Major Depressive Disorder Predicts Completion, Adherence, and Outcomes in Cardiac Rehabilitation: A Prospective Cohort Study of 195 Patients With Coronary Artery Disease

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ABSTRACT

Objective: To compare completion, adherence, and cardiac rehabilitation (CR) outcomes between participants with and without major depressive disorder (MDD) undertaking CR.

Method: In a prospective cohort study of consecutive patients with coronary artery disease (n = 195) entering 1-year outpatient CR between January 2006 and August 2008, rates of noncompletion (comprehensive CR criteria), nonadherence (< 70% attendance at scheduled CR visits), and CR outcomes were compared between patients with and without MDD based on the Structured Clinical Interview for *DSM-IV* criteria.

Results: Major depressive disorder was diagnosed in 22.1% of participants. Rates of noncompletion were 44.2% and 28.9%, and rates of nonadherence were 53.0% and 34.9% for those with and without MDD, respectively. Major depressive disorder was associated with increased risks of noncompletion (multivariate hazard ratio [HR], 2.5; 95% confidence interval [CI], 1.3–4.7) and nonadherence (multivariate HR, 2.4; 95% CI, 1.3–4.2). More participants with MDD failed to complete CR for medical reasons than those without MDD (25.6% vs 12.3%, respectively; $P = .031$) in post hoc comparisons. Participants with MDD achieved poorer cardiopulmonary fitness increases (change in mean ± SD peak oxygen uptake of 3.3 ± 3.2 vs 6.6 ± 5.7 mL/kg/min; $P = .021$) and poorer body fat outcomes (a mean ± SD increase of 2.1% ± 4.5% vs a decrease of 0.4% ± 3.4%, $P = .009$) than those without MDD.

Conclusions: Major depressive disorder was associated with poorer rates of completion and adherence in CR, and it mitigated improvements in clinical outcomes. Despite depression screening and psychosocial support as structured components of care, MDD remained a significant barrier to effective CR.

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Coronary artery disease (CAD) is a leading cause of mortality in North America.[1] Major depressive disorder (MDD) is diagnosed in about 20% of outpatients with CAD,[2] and it is associated with mortality and morbidity independently of other cardiac risk factors.[3] As such, it is of substantial clinical importance to understand the factors underlying this association. Physical inactivity has recently been suggested to mediate the association between depressive symptoms and recurrent acute coronary syndromes (ACS),[4] suggesting further exploration of fitness in CAD. Poor cardiopulmonary fitness is a modifiable risk factor associated with mortality, and improvement in cardiopulmonary fitness is a key outcome of cardiac rehabilitation (CR).[5–7] Comprehensive CR involves exercise training, education, lifestyle modification, and psychosocial support,[7] and it is highly effective in reducing long-term mortality and the recurrence of ACS.[8]

Cardiopulmonary improvement and reduced long-term mortality rates are observed in patients who complete CR programs, even in those who begin them with significant depressive symptoms.[9,10] However, depressive symptoms have been shown to increase the risk of noncompliance with CR programs[10–13] and with other risk-modifying behaviors, such as taking cardiac medications, adhering to a specialized diet, and participating in physical activity.[14] An appreciation of the importance of depressive symptoms in CAD has prompted many CR programs to implement systematic screening and to offer psychosocial support for those affected.[7] However, the validity of depression screening and the effectiveness of comprehensive CR specifically for patients with MDD have not been extensively studied. The primary purpose of the present study was to evaluate the association of a psychiatric diagnosis of MDD with completion of CR and adherence to CR over 1 year, when screening and psychosocial support are included as structured components of care. Secondly, clinical CR outcomes were compared between patients presenting with and without MDD.

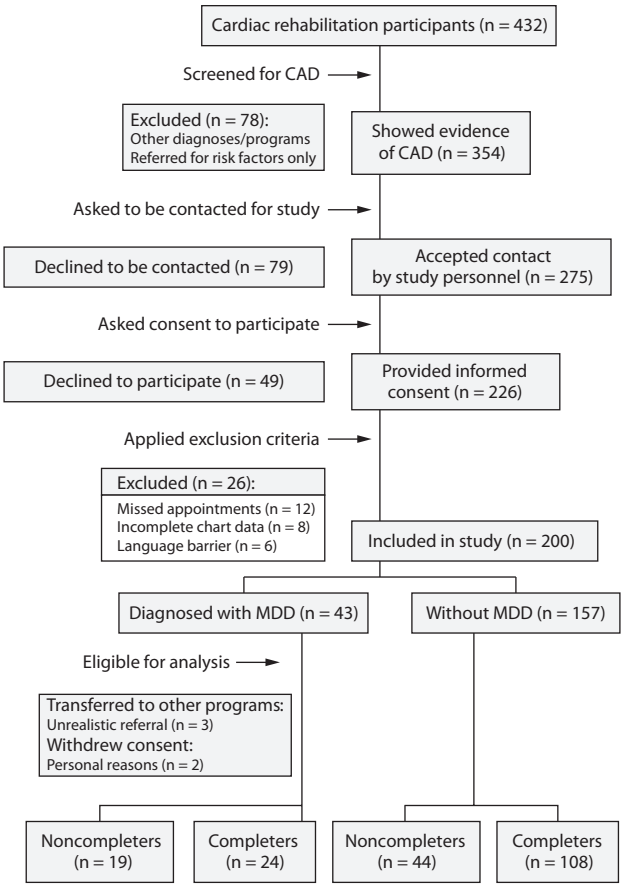
METHOD

Participants

Consecutively enrolled patients with documented CAD (myocardial infarction, angiographic evidence of ≥ 50% blockage in at least 1 major coronary artery, or prior revascularization) entering 1-year CR at the Cardiac Program of the Toronto Rehabilitation Institute between January 2006 and August 2008 were approached at intake for possible study participation. Patients were approached for the study if they had completed a cardiopulmonary fitness test, the Center for Epidemiologic Studies-Depression scale (CES-D), and if their medical records included sufficient information to determine cardiac and related diagnoses. Patients were excluded in the presence of neurodegenerative illness, cognitive impairment, active cancer, surgery planned within the next 12 months, or premorbid

psychiatric diagnoses other than depression. Participants provided informed written consent in accordance with local research ethics boards. After obtaining consent, participants were interviewed to assess appropriateness for the study on the basis of inclusion/exclusion criteria, to diagnose MDD, and to ascertain relevant baseline clinical characteristics (Figure 1).

Figure 1. Participant Recruitment and Study Design



Abbreviations: CAD = coronary artery disease, MDD = major depressive disorder.

CR Protocol

Participants could start CR a minimum of 6 weeks post coronary artery bypass graft surgery, 6 weeks post myocardial infarction, or 3 weeks post percutaneous coronary intervention. Participants attended weekly supervised exercise sessions for 6 months, followed by monthly visits for an additional 2 months as previously described.[6] On a weekly basis, participants were required to complete an additional 4 aerobic sessions and 1 to 2 resistance training sessions per week away from the center, and these were tracked via exercise log. A cardiopulmonary fitness assessment was performed at baseline and at 12 months. The initial walking prescription was set at a distance of approximately 1.6 km per day at an intensity equivalent to 60% of peak oxygen uptake (VO_{2Peak}). Prescriptions were progressed every 2 weeks, increasing distance to a maximum of 6.4 km per day and then increasing intensity to a maximum of 80% of VO_{2Peak} (maximum duration of 60 minutes). Thereafter, training intensity was adjusted to maintain an exercise heart rate equivalent to that achieved at 80% of VO_{2Peak} on the graded exercise test. Exercise log information, heart rates measured at the center, and communication with the patient assisted the CR supervisor in deciding when to increase the pace and/or distance of exercise.

Comprehensive lifestyle management resources offered to all participants included information sessions regarding risk factor management (eg, medication use, weight control, diet, and smoking cessation). Standard practice at the center included screening for depressive symptoms at intake and 12 months, using the CES-D. Participants with CES-D scores ≥ 16, those voicing subjective mood complaints, or those showing objective signs of depression during CR visits were approached and referred to a staff psychologist for assessment and treatment. Psychosocial interventions included stress management seminars, group therapy sessions, individual counseling, and/or psychiatric referral as appropriate. The use of antidepressants and psychosocial intervention(s) throughout CR was ascertained by CR staff or by study personnel.

Completion of CR and Adherence to CR

Participants were followed throughout the standard 48-week CR protocol, and attendance at weekly visits was recorded. Completion or noncompletion of CR was determined on the basis of the case manager's comprehensive assessment of compliance with individualized program expectations (a combination of daily exercise prescriptions, attendance at scheduled CR sessions, and completion of exercise tests). The date of completion or premature withdrawal was recorded along with the reason for dropout/discharge when appropriate. Because patients who attend sporadically are not necessarily discharged, patients were considered adherent if they completed CR with at least 70% attendance at scheduled CR sessions. While no consensus has been reached considering formal criteria for adherence to CR, 70% attendance is consistent with expectations within the program studied, and similar criteria have been found to be meaningful in previous investigations.[13,15]

Assessments

The Structured Clinical Interview for *DSM-IV* Axis I Disorders, Non-patient Edition,[16] was administered at baseline by a trained researcher under the supervision of the study psychiatrist to ascertain whether participants met *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*)[17] criteria for MDD. A clinically experienced psychiatrist conducted researcher training and quality assurance for interview skills and diagnostic accuracy and reviewed results. The CES-D, a 20-item questionnaire scored between 0 and 60, was used to quantify depressive symptoms. The CES-D was administered by CR staff at baseline and after 48 weeks of participation to those who completed CR. The CES-D has been used extensively in CAD populations demonstrating

utility,[18] and a cutoff of 16 has been adequately sensitive and specific to detect MDD.[19]

Sociodemographic information, cardiac factors, and medications were ascertained during the patient interview and by CR chart review. Cardiopulmonary fitness was assessed at baseline and at completion of CR using a symptom-limited graded exercise test on a cycle ergometer (Ergoline 800 EL; Ergoline GmbH, Bitz, Germany). Workload was increased by 16.7 watts every minute, and breath-by-breath gas samples were collected and averaged over a 20-second period via calibrated metabolic cart (Vmax SensorMedics 2900; CareFusion, Yorba Linda, California).[6] Resting and peak physiologic measurements were recorded. The VO_{2Peak} thus obtained is a highly reliable and reproducible measure of cardiopulmonary fitness,[5] and the change in VO_{2Peak} is considered a primary outcome of CR.[6] Anthropometric measurements were made; percentage body fat (bioelectric impedance), waist circumference, and body mass index (BMI; calculated per standard definition) were recorded. When available, coronary angiography reports were reviewed for indices of CAD severity, including the involvement of each major coronary artery (> 50% stenosis) and the presence of restenosis in any previously revascularized lesion.

Statistical Analyses

All analyses were 2-tailed, and they were performed using SPSS statistical software (version 16.0.1; SPSS Inc, Chicago, Illinois). Differences in baseline demographic characteristics, cardiac histories, cardiac risk factors, concomitant medication use, medical comorbidities, and reasons for noncompletion were assessed between participants presenting with and without MDD using Pearson χ^2 or univariate analyses of variance (ANOVAs) as appropriate.

Cox proportional hazards models were used to assess associations between MDD and time in CR. For primary analyses, MDD was entered as a key predictor into 2 Cox regression models on the basis of completion or adherence criteria, wherein those not meeting criteria were treated as censored observations at their last week of attendance. Statistics have been adjusted for multiple comparisons with results considered significant at $P < .025$. Possible confounders (participant characteristics from Table 1) were entered individually into each of the unadjusted models, and their effects on associations between MDD and time to noncompletion or nonadherence were determined. All variables found to influence the main effect of MDD by greater than ± 10% were entered into final Cox regression models to determine the independent effect of MDD on outcome variables.[20] Multicollinearity was assessed among predictors in the final models using the tolerance statistic (tolerance ≤ 0.4). Unadjusted hazards ratios (HRs) are presented for MDD and for those screening positive for depression using the CES-D.

Secondary objectives investigated possible differences in clinical outcomes associated with MDD. Changes in outcome measures were compared between participants with and without MDD in analyses of covariance (ANCOVA) including the baseline measure, age and sex as covariates. Further analyses post hoc used Pearson χ^2 tests to determine if reasons for noncompletion differed in proportion between participants with and without MDD and paired-sample *t* tests to compare fitness parameters before and after CR.

Sample Size and Study Power

Anticipating a 20% point-prevalence of MDD[2], a sample size of 200 is sufficient, at a 2-sided significance of 0.025, to achieve 80% power to detect noncompletion HRs of magnitudes suggested in previous studies (HRs = 1.86 to 5.65).[12,13] On the basis of internal audits, a 30% rate of noncompletion was anticipated.[21] A sample size of 200, anticipating 60 noncompleters, allows adjustment of hazards models with up to 5 covariates in addition to MDD.

RESULTS

Baseline Characteristics of Participants With and Without MDD

Analyses included 195 participants (Figure 1). Participants included were similar in mean ± SD age (64.3 ± 11.5 years), sex (79.5% male), and rate of CR completion (67.7%) to patients from the center database (mean ± SD age = 61.0 ± 10.5 years, 81.6% male, 70.0% completing CR, n = 5,922),[21] and the proportion of participants screening positive for depressive symptoms (26.2%) was comparable to that of patient samples from the center database (22.3%, n = 366).[22]

Major depressive disorder was diagnosed in 22.1% of participants. The sensitivity and specificity of depression screening with the CES-D to detect MDD were 92.9% and 78.0%, respectively. Overall, sociodemographic characteristics, cardiac factors, fitness parameters, and cardiac medication prescriptions were similar between participants who met diagnostic criteria for MDD and those who did not (Table 1); however, the mean ± SD age of participants with MDD was younger than that of other participants (60.7 ± 13.9 vs 65.3 ± 10.7 years, $F_{1,194} = 5.593$, $P = .019$). Participants with MDD were more likely to report a premorbid major depressive episode (37.2% vs 15.1%, respectively; Pearson $\chi^2 = 10.211$, $P = .001$), and a greater proportion were prescribed antidepressants (18.6% vs 5.3%, respectively, Pearson $\chi^2 = 7.921$, $P = .005$). Coronary angiographic data were available for 177 participants. Participants with and without MDD did not differ significantly in the involvement of any particular artery, in the total number of arteries involved, in the cumulative percentage of stenosis in all 4 main coronary arteries, or in incidence of restenosis ($P > .05$).

Completion of CR

Over 48 weeks, 32.3% of participants failed to meet CR criteria for completion (44.2% of participants with MDD and 28.9% of those without MDD), and only 45.1% of patients completed CR and attended at least 70% of scheduled CR visits (34.9% of participants with MDD and 48.0% of those without MDD). Sociodemographic characteristics, cardiac factors, fitness parameters, and cardiac medication

Table 1. Characteristics of Cardiac Rehabilitation Participants With and Without MDD at Baseline

Characteristic	MDD Diagnosed (n = 43)	MDD Not Diagnosed (n = 152)	*P* Value[a]
Sociodemographic			
Age, mean ± SD, y	60.7 ± 13.9	65.3 ± 10.7	.02
Employed, n (%)	20 (47)	72 (47)	.95
Partnered, n (%)	28 (65)	118 (77)	.07
Male, n (%)	31 (72)	125 (82)	.16
Ethnicity, n (%)			
White	30 (70)	122 (80)	.15
South Asian	5 (12)	12 (8)	.42
Asian	1 (2)	6 (4)	.63
Other	7 (16)	13 (9)	.13
Smoking			
Past smoker, n (%)	23 (53)	78 (51)	.80
Current smoker, n (%)	1 (2)	7 (5)	.51
Never smoked, n (%)	10 (44)	67 (44)	.99
Cigarettes/d, mean ± SD, no.	6.8 ± 8.8	10.2 ± 15.3	.17
Education, mean ± SD, y	16.1 ± 3.2	16.7 ± 3.2	.34
Cardiac factors, n (%)			
Hypertension	21 (49)	82 (54)	.58
PCI	17 (40)	69 (45)	.51
Diabetes	7 (16)	40 (26)	.17
Angina,	12 (28)	34 (22)	.47
Myocardial infarction	20 (47)	73 (48)	.89
CABG	5 (12)	12 (8)	.42
Psychometric			
CES-D score, mean ± SD	28.1 ± 10.4	6.7 ± 6.0	< .001
CES-D ≥ 16, n (%)	40 (93)	11 (7)	< .001
Premorbid depressive episode, n (%)	16 (37)	23 (15)	< .001
Concomitant medications, n (%)			
Statin	41 (95)	137 (90)	.30
ASA	35 (81)	138 (91)	.08
β-blockers	28 (65)	115 (76)	.25
Antihypertensive	24 (56)	102 (67)	.17
Nitroglycerin	23 (54)	67 (44)	.28
Antidiabetic agents	7 (16)	35 (23)	.33
Ca^{2+} channel antagonists	14 (32)	32 (21)	.12
Diuretics	6 (14)	36 (24)	.16
Anxiolytics	8 (19)	15 (10)	.11
Antidepressants	8 (19)	8 (5)	.004
Body composition, mean ± SD			
BMI, kg/m^2	27.8 ± 4.5	27.6 ± 4.8	.78
Body fat, %	28.8 ± 7.6	27.8 ± 8.1	.50
Waist circumference, cm	97.1 ± 10.7	98.3 ± 13.4	.58
Resting physiology, mean ± SD			
Resting heart rate, bpm	68.6 ± 14.1	66.9 ± 12.2	.45
Resting systolic BP, mm Hg	129.2 ± 19.6	129.5 ± 18.7	.93
Resting diastolic BP, mm Hg	75.1 ± 11.4	74.1 ± 99	.58
Fitness parameters, mean ± SD			
VO_{2Peak}, mL/kg/min	18.6 ± 5.5	17.9 ± 5.4	.49
Maximum heart rate, bpm	116.7 ± 23.4	114.9 ± 22.7	.64
Maximum systolic BP, mm Hg	170.5 ± 27.9	175.7 ± 24.8	.25
Maximum diastolic BP, mm Hg	81.2 ± 11.4	77.8 ± 10.9	.08

[a]Two-tailed significance (Pearson χ^2 or 1-way analysis of variance).
Abbreviations: ASA = acetylsalicylic acid, BMI = body mass index, BP = blood pressure, bpm = beats per minute, CABG = coronary artery bypass graft, CES-D = Center for Epidemiologic Studies-Depression scale, MDD = major depressive disorder, PCI = percutaneous coronary intervention, VO_{2peak} = peak oxygen uptake.

prescriptions were similar between participants who completed CR and those who did not ($P > .05$).

Analyses post hoc indicated that the percentage of participants with MDD who did not complete CR for medical reasons was greater than that of participants without MDD (25.6% vs 12.3%, Pearson $\chi^2 = 4.65$, $P = .031$). Medical reasons for noncompletion (Table 2) included unanticipated bypass

Table 2. Completion of Cardiac Rehabilitation and Psychosocial Interventions

Variable, n (%)	MDD Diagnosed (n = 43)	MDD Not Diagnosed (n = 152)	*P* Value[a]
Reasons for noncompletion			
Medical reasons	11 (26)	19 (13)	.03
CAD related	5 (12)	7 (5)	.08
Other medical reasons	6 (14)	12 (8)	.21
Nonmedical reasons	8 (19)	25 (16)	.70
Lack of interest	3 (7)	13 (9)	.67
Moved/transportation problems	0 (0)	4 (3)	.28
Work related	2 (5)	2 (1)	.17
Other	3 (7)	6 (4)	.39
Interventions for depression			
Referral to CR psychologist	15 (35)	3 (2)	< .001
CR counseling initiated	10 (23)	7 (5)	< .001
Antidepressant initiated	4 (9)	0 (0)	.004

[a]Two-tailed significance (Pearson χ^2).
Abbreviations: CAD = coronary artery disease, CR = cardiac rehabilitation, MDD = major depressive disorder.

(n = 7), unanticipated percutaneous coronary intervention (n = 3), myocardial infarction (n = 2), musculoskeletal problems (n = 6), and other (n = 12). No mortality was observed during this study.

Associations Between MDD and Completion of CR and Adherence to CR

Participants with MDD or those screening positive for depressive symptoms were more likely to prematurely discontinue CR, and they were less likely to remain adherent to CR sessions, than those without MDD (Table 3). Adjusting for possible confounders (Table 4; Figure 2), MDD was associated with HRs of 2.5 for noncompletion (95% CI, 1.3–4.7; $P = .005$) and 2.4 for nonadherence (95% CI, 1.3–4.2; $P = .003$).

Clinical Outcomes of Participants With and Without MDD

Baseline and follow-up cardiopulmonary fitness and body composition were compared for 103 participants who completed CR (Table 5). Participants finishing CR showed an increase of 6.00 ± 5.45 mL/kg/min in VO_{2Peak} ($t_{1,102} = 11.32$, $P < .001$); however, the mean ± SD increase in VO_{2Peak} was lower in participants with MDD than in those without MDD (3.28 ± 3.24 and 6.63 ± 5.68 mL/kg/min, respectively, $F_{1,98} = 5.49$, $P = .021$; Figure 3). Similar results were observed for changes in maximum heart rate. Major depressive disorder was associated with less improvement in body fat percentage over the course of CR; participants with MDD gained 2.11% ± 4.47%, whereas participants without MDD lost 0.42% ± 3.41% ($F_{1,98} = 7.22$, $P = .009$; Figure 3). Similarly, changes in waist circumference differed between groups at trend level; participants with MDD gained 2.10 ± 4.83 cm, whereas participants without MDD lost 0.49 ± 5.25 cm ($F_{1,98} = 3.095$, $P = .051$). A similar association was not observed between MDD and change in BMI ($P = .751$). The associations between MDD and CR outcomes were independent of adherence to CR sessions.

Table 3. Coefficients of Unadjusted Regression Models Predicting Cardiac Rehabilitation Noncompletion and Nonadherence

	Coefficients of Predictor Variable					Overall Model	
Condition	B	SE	Wald	Relative Risk (95% CI)	*P* Value	χ^2	*P* Value[a]
Noncompletion							
MDD	.612	.280	4.78	1.85 (1.07–3.19)	.029	4.90	.026
CES-D ≥ 16	.589	.269	4.80	1.80 (1.06–3.05)	.028	4.94	.026
Nonadherence							
MDD	.548	.225	5.90	1.73 (1.11–2.69)	.015	6.05	.014
CES-D ≥ 16	.469	.215	4.75	1.60 (1.05–2.44)	.029	4.83	.028

[a]Two-tailed significance.
Abbreviations: CES-D = Center for Epidemiologic Studies-Depression scale, MDD = major depressive disorder.

Table 4. Coefficients of Adjusted Regression Models Predicting Cardiac Rehabilitation Noncompletion and Nonadherence[a]

Variable	B	SE	Wald	Adjusted Relative Risk (95% CI)	*P* Value[b]
Noncompletion ($\chi^2_6 = 14.35$)					.03
MDD	.920	.325	8.005	2.51 (1.33–4.75)	.005
Age	–.006	.011	0.351	0.99 (0.97–1.02)	.55
Years of education	.014	.041	0.120	1.01 (0.94–1.10)	.73
Use of an ACE inhibitor	.506	.307	0.099	1.66 (0.91–3.03)	.10
Use of a β-blocker	.289	.319	0.821	1.34 (0.72–2.49)	.37
Use of ASA	.882	.608	2.104	2.42 (0.73–7.96)	.15
Nonadherence ($\chi^2_8 = 20.95$)					.007
MDD	.869	.293	8.774	2.38 (1.34–4.23)	.003
Age	–.014	.009	2.521	0.99 (0.97–1.00)	.11
Years of education	.039	.033	1.385	1.04 (0.98–1.11)	.24
Weeks since event	.001	.005	0.074	1.00 (0.99–1.01)	.79
White	–.092	.278	0.111	0.91 (0.53–1.57)	.74
Use of psychosocial support	–.146	.385	0.144	0.86 (0.41–1.84)	.70
Use of an ACE inhibitor	.569	.241	5.556	1.77 (1.10–2.84)	.02
Use of a β-blocker	.088	.254	0.121	1.09 (1.09–1.79)	.73

[a]Models contain all variables found to influence the unadjusted B for major depression by ≥ 10%.
[b]Two-tailed significance.
Abbreviations: ACE = angiotensin-converting enzyme, ASA = acetylsalicylic acid, MDD = major depressive disorder.

Table 5. Cardiac Rehabilitation Outcome Measures Among Completers With and Without MDD

	MDD Diagnosed (n = 20)		MDD Not Diagnosed (n = 83)		*P*
Measure, Mean ± SD	Baseline	Follow-Up	Baseline	Follow-Up	Value[a]
Fitness parameter					
VO_{2Peak}, mL/kg/min	16.8 ± 3.9	20.1 ± 5.1	17.5 ± 5.3	24.1 ± 7.5	.02
Maximum heart rate, bpm	115.3 ± 19.5	116.3 ± 22.4	112.4 ± 22.4	125.6 ± 23.8	.03
Maximum systolic BP, mm Hg	167.5 ± 25.0	167.8 ± 27.9	175.4 ± 23.5	181.7 ± 26.5	.61
Maximum diastolic BP, mm Hg	79.0 ± 10.6	77.1 ± 9.2	78.1 ± 10.4	77.5 ± 11.8	.85
Anthropometrics					
BMI, kg/m^2	26.5 ± 4.6	28.8 ± 8.1	27.0 ± 7.8	27.6 ± 7.0	.75
Body fat, %	27.3 ± 6.4	30.5 ± 8.8	27.2 ± 7.8	26.8 ± 7.6	.009
Waist circumference, cm	94.1 ± 12.8	97.5 ± 11.7	96.8 ± 13.3	96.5 ± 12.5	.05
Psychological					
CES-D score	26.7 ± 9.2	21.7 ± 12.1	6.8 ± 6.4	6.5 ± 6.9	.09

[a]Mean change in measurements from baseline to follow-up between groups diagnosed with and without MDD (2-tailed significance in univariate ANCOVA controlling for the baseline measure, age, and sex).
Abbreviations: ANCOVA = analysis of covariance, BMI = body mass index, BP = blood pressure, bpm = beats per minute, CES-D = Center for Epidemiologic Studies-Depression scale, MDD = major depressive disorder, VO_{2Peak} = peak oxygen uptake.

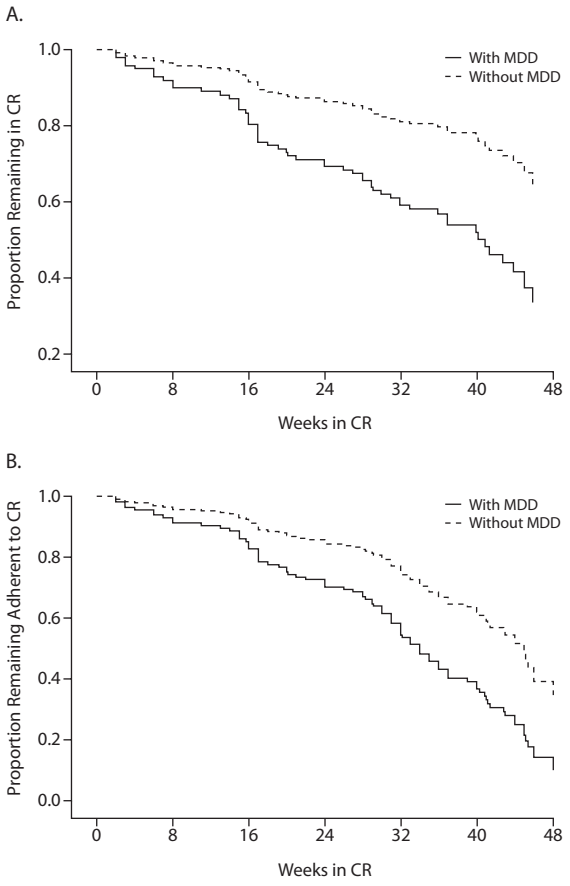
Psychosocial Support Utilization and Outcomes

Treatments for depression initiated over the course of CR are summarized in Table 2. Of the participants who presented with MDD, 34.8% agreed to be referred to a CR staff psychologist. Of participants initially presenting with MDD, 23.3% participated in counseling, group therapy, and/or stress reduction classes, while 9.3% began taking an antidepressant. The use of an antidepressant did not influence the strength of the associations between MDD and noncompletion or nonadherence in the primary analyses. Utilization of psychosocial support warranted inclusion in the model predicting nonadherence; however, its effect was not significant ($P = .70$). The mean ± SD CES-D score of the MDD group decreased by 5.0 ± 10.8, although depressive symptoms remained elevated compared to those not diagnosed with MDD at baseline (mean ± SD CES-D score 21.7 ± 12.1 vs 6.5 ± 6.9, $F_{1,102} = 40.57$, $P < .001$; Table 5). Among participants who did not present with MDD, depressive symptoms remained low after CR ($P = .531$).

DISCUSSION

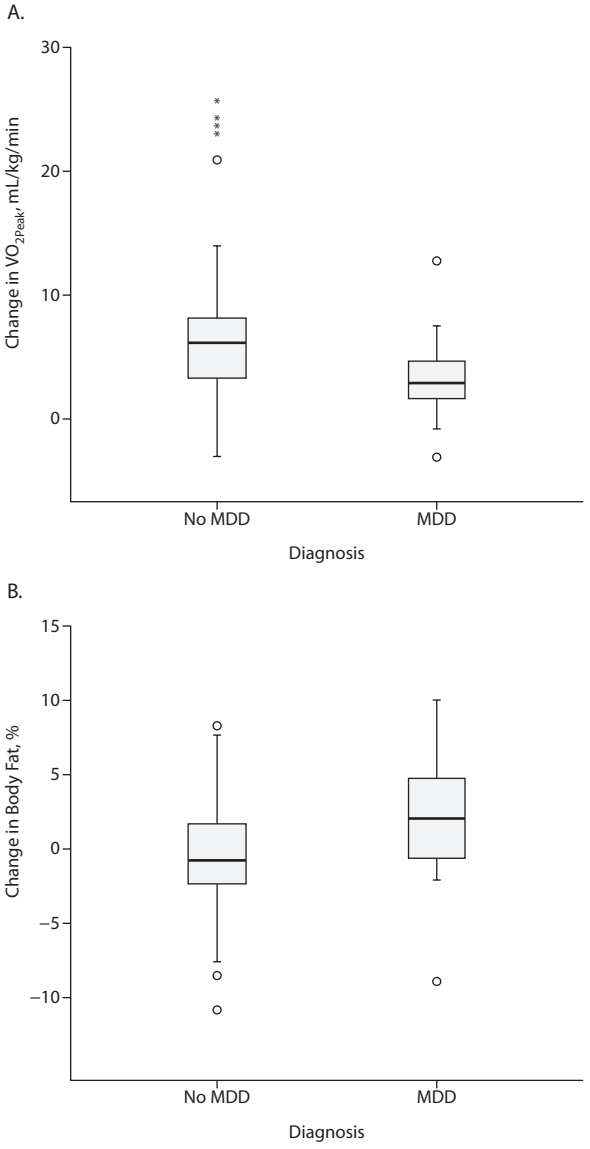
In time-to-event analyses, MDD was associated with HRs of 2.5 and 2.4 for noncompletion and nonadherence, respectively, when controlling for pertinent clinical confounders (Figure 2). Completion of CR has been associated with lower mortality,[8] while adherence to CR over time has been shown necessary for optimal gains in fitness and quality of life.[23] The observed HRs are consistent with associations between screening positive for depression and noncompletion in previous studies.[10–13] In the present study, the HRs for noncompletion and nonadherence were comparable for those diagnosed with MDD using a structured clinical interview and those screened positive for depressive symptoms using the CES-D. The clinical utility of screening instruments can be limited by their specificities and sensitivities to detect psychiatric diagnoses,[24] a common limitation in previous studies of CR compliance.[10–13] Thus, participants with MDD may not have been consistently differentiated from those with minor depression or adjustment disorders, which are common in patients with recent ACS and which may follow different courses and have differential effects on long-term medical prognosis.[25,26] However, the present study qualified that a baseline CES-D

Figure 2. Survival Functions of Participants With and Without MDD Over 48 Weeks of Cardiac Rehabilitation (CR)[a,b]



[a]Time in CR over 48 weeks with values right-censored for noncompleters (A) or for those who had not completed and adhered to at least 70% of CR sessions (B) at the time of their last CR session attendance. [b]Survival patterns shown for participants who presented with (solid lines) and without (dotted lines) MDD.
Abbreviation: MDD = major depressive disorder.

Figure 3. Cardiac Rehabilitation Outcomes in Participants With and Without MDD[a,b,c]



[a]Changes from baseline in VO_{2Peak} (A) and body fat percentage (B) in participants presenting with and without MDD (n = 103). [b]Both changes differ significantly between groups in ANCOVA, controlling for the baseline measure, age, and sex ($P < .05$). [c]Whiskers indicate upper and lower boundaries of the upper and lower quartiles.
Abbreviations: ANCOVA = analysis of covariance, MDD = major depressive disorder, VO_{2Peak} = peak oxygen uptake.
Symbols: ○ = outlier, * = extreme outlier.

score of 16 or greater was of clinical utility comparable to a diagnosis of MDD in predicting noncompletion over 48 weeks.

Poorer cardiopulmonary fitness and body composition outcomes were observed among completers of CR with MDD (Figure 3). In community samples of medically healthy participants, MDD has been associated with poorer VO_{2Peak}.[27] The present study demonstrates that, over time, CR cannot fully mitigate the association of MDD with poorer cardiopulmonary fitness in those with CAD; on the contrary, differences between patients with MDD and those without emerged over the course of CR. Although the mean VO_{2Peak} improved in participants with MDD, as previously observed in participants with depressive symptoms,[9,10,23] less improvement was observed in participants with MDD than in participants without MDD (17.8% vs 37.1%), and this difference was independent of adherence to CR. Smaller changes in VO_{2Peak} over the course of CR are of considerable clinical significance, since they have been shown to predict cardiovascular mortality. In a study by Vanhees et al,[28] a 1% greater increase in VO_{2Peak} was associated with a 2% decrease in cardiovascular mortality.

Divergence in body fat percentages between participants with and without MDD over the course of CR has not been documented in previous reports.[9,10] However, MDD has been associated with higher body fat in community samples,[29] which may reflect neuroendocrine differences, such as lower levels of leptin, an adipose-derived hormone regulating appetite and metabolism.[30] Central adiposity has been associated with elevated levels of inflammatory mediators.[31] The MDD-related differences in body fat percentage

and waist circumference after CR may be of significance to the progression of underlying inflammatory cardiovascular disease processes[32] and possibly to the perpetuation of mood symptoms themselves.[33] Elevated inflammatory markers have been associated with depressive symptoms in this population, and they may also contribute to decreased participation in CR through their association with subjective feelings of failure and fatigue.[33] No differences between participants with and without MDD could be detected in BMI or change in BMI over the course of CR, suggesting that body composition may be more sensitive and meaningful than BMI in participants with MDD, in concordance with current clinical opinion concerning cardiovascular risk.[34]

Despite effective screening for depressive symptoms and the availability of CR psychosocial supports, only 23.3% of patients with MDD accessed resources, and depressive symptoms remained elevated after 48 weeks. Depressive symptoms have often been found to persist over 1 year following an ACS.[35] In this study, CR-based psychosocial supports could not be demonstrated to attenuate the increased risk of noncompletion, possibly due to a low rate of utilization and hence, inadequate statistical power. However, the persistence of depressive symptoms and the observed association between MDD and noncompletion strongly suggest the need for psychosocial intervention. Further research might focus on increasing utilization. The mean age of patients with MDD was 4.6 years younger than those without. Presentation with CAD at a younger age has been associated with higher anxiety and hostility scores,[36] which may have implications for structuring CR-based psychosocial support.

The present study reports a pronounced association between MDD and adverse medical outcomes' interrupting CR. This finding is consistent with other reports of increased medical morbidity and increased recurrence of ACS in CAD patients with elevated depressive symptoms.[3,35] While CR can improve fitness and cardiac risk factors in patients presenting with depressive symptoms,[9,10,36] the present study demonstrates that, in practice, a larger proportion of patients with MDD are unable to benefit fully from CR due to an excessive burden of CAD-related or other medical morbidity. It remains unclear whether depression screening and treatment in the context of CR can impact medical outcomes during CR.[24] However, depressive symptoms leading to poorer compliance with medical management, such as diet and adherence to cardiac medications following an ACS, may contribute to the poorer prognoses here observed to complicate secondary prevention.[14] Further research might explore methods by which psychosocial support could be integrated between primary care physicians, cardiologists, and secondary prevention teams to increase utilization; it has been suggested that the collaborative care model may be appropriate to ensure that patients with CAD receive timely, effective, and consistent support.[37]

This investigation was strengthened by a prospective study design, a comprehensive definition of CR completion and measures of adherence, by the use of *DSM-IV* criteria to diagnose MDD, and by time-sensitive analyses carefully controlling for potential confounders. However, the small number of MDD participants precluded their differentiation in analyses with respect to psychiatric histories. For instance, some MDD participants presented with depressive episodes that predated their coronary events, some began an antidepressant medication prior to entering CR, some began an antidepressant or counseling over the course of CR, and a small minority of nondepressed participants were using an antidepressant at baseline, suggesting depressive diatheses in some nondepressed participants. Although potential confounders did not impact the clinical significance of MDD comorbidity, the study was not powered to detect their specific effects. Also, it is possible that some participants receiving counseling outside of CR did not report this to CR or study staff. As a potential limitation, coronary angiographic data were not available for all participants; however, data from 177 extant reports suggest that CAD severity does not account for the associations between MDD and noncompletion or nonadherence. Although the sample was representative of center database samples on the basis of CES-D scores and completion rates, the possibility that some bias might have been introduced at the level of recruitment cannot be ruled out. Further, all noncompleters and some completers were unavailable for follow-up cardiopulmonary testing, introducing a bias into estimates of CR efficacy; the impact of MDD is very likely to be greater than that observed within this limitation, since a higher proportion of participants with MDD was unavailable to follow-up. Nonetheless, the available sample was sufficient to detect differential responses in cardiopulmonary fitness and body composition between participants with and without MDD. As a further potential limitation, determination of adherence to home exercise prescriptions relied on self-reported exercise diaries, and it may not have accurately reflected offsite exercise frequency and intensity. It should also be considered that the length, intensity, and cost to the consumer of CR programs and associated care vary significantly. In the present study, CR and related care were publicly funded by national health coverage. In spite of whatever advantage intensive, publicly funded care may have afforded these participants, the utilization of psychosocial supports remained low, and MDD remained associated with increased risks of noncompletion and nonadherence.

For participants with CAD, MDD was associated with poorer rates of completion and adherence, increased impact of medical morbidity, and poorer fitness outcomes in CR. Utilization of CR psychosocial resources by participants with MDD was not extensive despite effective screening. Further strategies for comprehensive management or earlier intervention may be required to optimize clinical outcomes for CAD patients with MDD.

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