

DEPRESSION, EXERCISE AND CORONARY HEART DISEASE

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Abstract

Mounting evidence suggests that depression is an important primary and secondary risk factor for coronary heart disease (CHD). Depression is quite common among patients with CHD, with prevalence estimates of 15% or higher, and an additional 20% with subclinical or minor depression. This review describes evidence that depression is a risk factor in patients with established CHD and suggests potential mechanisms underlying the relationship between depression and adverse outcomes. In addition, we summarise evidence for the efficacy of exercise in improving both depression and clinical outcomes and discuss areas for future research in the area.

Introduction

The term 'depression' is often used to refer to an emotional condition ranging from a transient, affective state of sadness or mild dysphoria to a chronic and severe psychiatric illness. The fourth edition of the *Diagnostic and Statistical Manual* lists two depressive disorders: major depressive disorder (MDD) and dysthymic disorder.¹ The criteria for diagnosing MDD are listed in Table 1. The diagnosis requires the presence of at least five symptoms over a period of at least two weeks, which must include either depressed mood or loss of interest or pleasure. Dysthymic disorder is marked by mild depressive symptoms that are more chronic in nature, lasting at least two years. Minor depressive disorder (mDD) is similar to MDD in duration, but only two to four symptoms are present.

Depression is a widespread and often chronic condition. Lifetime prevalence estimates for MDD are approximately 17%,^{2,3} one year prevalence estimates fall between 5% and 10%,^{2,4} and point prevalence estimates range from 4% to 7%.^{3,5} In addition, MDD is marked by high rates of relapse with 22-50% of patients suffering recurrent episodes within six months of recovery.⁶ Women are at approximately two times the risk for MDD with lifetime prevalence rates of 10-25% compared to 5-12% in men.¹ Furthermore, although rates of depression do not increase with age according to most reports, MDD often goes undertreated in older adults⁷ and CHD patients.⁸

Assessment of depression

The gold standard to diagnose MDD is a clinical interview. Commonly used fully structured interviews include the

Table 1. DSM-IV criteria for MDD

A. Five (or more) of the following symptoms have been present during the same two week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

- (1) Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g. feels sad or empty) or observation made by others (e.g. appears tearful). Note: In children and adolescents, can be irritable mood.
- (2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others).
- (3) Significant weight loss when not dieting or weight gain (e.g. a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.
- (4) Insomnia or hypersomnia nearly every day.
- (5) Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
- (6) Fatigue or loss of energy nearly every day
- (7) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
- (8) Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
- (9) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

B. The symptoms do not meet criteria for a mixed episode.

C. The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning.

D. The symptoms are not due to the direct physiological effects of a substance (e.g. a drug of abuse, a medication) or a general medical condition (e.g. hypothyroidism).

E. The symptoms are not better accounted for by bereavement, i.e. after the loss of a loved one, the symptoms persist for longer than two months or are characterised by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms or psychomotor retardation.

Table 2. Studies assessing the effect of depression on outcomes in CAD samples					
Author	N/ # events	Patients	Follow up time	Endpoint (s)	Adjusted relative risk
Carney et al ²³	52 /22 cardiac events	CAD	12 months	Cardiac event	RR=2.2
Frasure-Smith et al ^{25,36}	222/12 deaths	MI	6 months	Cardiac mortality	DIS:HR=4.29
	222/21 deaths		18 months		DIS n.s.; BDI OR=6.64
Frasure-Smith et al ^{37,38}	896/39 deaths	MI	1 year	Cardiac mortality	men OR=3.05; women OR=3.29
	896/155 deaths		5 years		HR: 3.13-3.17
Lane et al ⁴²⁻⁴⁴	288/25 deaths	MI	4 months	Cardiac or all-cause mortality	n.s.
	288/82 deaths		1 year	Cardiac or all-cause mortality	n.s.
	288/31 deaths			CHD events	n.s.
Ahern et al ³⁹	265/N/A	MI	Varying	Mortality; Cardiac arrest	RR=1.38
Jenkinson et al ⁴⁶	1376/247 deaths	MI	3 years	All-cause mortality	n.s.
Ladwig et al ⁴⁷	560/12 deaths; 17 arrhythmic events	MI	6 months	Cardiac death Arrhythmic event	n.s.
Welin et al ⁴⁰	275/167 deaths	MI	10 years	Coronary mortality	RR=3.16
Bush et al ⁴¹	144/17 deaths	MI	4 months	Mortality	RR=3.5
Horsten et al ⁴⁵	292/81 deaths	Acute CHD event (MI or angina)	5 years	Death or cardiac event	RR=1.9
Lesperance et al ²⁸	430/ 16 deaths; 28 events	Unstable angina	1 year	Cardiac death or MI	OR=6.73
Connerney et al ²⁹	309/8 deaths; 42 events	CABG	1 year	Cardiac event; mortality	cardiac events, RR=2.3 ; mortality n.s.; BDI: n.s.
Baker et al ³⁴	158/ 6 deaths	CABG	Median=24 months	Mortality	OR=6.24
Saur et al ⁴⁹	416/ NA	CABG	1 year	Mortality	n.s.
Blumenthal et al ⁵¹	817/122 deaths	CABG	Mean=5.2 years	Mortality	Moderate-severe depression HR=2.84; persistent depression HR=2.33
Burg et al ⁵⁰	89/7 deaths	CABG	2 years	Cardiovascular mortality	OR=23.16

Diagnostic Interview Schedule (DIS)⁹ and the Composite International Diagnostic Interview (CIDI).¹⁰ The Structured Clinical Interview for DSM-IV Disorders (SCID)¹¹ and the

Schedule for Affective Disorders and Schizophrenia (SADS)¹² are commonly used semi-structured interviews.

Several scales have been developed to assess the degree of

severity of depressive symptoms. The Hamilton Rating Scale for Depression (HAM-D)¹³ and the Montgomery-Asberg Depression Rating Scale (MADRS)¹⁴ are scales that are rated by clinicians. There are several paper and pencil self-report questionnaires that assess depressive symptoms such as the Beck Depression Inventory (BDI)¹⁵ and BDI-II,¹⁶ Center for Epidemiological Studies Depression Scale (CES-D),¹⁷ Zung Self-Rating Depression Scale,¹⁸ Minnesota Multiphasic Personality Inventory Depression Scale (MMPI-D),¹⁹ MMPI2-D²⁰ and Symptom Checklist 90-R.²¹

Depression and CHD

We have recently reviewed evidence that depression is a primary risk factor in healthy individuals, and concluded that depression in healthy individuals confers about a 1.5 to 2.0-fold adjusted relative risk for the later developing CHD.²² However, for the purposes of this review, we focus on depression as a secondary risk factor, highlighting the evidence for an association between depression and prognosis for patients with existing CHD.

Preliminary evidence in support of a relationship between depression and CHD has been provided by cross-sectional studies of CHD patients. These studies have documented a higher prevalence of depression in CHD patients than in the general population. Point estimates range from 14% to as high as 47%, with higher rates recorded most often in patients with unstable angina or in patients awaiting coronary artery bypass graft (CABG) surgery.²³⁻³⁵ When DSM criteria are used to establish diagnosis, prevalence estimates are lower at 15-20%.^{23,25,26,29,31}

In addition to cross-sectional studies, several prospective studies have been conducted. Patients with CHD are assessed for depression and followed over time to assess the extent to which depression predicts clinical outcomes over and above any association with other CHD risk factors such as disease severity or demographic risk factors. Such studies have been conducted in several CHD populations including patients with stable CHD, patients recovering from acute myocardial infarction (AMI), and patients awaiting CABG surgery. Table 2 contains a summary of these studies, particularly those that have utilised objective clinical endpoints like AMI or mortality.

A number of studies have assessed the relationship between depression and CHD outcomes in patients hospitalised for AMI. Although there have been some null findings, most have reported large effect sizes, suggesting that the presence of depression confers about 2.5 times the risk for mortality or non-fatal cardiac events.^{25,36-47} For example, Frasure-Smith et al³⁷ followed 896 patients with a recent AMI for one year. The presence of elevated depressive symptoms on the BDI was a significant predictor of cardiac mortality after controlling for other multivariate predictors of mortality (odds ratio [OR]=3.29 for women; 3.05 for men).

Studies of patients with stable CHD have also reported a consistent significant association of depression and clinical

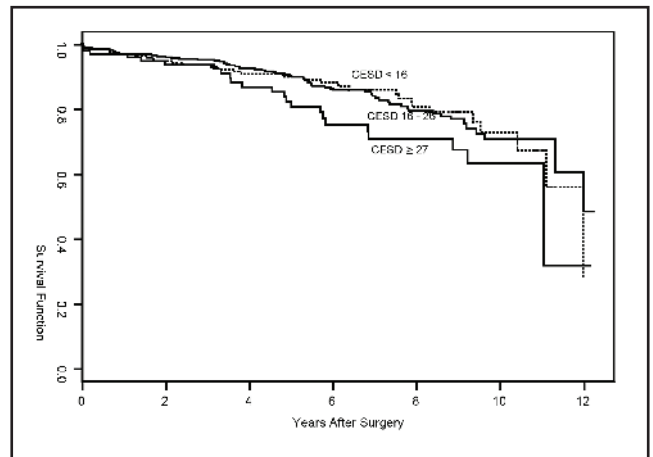


Figure 1. Kaplan-Meier survival curves for all-cause mortality among three categories of pre-surgery (baseline) depressive symptoms. Compared to the absence of depressive symptoms, the presence of moderate-to-severe symptoms was associated with a relative hazard of 2.4 (95% CI=1.40-4.00, p=0.001). The risk for mild symptoms was not different from the absence of symptoms (HR=1.08, 95% CI=0.70-1.67, p=0.723). Reprinted with permission from Elsevier, *The Lancet* 2003; 362 (9384): 604-9.

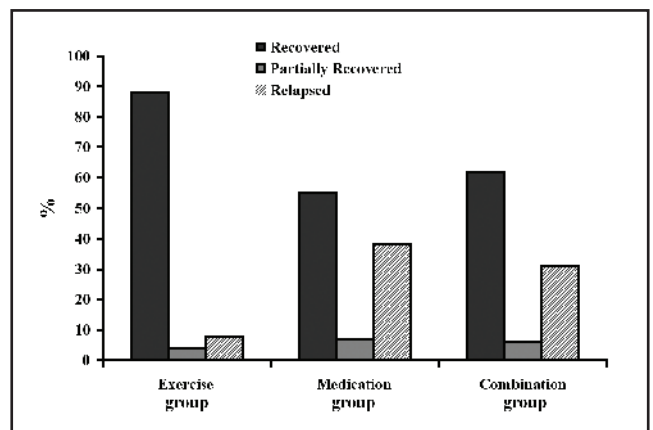


Figure 2. Clinical status at 10 months (6 months after treatment) among patients who were remitted (n=83) after four months of treatment in exercise (n=25), medication (n=29) and combination (n=29) groups. Compared with participants in the other conditions, those in the exercise condition were more likely to be partially or fully recovered and were less likely to have relapsed. Reprinted with permission from Lippincott Williams & Wilkins, Babyak M, Blumenthal JA, Herman S, Khatri P, Doraiswamy M, Moore K et al. Exercise treatment for major depression: maintenance of therapeutic benefit at 10 months *Psychosomatic Medicine* 2000; 62 (5): 633-8.

outcomes. For example, Barefoot et al⁴⁸ assessed 1,250 patients with documented CHD using the Zung Self-Report Depression Scale at the time of diagnostic coronary angiography and followed patients for up to 19.4 years. Results showed that patients with moderate to severe depression were at 69% greater risk for cardiac death and 78% greater risk for all-cause death.⁴⁸

More recently, prospective studies have been conducted to

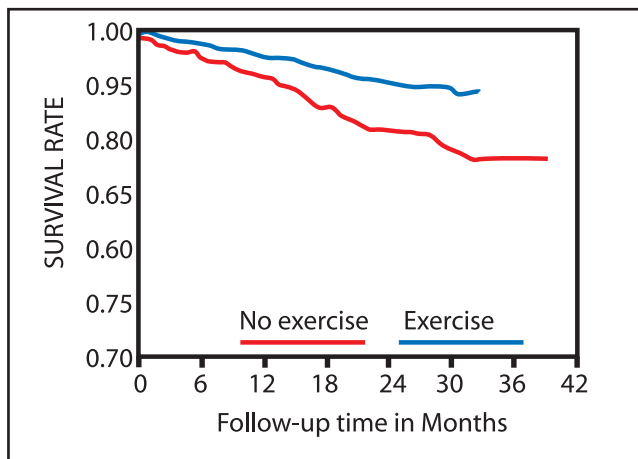


Figure 3. The predicted survival functions for patients who exercised regularly during the 6 months following the index MI (n=952) compared with those who did not exercise (n=1096). There was a total of 187 fatal events; 5.6% of the deaths occurred in exercisers compared with 12.95% of non-exercisers. *Reprinted with permission from Lippincott Williams & Wilkins. Blumenthal JA et al. Exercise, Depression, and Mortality after Myocardial Infarction in the ENRICHD Trial. Medicine and Science in Sports and Exercise May 2004; 36 (5): 746-754.*

assess the effect of depression on prognosis after CABG surgery.^{29,34,49-51} Blumenthal et al⁵¹ assessed the effect of depression on mortality after CABG surgery in 817 patients followed for up to 12 years (mean=5.2 years). On the day prior to surgery, the CES-D¹⁷ was used to categorise patients as having no depression (CES-D<16), mild depression (CES-D=16-26) or moderate to severe depression (CES-D≥27). Results indicated that moderate to severe depression was independently associated with a two to three-fold increased risk of mortality even after statistically controlling for age, gender, number of grafts, diabetes, smoking, left ventricular ejection fraction and history of AMI. Figure 1 depicts the unadjusted Kaplan-Meier survival curves for patients with no depression, mild depression and moderate to severe depression.

Biobehavioural mechanisms linking depression and CHD

A number of biobehavioural mechanisms have been hypothesised to underlie the relationship between depression and CHD, many of which may be targeted by exercise treatments. Thus far, most evidence for mechanisms comes from cross-sectional studies, and prospective studies that track depression, the hypothesised mechanism and CHD outcomes over time are needed to provide more conclusive support.

Nonetheless, there is evidence that depression is associated with traditional risk factors for CHD such as hypertension, diabetes and insulin resistance,^{52,53} as well as changes in platelet reactivity,⁵⁴ dysregulation of the autonomic nervous system⁵⁵ and hypothalamic pituitary adrenal axis,⁵⁶ and alterations in the immune response/inflammation.⁵⁷ Depression is also associated with behavioural factors that are in turn associated

with CHD risk, such as treatment adherence,⁵⁸ smoking,⁵⁹ heavy alcohol use and physical inactivity.⁶⁰

Treatment studies with depressed cardiac patients

Successful treatments for depression in CHD patients may have the potential to improve not only quality of life but also cardiovascular and physical health. Several treatments for depression exist for use in the general population, such as antidepressant medication or psychotherapy.⁶¹ However, there have only been two studies that have tested the efficacy of these treatments in CHD patients: SADHART was a safety and efficacy trial of antidepressant medication,⁶² while ENRICHD was a survival trial of psychosocial treatment.⁶³ The SADHART trial showed only modest differences between treated patients and placebo controls, and lacked adequate statistical power to examine the impact of treatment on hard clinical endpoints.

In contrast, the ENRICHD trial enrolled more than 2,400 patients but failed to demonstrate that treating depression and low social support was associated with increased survival compared to controls. Therefore, there is a need to identify effective treatments for depression that may also impact clinical outcome.

Exercise as a treatment for depression

There is growing evidence that exercise may be an effective treatment for depression.^{64,65} Most of the existing studies of exercise as a treatment for depression have focused on aerobic exercise. In one of the larger studies in this area,⁶⁶ 156 depressed adult patients with MDD were randomised to four months of treatment with supervised aerobic exercise, antidepressant medication (sertraline), or a combination of exercise and medication. Although antidepressant medication was associated with faster reductions in depression in the first four weeks of treatment, exercise was as effective as antidepressant medication in treating depression by the end of the 16 week intervention. Dropout rates also were similar in the exercise and medication conditions.⁶⁷ Moreover, as is shown in Figure 2, six month follow up of participants revealed that those who continued to exercise were half as likely to relapse.⁶⁸

Exercise generally is considered safe for most patients with stable CHD.^{69,70} Some studies of exercise treatments for CHD patients have tracked depressive symptoms and thus have provided some insight into the potential efficacy of exercise as a treatment for depression in this population.⁷¹⁻⁷⁹ Although most of the studies in the area have reported significant improvements in depression after completion of an exercise programme, many have had important methodological limitations including the failure to include a control group. In one of the few controlled studies in this area, Stern et al⁷⁹ randomised 106 male patients with a recent AMI and elevated depression, anxiety or low fitness to 12 weeks of exercise training, group therapy or a usual care control group. At one year follow up, both the counselling and the exercise group showed improvements in depression relative to controls.

Effect of exercise on CHD risk factors and outcomes

Exercise is a particularly promising intervention for depression in CHD patients because it has well documented cardiovascular benefits. In addition to its well-established role in primary prevention,⁸⁰⁻⁸⁴ exercise interventions have been shown to improve outcomes for patients with CHD.^{85,87} Most recently, Jolliffe et al⁸⁷ conducted a meta-analysis comparing exercise-only interventions, comprehensive rehabilitation (which includes educational and behavioural components such as dietary changes and stress reduction in addition to exercise) and usual care. Exercise-only interventions were associated with a decrease in both all-cause and cardiac mortality. Comprehensive rehabilitation, on the other hand, was not associated with statistically significant reductions in all-cause mortality, but was associated with a decreased risk for cardiac mortality, to a slightly lesser extent than exercise-only interventions.

Recent data from the ENRICHD trial suggest that exercise may reduce the rates of mortality and non-fatal reinfarction in patients with depression or in socially isolated post-MI patients.⁸⁸ Self-report data were used to categorise participants as exercising regularly or not exercising regularly. After controlling for medical and demographic variables, the magnitude of reduction in risk associated with regular exercise was nearly 40% for non-fatal reinfarction and 30% for mortality. Figure 3 depicts the Kaplan-Meier survival curves for patients who exercised regularly and for those who did not. The evidence that exercise affects depression, CHD risk factors

and CHD outcomes suggests that exercise is a particularly promising intervention for depression in this population.

Conclusions

Although depression has emerged as an important risk factor for CHD, there is no consensus on the optimal way to treat depression in CHD patients.⁸⁹ Interventions guided by an understanding of the mechanisms linking depression and CHD may prove to be the most effective in improving both depression and physical health outcomes. Exercise targets many of the mechanisms for which there is growing evidence, including autonomic nervous system and hypothalamic pituitary adrenal axis functioning, hypertension, insulin resistance and inflammation.⁹⁰⁻⁹³ Of equal importance, a growing body of evidence suggests that exercise is an effective treatment for depression, comparable in its effect to antidepressant medication.

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