3%	PHQ-9 ≥10 n=886, 38.7%	*P* value
Final AMI diagnosis: STEMI	542 (61)	138 (56)	0.1764	697 (50)	408 (46)	0.1002
Experienced typical chest pain	745 (84)	195 (80)	0.1043	1098 (78)	677 (76)	0.3478
Experienced atypical chest pain	115 (13)	46 (19)	0.0212	260 (18)	186 (21)	0.1408
Experienced back pain	91 (10)	22 (9)	0.5542	231 (16)	154 (17)	0.5528
Experienced abdominal pain	26 (3)	15 (6)	0.0180	64 (5)	47 (5)	0.4136
Experienced nausea	298 (34)	94 (38)	0.1647	620 (44)	409 (46)	0.3329
Experienced other type of pain	165 (19)	59 (24)	0.0567	290 (21)	177 (20)	0.7074
Experienced shortness of breath	364 (41)	130 (53)	0.0008	565 (40)	452 (51)	<0.0001
Experienced fatigue	80 (9)	33 (13)	0.0397	141 (10)	117 (13)	0.0191
Experienced other symptoms	544 (61)	164 (67)	0.1084	904 (64)	575 (65)	0.7691
Had other acute noncardiac conditions at arrival	23 (3)	17 (7)	0.0012	65 (5)	55 (6)	0.1099
Number of symptoms, median (IQR)	3 (2, 4)	3 (2, 4)	0.0004	3 (2, 4)	3 (2, 4)	0.0035
Depression treatment information during AMI admission						
Antidepressant use at discharge	60 (7)	47 (19)	<0.0001	217 (15)	274 (31)	<0.0001
Newly prescribed antidepressants	15 (2)	6 (3)	0.29	25 (2)	44 (7)	<0.0001

AMI indicates acute myocardial infarction; BMI, body mass index; CABG, coronary artery bypass grafting; IQR, interquartile range; PCI, percutaneous coronary intervention; PHQ, 9-item Patient Health Questionnaire; PSS-14, 14-item Perceived Stress Scale; SAQ, Seattle Angina Questionnaire; STEMI, ST-elevation myocardial infarction; TIA, transient ischemic attack.

Table 4. Sequential Logistic Regression Results for the Relationship Between Female Sex and PHQ-9 Scores ≥10

Model Number	Odds Ratio for Female Sex (95% CI)	Covariates Included in the Model
1	2.28 (1.94 to 2.69)	Sex
2	2.30 (1.95 to 2.71)	Sex, age, race
3	1.99 (1.68 to 2.36)	Sex, age, race, marital status, education level, employment status
4	1.86 (1.56 to 2.22)	Sex, age, race, marital status, education level, employment status, congestive heart failure, prior AMI/PCI/CABG, prior stroke/TIA, peripheral arterial disease, history of diabetes, STEMI, smoking in past 30 days, obesity status, chronic lung disease
5	1.64 (1.36 to 1.98)	Sex, age, race, marital status, education level, employment status, congestive heart failure, prior AMI/PCI/CABG, prior stroke/TIA, peripheral arterial disease, history of diabetes, STEMI, smoking in past 30 days, obesity status, chronic lung disease, SAQ physical limitation, SAQ quality of life

AMI indicates acute myocardial infarction; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; SAQ, Seattle Angina Questionnaire; STEMI, ST-elevation myocardial infarction; TIA, transient ischemic attack.

AMI than among young men. Even after adjusting for numerous sociodemographic, clinical, and disease severity characteristics, young women with AMI had 60% greater odds of having significant depressive symptoms than young men. Moreover, at the time of their AMI, women with a history of clinical depression were particularly vulnerable to experiencing depressive symptoms compared with men with a history of depression; up to a quarter of women with a history of depression had current depressive symptoms versus 10% of men with had a history of depression. Although there is literature documenting sex differences in depression and cardiovascular disease, the finding of higher prevalence of depressive symptoms in young women with AMI compared with men, in particular, has important implications.

Although preliminary studies have shed important insight in this area, young women were often underrepresented in prior studies of patients with AMI, and the studies are old or missed detailed patient and depression information.[1,4,5,8,26] The VIRGO study was able to accommodate these shortcomings and added new insights into the extent of patients'

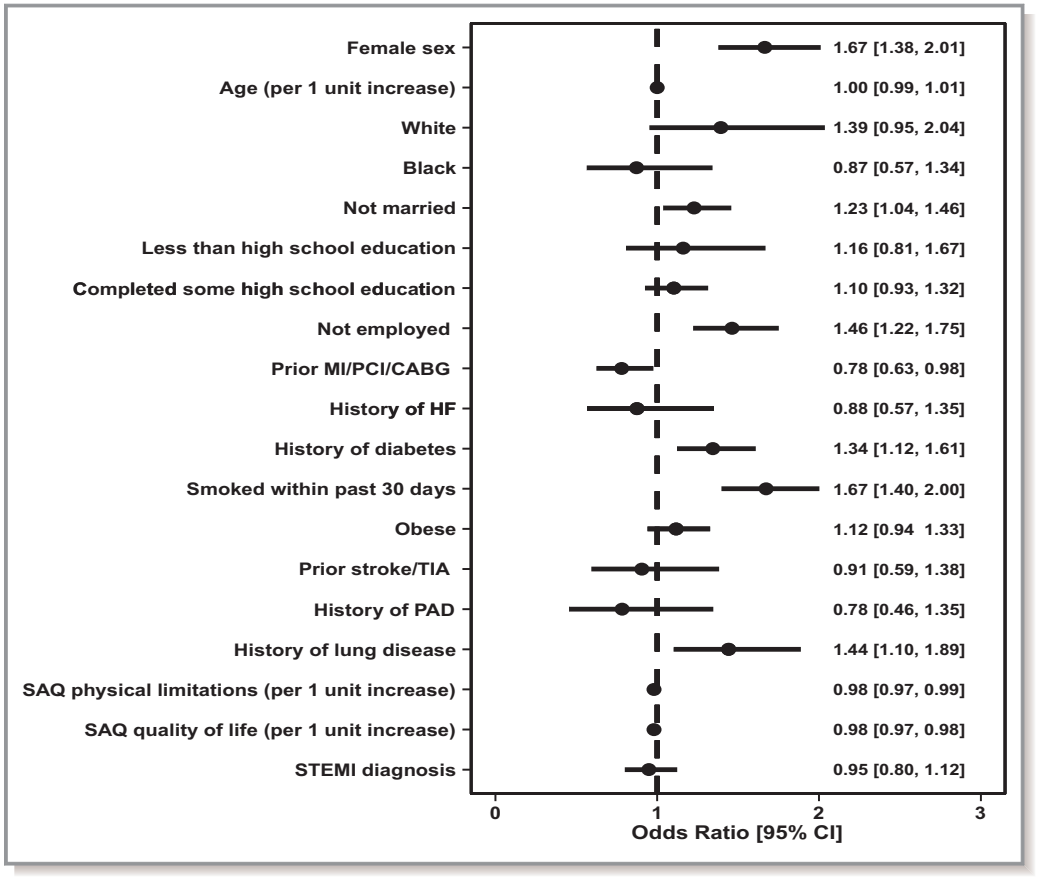

Figure. Forest plot of the fully adjusted logistic regression model to assess the relationship between female sex and scores ≥10 on the 9-item Patient Health Questionnaire. Odds ratios and 95% CIs are depicted. CABG indicates coronary artery bypass grafting; HF, heart failure; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; SAQ, Seattle Angina Questionnaire; STEMI, ST-elevation myocardial infarction; TIA, transient ischemic attack.

depressive symptomatology. This understanding may be helpful in future studies examining depression as a potential explanatory mechanism for the adverse outcomes of younger women recovering from an AMI. Importantly, a novel finding of this study, the long lifetime history of depression with greater depressive symptoms at the time of an AMI, suggests inadequate treatment of known depression and warrants further investigation into biological (eg, genetic, inflammation) and psychosocial triggers that may underlie this unusually high depression burden among young women. An alternative explanation for the increased depressive symptom burden may be that women with depression suffered from a high comorbidity burden (eg, diabetes, obesity, chronic lung disease). This burden may predispose women to experiencing more depressive symptoms, although adjustment for these factors did not affect the association between female sex and having increased depressive symptoms in the current study.

Regardless of cause, having depressive symptoms that interfere with daily functioning warrants appropriate treatment in its own right. Experiencing depressive symptoms and also having coronary disease may further complicate recovery because both limit daily function and may negatively affect patients' rehabilitation.[27] Another reason why depressive symptoms in cardiac patients deserve special consideration is that prevalence seems to be disproportionately high, and this remains the case over the years. Both in women and men with AMI who were aged 18 to 55 years, 3 times as many patients had PHQ-9 scores ≥10 compared with the general population (depression rates among men and women aged 40 to 59 years are 7% and 12%, respectively, as measured in the US National Health and Nutrition Examination Survey study[28] with the PHQ-9 ≥10 criterion).[29] The prevalence estimates for depression in the younger patients with AMI in this study are also fairly consistent with those obtained from data collected 5 to 8 years ago. In the PREMIER study, 40% of women aged <60 years had PHQ-9 scores ≥10 and 22% of younger men had increased PHQ-9 scores, suggesting that little progress has been made to effectively address this burden.[4] Despite several initiatives to better recognize and treat depression in coronary artery disease[30,31] and the knowledge that depression

constitutes a major risk for future adverse AMI prognosis,[5,6] prevalence rates for depression remain exceedingly high.

A study finding that requires further reflection is that nearly half of younger women (≤55 years) had a diagnosis of depression at some point in their lives versus 24% of younger men (≤55 years); however, half of those who had PHQ-9 scores ≥10 around the time of their AMI did not have a history of depression. The same pattern was observed for younger men, except that their depression history rates were half those of younger women. Although our cross-sectional design and the self-report of lifetime history of depression may limit us in finding an actual explanation for our findings, several hypotheses can be formulated and will need further testing in the future. Patients' new depressive symptoms may have been specifically associated with the impending AMI or perhaps, in a substantial amount of patients, depressive symptoms went unnoticed and untreated in the past. It is known that women who present with chest pain at the emergency department without evidence of coronary disease but with cardiac risk factors already seem vulnerable to experiencing high rates of depressive symptoms.[32] The tenacity of women's depressive symptom burden in cardiac disease requires more extensive evaluation to understand whether patients' symptoms of depression were correctly diagnosed or adequately treated in the past, whether other psychological comorbidities are present that need to be addressed along with the depression, whether the depression had been completely in remission in the past, or whether women tend to experience more treatment-resistant symptoms of depression. Another potential explanation may be that the very high rate of depressive symptoms is, in part, secondary to the experience of the AMI. Regardless, depression seems to be a recurrent concern over the course of life in a large group of patients with AMI.

Increased awareness and intensified treatment for coronary patients' depressive symptoms can be very beneficial. Similarly, the high stress scores noted in both younger men and women who had PHQ-9 scores ≥10 are modifiable and important treatment targets that are also associated with adverse cardiac disease outcomes.[22,33] Recently, several intervention studies have been shown to be helpful in reducing depressive symptoms and stress, improving patients' quality of life, and rendering promising results with regard to patients' cardiovascular prognosis.[30,31,34] These intervention studies combined elements of cognitive–behavioral and problem-solving therapies, stress-reduction techniques, and stepped depression and collaborative care programs. The profile information provided in this study could be used to design a tailored prevention or intervention program incorporating these techniques. Through existing community programs that have already identified younger persons with vulnerable socioeconomic positions (eg, not having a partner, being unemployed, having less education), one could focus on preventive strategies and improving recognition of depression and on aggressive management of cardiovascular risk factors. The current study highlights that in such programs, potentially lower literacy levels and other socioeconomic barriers need to be considered because younger patients with depressive symptoms presented with very unfavorable socioeconomic profiles. Having this specific information about this younger population facing depression is important for designing targeted depression-intervention programs. The correlates of depression seem to be unique to the challenges of the phase of life that each individual faces. As a comparison, at older ages, female sex is still a predictor of having depression, but other factors like functional and cognitive decline and social isolation seem to be more prominent characteristics of persons dealing with depressive symptoms.[35] Providing access to tailor-made programs that address the risk factors unique to a younger population like that studied in VIRGO and using some of the elements studied in recent depression-intervention studies could offer a way to attenuate the high coronary and psychiatric risk of these younger persons.

This study should be interpreted within the context of several potential limitations. It is impossible to discern whether the depressive symptoms noted in this observational study were a cause or an effect of patients' AMI, although the PHQ-9 inquires about symptoms over the past 2 weeks (prior to the AMI), and women's increased risk of depression was independent of AMI severity, comorbid conditions, cardiovascular risk factors, and health status. Regardless of the direction of the relationship, it is important to note that depressive symptoms can be treated successfully. There is a potential concern about recall bias associated with the self-report data on lifetime history of depression; however, previous research has indicated that this way of measuring lifetime history of depression may result in underreporting of lifetime history of depression rates; if anything, the estimates of the depressive symptom burden in our AMI population may reflect underrepresentation.[36,37] Other limitations of this study include the potential for residual confounding, the lack of a diagnostic interview for a DSM diagnosis of current depression,[13] and the inability to look at potential mechanisms as to why women incurred the highest risk of experiencing depressive symptoms prior to their AMI. Hormonal differences, combining several life roles, being a single parent, and working in lower paid jobs are just a few potential reasons identified in the past that could help explain the observed sex differences in depressive symptoms.[38] Future studies will be needed to replicate our findings and to better define the mechanisms of young patients' depressive symptoms.

In summary, the burden of depressive symptoms is very high among young patients with an AMI, particularly among younger women. Regardless of sex, depressive symptoms seem to primarily strike patients with lower socioeconomic status and are accompanied by high levels of stress and decreased functional status. This information will be useful to target future prevention and intervention programs that can help address depression as an important cardiac risk factor in this vulnerable group of patients.

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