Depression and coronary heart disease

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Abstract | Depression is a highly prevalent risk factor for incident coronary heart disease (CHD) and for cardiovascular morbidity and mortality in patients with established CHD. Several biological and behavioural mechanisms have been hypothesized to underlie the relationship between depression and CHD, but none has been shown to account for more than a small proportion of the risk. Only a few clinical trials have examined whether treating depression decreases the risk of cardiac events in patients with established CHD. None of these trials has shown that treatment results in improved cardiac outcomes, but the differences in depression outcomes between the intervention and control groups have been small and not clinically significant. Nevertheless, secondary analyses of these trials suggest that prognosis improves when depression improves. Concerted efforts to develop more potent interventions for depression, identification of high-risk subtypes of depression, and further research on the biobehavioural mechanisms linking depression to CHD are needed to pave the way for definitive clinical trials.

Sir William Harvey observed over 350 years ago that negative emotions adversely affect the heart[1], but scant scientific evidence was available to support this claim until the 1930s, when two longitudinal studies of psychiatric patients found that depression might be a risk factor for early death, especially death owing to cardiovascular disease[2,3]. These observations were largely ignored until the late 1980s when interest in the role of depression in coronary heart disease (CHD) surged. Most of the studies during this period focused not on psychiatric patients with depression, but on clinically depressed patients with established CHD[4–7] or on community-dwelling populations at risk of CHD[8,9].

Since then, hundreds of studies from around the world have evaluated depression as a risk factor for incident CHD or for cardiovascular morbidity and mortality in patients with established CHD. Researchers have also investigated the relevance of other psychiatric disorders in relation to heart disease[10–13], but these disorders are beyond the scope of this article. In this Review, we consider the evidence for depression as a cardiac risk factor and summarize the research that has been conducted on selected biological and behavioural mechanisms that might link depression to CHD. We also consider whether treatment of depression can prevent cardiac morbidity and mortality in patients with CHD.

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Defining and measuring depression

Efforts to develop a biological test for major depression are ongoing[14], but structured clinical interviews are still the only well-validated method for its diagnosis. In some studies, however, cut-off scores on symptom questionnaires are used to define 'clinically significant' depression. Many, but not all, individuals who are classified as having clinically significant depression also meet the standard criteria for major depression, and *vice versa*. Despite efforts to promote specific instruments to assess depression in studies of patients with cardiac disease in order to facilitate the comparison of these studies[15], many different interviews and questionnaires have been used in this area of research. This variation can make comparing studies and interpreting divergent findings difficult.

The criteria for a major depressive episode, as outlined in the latest edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)[16], require the presence of depressed mood or loss of interest or pleasure in daily activities (anhedonia) nearly every day for ≥2 weeks. In addition, five or more of the following symptoms must be present nearly every day: depressed or irritable mood, loss of interest, significant change in weight or appetite (increase or decrease), change in sleep (insomnia or hypersomnia), change in activity level (psychomotor agitation or retardation), fatigue, poor concentration, excessive feelings of guilt or worthlessness, and thoughts of death or suicide[16]. The symptoms cannot be caused by the direct physiological effects of a drug or a medical condition, and they must cause substantial distress or impairment.

Some of the most widely-used depression questionnaires include symptoms that were omitted from the DSM criteria, such as feelings of hopelessness, helplessness, and social isolation. Both DSM and non-DSM symptoms count when questionnaires are used to identify

Key points

- Depression is prevalent in the general population, and even more common among patients with coronary heart disease (CHD)
- Depression is a risk factor for incident CHD, and for cardiovascular morbidity and mortality in patients with established CHD
- Potential biological and behavioural mechanisms for this risk have been identified, but no single factor has been shown to account for more than a fraction of the total risk
- Very few clinical trials have been conducted to determine whether treating depression decreases the risk of cardiac events in patients with established CHD
- Each of the trials has substantial shortcomings, and more trials are needed
- Effective treatments for depression, identification of 'high-risk' depression subtypes, and an improved understanding of the biobehavioural pathways linking depression to cardiac morbidity and mortality are needed

clinically significant depression. Evidence exists for a dose–response relationship between depression severity and cardiac risk, such that the presence of even a few mild symptoms carries some risk[17,18]. However, patients with only a few symptoms of depression might be categorized as 'nondepressed' according to the scoring rules of widely used depression questionnaires. Consequently, artificial categorization of depression severity scores (for example, 'nondepressed' versus 'depressed') might attenuate the strength of the association between depression measures and cardiac outcomes.

Depression screening. A number of depression screening instruments have been recommended for patients with CHD[15]. Two of the most popular and easiest to use are the Patient Health Questionnaire (PHQ)-2 and the PHQ-9 (REFS 19,20). The PHQ-2 is a two-item questionnaire that screens for depressed mood and loss of interest — the two cardinal symptoms of major depression. The PHQ-9 includes these two cardinal symptoms along with the other seven DSM-5 criterion symptoms of major depression. In some studies, the PHQ-9 has been used only with those patients with a positive PHQ-2. In other studies, this two-step screening process has been replaced by single use of the PHQ-9. Both forms of the PHQ are sensitive and fairly specific for major depression as well as for clinically significant depression in patients with cardiac disease[21]. However, a diagnostic interview is advised before beginning treatment to confirm a diagnosis of major depression and rule out other psychiatric disorders.

Depression and incident CHD

More than 100 studies and at least six meta-analyses of depression as a risk factor for incident heart disease in individuals without evidence of CHD at baseline have been published. Two limitations have made conducting meta-analyses of these studies difficult. First, the populations have varied widely between studies. Some studies have focused on elderly people, on men or women only, on community residents, ethnic groups, or on specific medical populations (such as patients with hypertension)[22–27]. Second, many different diagnostic interviews and questionnaires have been used to assess and define depression in these studies.

Another challenge in this area of research is that depression is associated with several other cardiac risk factors, including smoking, diabetes mellitus, sedentary lifestyle, and obesity[28]. These relationships can make it difficult to determine whether depression is an independent risk factor. Although including these other risk factors as covariates in predictive models is possible, some of them might mediate rather than confound the association between depression and CHD. For example, if depression leads to a sedentary lifestyle, which in turn leads to the early development of atherosclerosis, covariate adjustment for sedentary lifestyle would be inappropriate because this covariate would be on the causal pathway between depression and CHD.

Six meta-analyses of this literature have been published[29–34] (TABLE 1). Various differences exist between these studies, including the study selection criteria. Nevertheless, all six meta-analyses reported a significant relationship between depression and incident CHD. Five studies reported a large (60% to 80%) increased risk of CHD associated with depression[29–33], and one found a more modest (30%) increased risk[34].

Some of the studies that were included in these meta-analyses, especially those with small sample sizes, adjusted for only a few potential confounders, and others did not adjust for any. The risks attributable to depression tend to be reduced, but not eliminated, in the covariate-adjusted models compared with the univariate models. Nicholson and colleagues identified 11 studies that reported both unadjusted and adjusted risk estimates for depression[30]. These investigators found a 12% lower risk of CHD in an adjusted compared with an unadjusted risk estimate, suggesting that some confounding by other cardiac risk factors existed[28]. Nevertheless, the adjusted risk was still considerable. Similarly, Gan and colleagues found that studies that adjusted for established cardiac risk factors, including smoking, BMI, hypertension, diabetes, physical activity, and socioeconomic status, did not greatly influence the risk estimates for depression that included studies without adjustment for these covariates[34]. In one of the larger studies of depression and cardiovascular mortality, after adjusting for nearly all the major cardiac risk factors, including age, smoking, sex, systolic blood pressure, BMI, diabetes, social class, heavy alcohol use, and antidepressant medications, Surtees and colleagues found a 2.7-fold increased risk of cardiac death in patients with depression over a median follow-up period of 8 years[35]. Thus, although depression is associated with other cardiac risk factors, the evidence suggests that depression is an independent risk factor for incident CHD. However, residual confounding must be considered as a possible explanation for at least part of the association, because no study has adjusted for all known potential confounders, and because unknown confounders might exist.

Publication bias can lead to inflated meta-analytical risk estimates. Gan and colleagues conducted a sensitivity analysis by use of the trim-and-fill method to correct for potential publication bias in their meta-analysis, but this adjustment had little effect on the

risk estimates[34]. No evidence indicates that publication bias explains the documented effect of depression on incident CHD.

Three of the meta-analyses found that studies based on clinical diagnoses of depression reported higher risk estimates than studies based on depression symptom questionnaires[30–32]. By contrast, one meta-analysis found no difference between the two methods[29], and one found that clinical diagnoses were associated with lower risk estimates than symptom questionnaires[34]. Although patients with major depression tend to have more severe depression than those patients classified as 'clinically depressed' on symptom questionnaires, patients with major depression might also be more likely to receive treatment, which can attenuate the risks associated with major depression in some studies. Also, the composition of the 'nondepressed' comparison groups might differ between studies of major depression and studies of clinically significant depression. Comparison groups in studies of major depression often include patients with mild or subthreshold depression, which can make detecting an effect of depression more difficult, because the presence of even a few symptoms of depression increases the risk of cardiac events[17,18]. Nevertheless, the results of these meta-analyses suggest that clinically significant depression, whether defined by questionnaire scores or interview-based diagnoses of major depression, increases the risk of developing CHD.

These meta-analyses were limited by significant heterogeneity of the risk estimates. The estimates have varied between studies as a result of differences in the definition and assessment of depression, the populations, the length of follow-up, and the definition of incident CHD. In addition, depression was assessed only once in most of the studies[32], despite the knowledge that depression can follow a variety of course patterns. Depression can remit and never recur, remit and recur one or more times, or become chronic with or without a fluctuating pattern of severity. Consequently, repeated measures would provide more-valid estimates of exposure to depression than a single assessment, and would make it possible to determine how much exposure to depression is needed to increase the risk of developing CHD.

Table 1 | **Depression as a risk factor for incident CHD**

Meta-analysis	Number of studies	Number of participants	Odds ratio or relative risk (95% CI) of CHD
Rugulies (2002)[31]	11	36,549	1.64 (1.29–2.08)
Cuijpers & Smit (2002)[29]	25	106,628	1.81 (1.58–2.07)
Wulsin & Singal (2003)[33]	10	NR	1.64 (1.41–1.90)
Nicholson *et al.* (2006)[30]	21	124,509	1.81 (1.53–2.15)
	11*	NR	• 2.08 (1.69–2.55) unadjusted • 1.90 (1.48–2.42) adjusted
Van der Kooy *et al.* (2007)[32]	16‡	659,991	1.57 (1.36–1.81)
Gan *et al.* (2014)[34]	30	893,850	1.30 (1.22–1.40)

CHD, coronary heart disease. *Studies that included unadjusted and adjusted analyses. ‡Includes only those studies of participants without CHD at baseline.

Most of the literature in this area has focused on adults, but evidence also exists that depressed children can be at risk of developing early atherosclerosis. A 2015 scientific statement from the AHA concluded that major depressive disorder and bipolar disorder in children and adolescents are associated with a moderate risk of accelerated atherosclerosis and early cardiovascular disease, independent of traditional CVD risk factors[36].

Depression and established CHD

Prevalence of depression in patients with CHD. Numerous studies have reported the prevalence of major depression or clinically significant depression in patients with established CHD[28]. In a comprehensive review of the literature, Thombs and colleagues identified eight studies with a total of 10,785 patients with a recent acute myocardial infarction (MI) that used a structured clinical interview to diagnose major depression[37]. Major depression was present in 19.8% (95% CI 19.1–20.6%) of these patients. To estimate the proportion of patients with previous MI and clinically significant depression symptoms, the investigators analysed studies that used the Beck Depression Inventory (BDI), a widely used questionnaire. The analysis showed that 31.1% (95% CI 29.2–33.0%) of these patients had clinically significant depression (defined as a BDI score >10)[37]. An estimated 15–18% of patients with medically stable CHD have major depression, and the 1-year prevalence of clinically significant depression is about 30% in these patients[28]. By comparison, the National Comorbidity Study[38] estimated the point prevalence of major depression in the general population to be about 5%.

Depression as a risk factor in established CHD. More than 200 studies have evaluated depression as a risk factor for cardiac events in patients with established CHD. Between 2004 and 2013, five meta-analyses of this literature were published[30,39–42] (TABLE 2). Three meta-analyses evaluated studies of depression as a risk factor for all-cause or cardiac-related mortality after an acute MI or acute coronary syndrome (ACS)[39–41], and two included both post-MI and post-ACS studies as well as studies of patients undergoing revascularization or cardiac catheterization and angiography[30,42]. All the meta-analyses found that depression was predictive of all-cause mortality, cardiac-related mortality, and/or a combined end point of all-cause mortality and cardiac morbidity.

The largest meta-analysis comparing patients with or without depression after an MI included 29 studies[40]. Depression was associated with a 2.7-fold increased risk of cardiac-related death, a 2.3-fold increased risk of all-cause death, and a 1.6-fold increased risk of cardiovascular events in the 2 years after an acute MI[40].

An individual patient-level meta-analysis by the same group examined depression severity scores as a continuous variable instead of classifying patients as depressed or nondepressed[39]. The hazard ratios and odds ratios in this report represent one standard deviation of the mean depression score. For the three studies that included data

for all the covariates, the analysis found an unadjusted hazard ratio of 1.33 (95% CI 1.23–1.44, $P<0.001$) per standard deviation, and 1.23 (95% CI 1.15–1.31, $P<0.001$) after adjusting for age, sex, history of MI, left ventricular ejection fraction, Killip class, smoking, diabetes, and BMI[39]. For the five studies that did not have time-to-event data, the odds ratio adjusted for age and sex was 1.41 (95% CI 1.34–1.49, $P<0.001$) per standard deviation[39].

As in studies of depression as a risk factor for incident CHD, the potential for residual confounding is a concern in studies of depression in established CHD. Although efforts were made to adjust for major cardiac risk factors in many of these studies, none adjusted for every possible risk factor. Because the risk associated with depression usually decreases after adjustment for potential confounders[30], some researchers have speculated that some of the depression symptoms that are present in patients with heart disease might be expressions of severe heart disease rather than of a comorbid depressive disorder. These researchers further speculate that depression predicts worse outcomes, because patients with depression have worse heart disease than patients without depression-like symptoms. This speculation is essentially a reverse causality hypothesis, but the observation that the risks associated with depression continue to be significant after adjustment for multiple indices of CHD severity[5,43] casts doubt on it. Nevertheless, severe heart disease increasing the risk or severity of comorbid depression does seem plausible. This situation has led some researchers to argue that the relationship between depression and CHD is bidirectional[44], and this model does seem to fit the findings. However, this hypothesis poses some additional challenges for understanding this common form of comorbidity. In addition to providing careful attention to potential confounding, long-term studies are needed to track the interrelationships over time between CHD, mood, depression, and psychosocial functioning.

Recognizing how difficult it can be to adjust for multiple cardiac risk factors, especially in smaller studies in which statistical overfitting is a concern[45], two research teams chose instead to use the Global Registry of Acute Coronary Events (GRACE) score to evaluate the independent effect of depression on recurrent cardiac events after an ACS[46,47]. The GRACE score was developed to estimate the risk of death in patients with a recent ACS[48]. This score is highly predictive of cardiac outcomes even 5 years after a cardiac event[49]. Adjustment for the GRACE score reduced the estimated risk, but depression was still an independent predictor of all-cause mortality[46] and of a composite index of fatal and nonfatal cardiac events[47]. The GRACE score, and perhaps other validated prediction models, might offer a useful alternative to adjusting for the large number of risk factors that could be considered as confounders in a study of depression as a risk factor for cardiac mortality after ACS.

A scientific advisory statement from the AHA published in 2014 critically reviewed the evidence for depression as a risk factor for morbidity and mortality after an ACS[50]. A total of 53 studies met the review panel's criteria for study quality. The statement concluded that "despite the heterogeneity of published studies included in this review, the preponderance of evidence supports the recommendation that the American Heart Association should elevate depression to the status of a risk factor for adverse medical outcomes in patients with acute coronary syndrome" (REF. 50). Nevertheless, until the biobehavioural mechanisms by which depression affects the course and outcome of heart disease have been identified, and until treating depression has been shown to improve cardiac outcomes, the question of whether depression is a causal risk factor for cardiac events or merely an epiphenomenon will remain controversial.

Biobehavioural mechanisms

This section provides a brief overview of some of the potential mechanisms that have been proposed to explain the relationship between depression and CHD[51–54] (FIG. 1). For a more comprehensive evaluation of the literature on these and other potential mechanisms, see the Review published previously in this journal[55].

Since the 1970s, studies of psychiatric patients with depression have shown evidence of dysregulation of the

Table 2 | **Depression as a predictor of morbidity or mortality in patients with CHD**

Meta-analysis	Number of studies	Number of participants	Outcomes	Odds ratio or relative risk (95% CI) of CHD	*P* value
Van Melle *et al.* (2004)[41]	16	6,367	All-cause mortality	2.38 (1.76–3.22)	<0.00001
			Cardiac mortality	2.59 (1.77–3.77)	<0.00001
			Cardiovascular events	1.95 (1.33–2.85)	<0.0006
Barth *et al.* (2004)[42]	20*	NR	All-cause mortality	2.24 (1.37–3.60)	NR
Nicholson *et al.* (2006)[30]	34	17,842	All-cause mortality	1.80 (1.50–2.15)	<0.00001
Meijer *et al.* (2011)[40]	29	16,889	All-cause mortality	2.25 (1.73–2.93)	<0.001
			Cardiac mortality	2.71 (1.68–4.36)	<0.001
			Cardiovascular events	1.59 (1.37–1.85)	<0.001
Meijer *et al.* (2013)[39]	3‡	10,175	All-cause mortality	1.33 (1.23–1.44)§	<0.001
			Cardiovascular events	1.19 (1.14–1.24)	<0.001

*Includes five studies of patients with documented CHD, but no recent myocardial infarction. ‡Data from studies included in the 2011 meta-analysis, but combined into one database. §Hazard ratios indicate increased risk per standard deviation above the mean depression score.

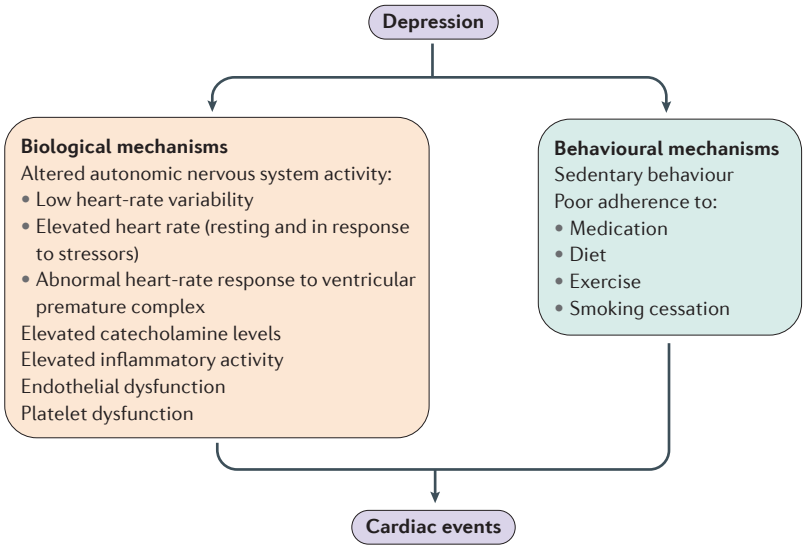

Figure 1 | **Potential mechanisms linking depression and coronary heart disease.** Several biological and behavioural mechanisms linking depression and adverse cardiac outcomes have been hypothesized.

autonomic nervous system including higher levels of plasma and urinary catecholamines and higher resting heart rates compared with control individuals without depression[56–59]. Veith and colleagues showed that elevated circulating levels of plasma catecholamines were caused by systemic increases in sympathetic activity in these patients[60]. Other studies found elevated cortisol levels or that dexamethasone did not suppress the rising morning levels of cortisol[61,62]. The potential effect of altered autonomic nervous system or hypothalamic–pituitary–adrenal axis functioning on cardiac outcomes in patients with CHD and depression was clear, leading to studies in patients with CHD and depression.

Cardiac autonomic dysfunction. Studies of patients with CHD and depression have found many indications of cardiovascular dysregulation, including elevated 24-h and resting heart rates[52,63–65], increased heart-rate responses to physical stressors[66], reduced heart-rate variability (HRV) and decreased baroreceptor sensitivity[52,65,67–69], increased QT variability reflecting abnormal ventricular repolarization[70], and heart-rate turbulence (that is, abnormal heart rate responses to ventricular arrhythmias)[71]. All these indicators have been associated with an elevated mortality and cardiac morbidity, especially in vulnerable populations such as patients with previous MI[72].

Measures of HRV are widely used to study cardiac autonomic activity in humans[73]. Beat-to-beat variability in the heart's rhythm is determined primarily by autonomic nervous system modulation of the intrinsic cardiac pacemakers. HRV reflects the balance between sympathetic and parasympathetic regulation of heart rate, with low HRV reflecting inadequate cardiac parasympathetic and/or excessive cardiac sympathetic modulation[73]. Low HRV is a strong predictor of mortality in patients with a recent MI[74–77], and of morbidity and mortality even in patients with stable CHD[78].

Most studies of patients with CHD have found lower HRV and higher heart rate in those patients with depression compared with those without depression[52,65–67,79,80]. One exception, however, found no association between HRV and high scores on a depression questionnaire in patients with stable CHD[81]. However, a secondary analysis of these data found that somatic (for example, insomnia) but not cognitive (for example, sense of guilt) symptoms of depression were associated with lower HRV[82]. This observation raises the possibility that low HRV might be more common in some subtypes of depression than in others.

In an attempt to determine whether low HRV accounts for the effect of depression on mortality, we studied 311 patients with depression and a recent acute MI who were enrolled in the ENRICHD clinical trial[83], and 367 patients who met the ENRICHD medical inclusion criteria but who were not depressed[84]. Very low frequency power (VLF; 0.0033–0.04 Hz) was selected as the primary index of HRV for this study because of the prognostic importance of this index in patients with previous MI[74,75]. Although the physiological determinants of HRV are not completely understood, VLF is unaffected by β-blockade, but greatly reduced by atropine, suggesting that the parasympathetic nervous system is an important determinant[85]. VLF was significantly lower in patients with depression compared with patients who were non-depressed[84]. During a median follow-up of 24 months, a total of 47 deaths occurred (6.1% of the cohort). The patients with depression were found to be at higher risk of all-cause death, even after adjusting for potential confounders (HR 2.8, 95% CI 1.4–5.4, $P<0.003$)[84]. When VLF was entered into the model, the hazard ratio for depression dropped to 2.1 (95% CI 1.1–4.2, $P=0.03$), indicating that VLF accounted for about one-quarter of the overall mortality. When a measure of the heart's response to premature ventricular contraction (heart-rate turbulence) was added to the model, the adjusted hazard ratio decreased to 1.6 (95% CI 0.8–3.4, $P=0.18$)[71]. Thus, the combination of VLF and heart-rate turbulence explained nearly half of the effect of depression on survival in these patients. These results do not prove that a causal connection between depression, autonomic nervous system dysfunction, and mortality after acute MI exists, but these findings are consistent with this possibility.

Conversely, Whooley and colleagues found that adding VLF to their model did not reduce the effect of depression on cardiac events in a sample of medically stable patients with CHD[86]. Their previous study showed that somatic, but not cognitive, symptoms of depression were associated with low HRV[81], but their subsequent study examined only the relationship between VLF and a depression scale score that counted both cognitive and somatic symptoms.

Inflammation. Inflammatory processes have been associated with the progression of coronary artery disease and with cardiac events, including MI. Depression is associated with elevated levels of inflammatory biomarkers, including proinflammatory cytokines, acute

phase proteins, chemokines, and adhesions molecules[87]. Meta-analyses have found increased levels of C-reactive protein (CRP) and interleukin-6 (IL-6) to be associated with depression[88]. These markers have also been found to be elevated in patients with depression and comorbid CHD[88–90]. Another meta-analysis showed that levels of tumour necrosis factor are increased in major depression[91]. All three of these markers are associated with an increased risk of cardiac events in patients with established CHD[92–96]. Evidence also indicates that the relationship between inflammation and depression might be bidirectional[97,98], so that inflammation might lead to symptoms of depression, and depression might be proinflammatory.

Several studies have investigated the extent to which inflammation mediates the association between depression and the risk of incident CHD. Although most studies found that CRP, IL-6, and soluble intercellular adhesion molecule 1 tend to be elevated in patients with depression, these inflammatory markers explained ≤20% of the estimated risk[99–104]. Thus, although inflammation might contribute to the effect of depression on incident CHD, this mechanism accounts for a fairly small part of the total effect.

Little evidence indicates that inflammation accounts for much of the morbidity and mortality associated with depression in patients with established CHD. Whooley and colleagues found that CRP reduced the effect of depression on cardiac events by 11.3% in their adjusted model in a follow-up of 1,017 outpatients with stable CHD[86]. Two studies of patients with previous MI also found no evidence of higher levels of inflammatory markers in patients with depression compared with those who were nondepressed[105,106]. These data suggest that inflammation assessed shortly after an acute MI might not explain the effect of depression on cardiac outcomes. However, as more markers of inflammation are studied in patients with depression and CHD, including the activity of anti-inflammatory cytokines, inflammation might turn out to have a more prominent role in the link between depression and cardiac outcomes.

Levels of inflammatory markers are not elevated in everyone with depression[98,107]. For example, the relationship between inflammation and depression might even depend on race or ethnicity[98], as well as other factors. Thus, inflammation might have a role in the progression of CHD in some individuals with depression, but not others. Moreover, the way in which depression was assessed in many of these studies might not have been optimal. For example, CRP has been shown to be more strongly associated with persistent than with transient depression[108]. However, few studies have included repeated measures of depression. When cases of transient and persistent depression are combined in a single analysis, the former might attenuate the overall association with CRP.

Endothelial dysfunction. Endothelial dysfunction is associated with most of the traditional cardiac risk factors, and can be detected in the earliest preclinical stages of the atherosclerotic process. Normally, the vascular endothelium produces nitric oxide to maintain vascular tone and inhibit smooth muscle cell growth, leukocyte adhesion, and platelet aggregation. Endothelial dysfunction occurs when endothelial nitric oxide availability is reduced, thereby leaving the atherosclerotic process unopposed[109]. Evidence indicates that depression is associated with endothelial dysfunction, even in the absence of other cardiac risk factors[110–114].

Endothelial dysfunction can be identified by measuring flow-mediated dilatation (FMD). During FMD testing, endothelium-dependent vasodilatation is evoked by a reactive hyperaemia-induced increase in endothelial sheer stress[115]. In a comprehensive review and meta-analysis of the relationship between depression and FMD, Cooper and colleagues identified 12 studies with a total of 1,491 adults[111]. All studies included in the review were either cross-sectional or retrospective analyses of the correlation between FMD and depressed mood. Across diverse populations including healthy adults and patients with CHD, the meta-analysis found a combined effect size correlation of $r = 0.19$ (95% CI 0.08–0.29, $P = 0.001$)[111]. The relationship was stronger in patients with other cardiac risk factors or comorbidities ($r = 0.29$), and in studies in which maximum vasodilatation was used to quantify FMD ($r = 0.27$)[111].

Platelet dysfunction. Factors that promote coagulation, platelet activation, and platelet aggregation have a role in ACS. Available evidence, albeit mixed, shows that both psychiatric patients who are depressed but medically well, and patients who are depressed and have CHD, have elevated levels of markers of coagulation and platelet activity, especially β-thromboglobulin and platelet factor 4 (REFS 116–119). To date, these markers have not been evaluated as potential mediators of the relationship between depression and ACS. However, any attempt to measure platelet function and correlate this parameter with clinical outcomes is problematic, because no single measure or marker adequately reflects platelet biology or function[120]. Therefore, although platelet dysfunction might contribute to the relationship between depression and cardiac outcomes, evaluating this pathway might be challenging.

Adherence to medical treatment regimens. Depression is associated with poor adherence to prescribed treatments for chronic medical illnesses[121]. In patients with cardiac disease, depression predicts decreased adherence to medication regimens, risk-factor modification interventions, and cardiac rehabilitation[122–125]. Using electronic medication monitors to obtain objective data on adherence, our group found that patients with CHD and depression were significantly less adherent to a daily regimen of aspirin than patients with CHD without depression[122]. Rieckmann and colleagues reported similar findings in a sample of 172 patients who were studied for 3 months after an ACS[124]. These observations are potentially very important because nonadherence to medications such as aspirin, statins, antiplatelet drugs, and angiotensin-converting-enzyme inhibitors

is associated with cardiac morbidity and mortality in patients with CHD[126]. However, to our knowledge, only one study has examined whether poor adherence mediates the effect of depression on cardiac outcomes. Surprisingly, the study found that self-reported cardiac medication adherence accounted for only about 5% of the effect of the relationship between depression and cardiac events in patients with stable CHD[86]. Whether objective measures of adherence can explain a larger proportion of the effect of depression, or whether adherence mediates more of the effect in patients with recent cardiac events, is currently unknown.

Physical inactivity. Many studies have found that depression is associated with physical inactivity in patients with CHD[127,128]. Most[86,129–132], but not all[133], studies on the role of sedentary behaviour as a mediator between depression and cardiac outcomes have found that sedentary behaviour accounts for a substantial proportion of the risk of cardiac events associated with depression. In the Cardiovascular Health Study[131], depression symptoms were assessed annually and self-reported physical activity was assessed at baseline and at 3 and 7 years in a cohort of 5,888 older adults (mean age 72.8 ± 5.6 years). After an average of 10.3 years, both physical activity and depressive symptoms were independent predictors of cardiovascular mortality and were strongly associated with each other. When physical inactivity was added to the model for depression, the risk associated with depression decreased by 26%. The reduction in risk associated with depression was similar for subgroups with (25%) or without (23%) established CHD[131]. Most studies have used self-report questionnaires to measure physical activity, even though depression can bias patients' responses. However, Whooley and colleagues found a similar effect when they substituted an objective measure of exercise capacity for a self-report assessment in their model with depression and cardiac events[86].

Multiple factors model. In 2013, Burg and colleagues argued that linear models of cardiac outcomes, in which one or more risk factors are assumed to act independently, oversimplify the process[134]. As an alternative, the investigators proposed a 'perfect storm' conceptual model in which cardiac events result from a confluence of multiple factors and environmental events that activate the critical pathophysiological processes. In this model, depression might be associated with any or all of the factors described above, but no single factor invariably leads to a cardiac event[134]. This model is very compelling, but underscores the complexity of the processes through which depression can lead to cardiac morbidity and mortality.

Treatment

A number of treatments for depression in patients with CHD have been tested in randomized clinical trials, including antidepressants (such as citalopram, fluoxetine, mirtazapine, and sertraline), cognitive behavioural therapy (CBT), interpersonal psychotherapy, exercise, and stepped care[83,135–142]. Most trials have found that the intervention under study was superior to a control condition. Although the effect sizes reported in antidepressant monotherapy trials for patients with depression and CHD have been modest ($d = 0.20–0.38$)[143], the effect sizes are similar to those reported in published and unpublished trials of antidepressants in psychiatric patients ($d = 0.24–0.35$)[144,145]. Little evidence indicates that any form of treatment for depression is less effective in patients with CHD than in medically well patients. However, monoamine oxidase inhibitors and tricyclic antidepressants have cardiotoxic adverse effects and are seldom used to treat depression in patients with cardiac disease.

Several large, randomized, controlled trials have examined whether treating depression can improve medical outcomes in patients with CHD[83,136,140]. The largest of these, the ENRICHD study[83], was designed to determine whether treating depression and inadequate social support after acute MI reduced the risk of recurrent infarction and death. A sample of 2,481 patients (1,084 women, 1,397 men) with major or minor depression and/or low perceived social support were randomly assigned to receive either usual care alone or CBT in addition to usual care[83]. Patients in the intervention group who had severe depression or who did not respond to CBT were also given sertraline. The intervention group showed a significantly greater improvement in depression after 6 months than the usual-care group[83], but the difference between the groups was small and not clinically relevant. The other two trials also found modest differences in depression[136,140], and none of the trials (including ENRICHD) found a between-group difference in cardiac end points.

A smaller ($n = 157$) study, the COPES trial[146], was designed to determine the acceptability and efficacy of stepped-care depression intervention after ACS. The investigators found a significant difference between treated and control groups in depression outcomes and, despite the small sample size, a trend for a reduced risk of death or hospitalization in the intervention group during the trial period[146]. However, this trend was reversed at the 12-month follow-up, resulting in no overall difference between the groups[147].

A meta-analysis of studies on the use of selective serotonin reuptake inhibitor antidepressants to treat depression in patients with CHD reported an overall positive effect on depression, but no difference in mortality or CHD hospitalizations between intervention and control groups[148]. However, the study showed modest reductions in hospitalizations and mortality when nonrandomized studies were included in the analysis[148].

The small differences in depression outcomes between treated and control groups, and the small number of end points in the larger trials, have made the detection of an effect of depression treatment on cardiac morbidity or mortality difficult. However, secondary analyses of the three largest trials found that patients whose depression symptoms significantly improved with treatment tended to survive longer than those whose symptoms showed only minimal or

no improvement[82,149,150]. In the intervention group of ENRICHD[149], for example, a linear relationship was observed between improvement in depression symptoms from baseline to 6 months and survival beyond 6 months, which remained significant after adjustment for all major demographic and medical predictors of mortality (HR 1.05 per point on the BDI, 95% CI 1.01–1.09, $P<0.003$). Improvement in the intervention group was not related to the presence of medical or logistical problems that might have interfered with participation in treatment.

Secondary analyses of ENRICHD[149] and the other large trials[150,151] suggest, therefore, that survival might improve if depression improves. Similar findings have been reported in a nonrandomized trial of exercise training and cardiac rehabilitation in patients with depression and previous MI[152], and in a nonrandomized[153] and a randomized[154] clinical trial of depression interventions for patients with heart failure. Of course, demonstrating a relationship between improvement in depression and survival is not as convincing as showing that an intervention for depression improves survival compared with a control condition, but this evidence might be the best that can be obtained. To our knowledge, no large clinical trials are either ongoing or planned to address the question of whether treating depression can improve survival in patients with CHD.

Future research

Substantial evidence shows that depression is a risk factor for cardiac morbidity and mortality, both in patients without clinical evidence of CHD and in patients with established CHD. Although residual confounding remains a possible explanation for some of these effects, the preponderance of evidence supports an independent effect of depression. The lack of positive findings among the few clinical trials that examined the effect of treating depression on cardiac outcomes, however, has led some researchers to conclude that depression might not be an appropriate therapeutic target for these patients[155].

Compared with most trials in cardiology, the sample sizes in the existing clinical trials of treating depression in patients with CHD have been very small. As cardiovascular mortality continues to decline[156,157], detecting a survival benefit for any treatment becomes increasingly difficult. Unfortunately, depression treatments that are deemed safe in patients with CHD are only modestly effective. Ongoing research is directed towards developing more effective treatments for depression in these patients. However, additional research on factors that mediate the effect of depression on cardiac outcomes, and on the identification of high-risk subtypes or symptoms of depression, might help to provide better targets for intervention.

As discussed earlier, depression has been associated with plausible biological pathways, including elevated inflammation and altered autonomic nervous system functioning, and with behavioural pathways, including poor adherence to diet and medication treatments and a sedentary lifestyle. However, none of these mediators has accounted for more than a small proportion of the associated risk in mediation studies. Few studies of potential mechanisms have simultaneously evaluated multiple candidates. Consequently, little is known about the relationships between putative mediators. These mediators might be additive or synergistic, or they might represent different expressions of a common aetiology (such as hypothalamic–pituitary–adrenal axis dysfunction). Some putative mechanisms, such as increased inflammation, might be largely the result of other risk factors associated with depression, such as obesity, physical inactivity, or smoking[158–160]. Furthermore, not all patients with depression have low HRV, elevated levels of inflammatory markers, or any of the other possible mediators considered in this Review. Distinct pathways might mediate cardiac risk in different subgroups of patients with depression. Indeed, perhaps some, but not all, cases of depression are associated with elevated cardiac risk[161]. These questions should be explored in future studies.

Behavioural risk factors, especially sedentary behaviour and poor adherence to medical treatment regimens, might be targeted in addition to depression. Medications commonly administered to patients with cardiac disease might improve many of the putative biological mediators, but only if patients adhere to the treatment regimen. Methods to improve adherence in these patients have been studied, but research is needed to determine how best to improve adherence in patients with CHD and depression.

In 2012, we concluded that the research to identify depression subtypes or specific symptoms that confer a particularly high risk of cardiac events was promising, but methodological problems and contradictory findings made it premature to draw any definite conclusions[161,162]. Since then, studies have continued to find that the presence of somatic symptoms of depression, such as fatigue or problems sleeping, are better predictors of cardiac risk than cognitive symptoms, such as feelings of guilt or thoughts of death[163]. Other studies have found that fatigue and sleep problems are among the most common symptoms of depression before treatment, and two of the most likely symptoms to remain in patients meeting the standard criteria for remission[164–167]. In a 3-year study of primary-care patients, for example, loss of energy and sleep problems were reported in 90% and 85% of patients, respectively, before treatment[168]. These symptoms continued to be present in 35% and 39% of the patients, respectively, after remission of depression, whereas the two core symptoms of depression — sadness and loss of interest — were present in only 21% of the patients[168]. If somatic symptoms are more strongly associated with cardiac morbidity and mortality, these findings might help to explain the difficulty of improving survival even with 'successful' treatment of depression.

Research is needed to determine how best to target somatic symptoms of depression. Although little evidence exists that any traditional treatment has a greater effect on a specific symptom or group of depression symptoms[169–172], this area has not been well studied in

patients with CHD and depression. Exercise, which has been shown to reduce fatigue, improve sleep, and to be modestly effective in improving depression[173–176], might be considered as a primary intervention or as an augmentation strategy when these somatic symptoms remain after other depression treatments. Aerobic exercise can have the additional benefits of lowering heart rate, increasing HRV[177–179], and increasing anti-inflammatory and decreasing proinflammatory cytokine levels[180–183]. CBT for disordered sleep might also be considered as an adjunctive therapy when sleep problems do not improve after standard depression treatments[184–186]. Studies testing these interventions and others to address somatic symptoms at baseline or after traditional treatments are needed.

Conclusions

Since the late 1980s, hundreds of studies have been conducted on depression as a risk factor for the onset or progression of cardiovascular disease, together with studies of the biobehavioural pathways that might explain this risk, and several large treatment trials. Sir William Harvey would probably have been amazed if he had known how much work would eventually be devoted to this area, and perhaps at how long it took after his initial observation before this work began. How depression increases the risk of cardiac events, and whether successful treatment of depression can reduce this risk, are questions that remain to be answered. Further research will, we hope, give us definitive answers to these questions in much less time than it took to confirm Harvey's initial observation.

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