Depression and cardiac risk: present status and future directions

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Since the mid-1980s, an impressive body of epidemiological research has examined links between depression and coronary heart disease (CHD). Depression is more common in patients with CHD than in those without heart disease, with ≥20% of hospitalised patients after a myocardial infarction (MI) meeting modified psychiatric criteria for major depressive disorder (MDD).1 While available data suggest that depression rates are lower in patients with stable CHD than in hospitalised patients, depression is still more common than in the general community. Depression is associated with increased chances of developing CHD in apparently healthy subjects. In patients with CHD depression predicts cardiac admissions and death, increased healthcare costs and utilisation of services.2 3 There is evidence of an increased cardiac risk associated with measures of depression symptoms as well as with diagnosed MDD, and of a dose–response relationship between depression severity and prognosis in patients with CHD. Many plausible biological explanations have been suggested. The quantity and strength of the epidemiological data is comparable to that leading to the general acceptance of several other cardiac risk factors. Why, then, is depression not considered a major risk factor? Should it be?

DEPRESSION AND CHD: THE EPIDEMIOLOGICAL LINKS

Updating our previous systematic reviews3–4 to include publications through 15 September 2009, we found reports based on prospective studies, using established measures of depression published from at least 28 distinct cohorts each made up of more than 500 people who were apparently CHD-free at baseline, and at least 59 separate studies that examined depression as a predictor of risk for poor prognosis in samples of at least 100 patients with known CHD. The great majority of the 150 articles based on these studies document statistically significant relationships between depression and cardiac outcomes, and most, but not all, demonstrate that these relationships remain significant after statistical adjustment for a variety of covariates reflecting cardiac disease severity. This literature has been summarised and analysed critically in at least 200 editorials and review articles. Meta-analyses concerned with the role of depression in the development of CHD5–8 report effect sizes from approximately 1.5 to 2.7 depending on the definition of CHD, the measure of depression and the covariates for which adjustment was made. For studies of the predictive importance of depression in patients with CHD, meta-analytic effect sizes7 9 10 range between 1.6 and 2.2 depending on the original cardiac diagnosis, length of follow-up, definition of prognosis, measure of depression and covariates controlled.

Without question depression is related to both the incidence of cardiac disease and the prognosis of patients with established CHD. However, caution is warranted when speaking about depression as “a cardiac risk factor”. As long noted by epidemiologists, correlation between two variables does not equate with causation, even when the alleged cause appears to precede the outcome by many years. A major problem with depression as a risk factor for the development of cardiac disease is the extent to which depression may reflect preclinical cardiac disease. Similarly, in patients with existing CHD, even with extensive statistical control of reliably measured covariates, it is impossible to rule out the possibility that depression reflects some unknown indicator of more advanced cardiac disease, or that depression and CHD are the products of common causes—for example, genetic factors.11 Current evidence shows that depression is associated with about a doubling in risk of cardiac events in patients with CHD. This increase in risk is not in the same ball park as the ninefold increase in risk of lung cancer associated with smoking.12 According to Cornfield’s Inequality, a non-measured confounding variable which is at least nine times as common in smokers as non-smokers would be needed to fully explain the relationship between smoking and cancer. Because the chance of such a strongly influential unknown culprit variable is unlikely, this argument was used to help conclude that smoking causes lung cancer. However, the chances of there being an unknown variable that is twice as prevalent among the depressed as non-depressed is not small. This does not mean that any variable that is twice as common in the depressed accounts for the link with CHD, but that for a confounder to explain away the relationship between depression and CHD it would need to be at least twice as common in the depressed. We are much further away from causal inferences based on epidemiological data with depression and CHD than with smoking and lung cancer.
THE HISTORY OF CHOLESTEROL AND TYPE A BEHAVIOUR

In thinking about depression and cardiac risk, the history of cholesterol/low-density lipoprotein (LDL) and type A behaviour is informative. Both enjoyed periods as risk factors endorsed by consensus statements from the US National Heart Lung and Blood Institute (NHLBI), and/or American Heart Association (AHA). In each case, the consensus statement was followed by an accumulation of conflicting evidence bringing the risk status of the factor into question.\(^\text{15, 14}\)

Today, cholesterol, in the form of LDL, has bounced back as a major risk factor. This has occurred for two reasons. Cholesterol was dissected into component lipid fractions for which epidemiological data were stronger than for global cholesterol, and statins were developed, providing a powerful tool to lower lipid levels. Dismantling into components combined with development of a stronger treatment saved cholesterol/LDL, but did not help type A behaviour.

The largest body of early research on psychological risk factors and CHD focused on type A or coronary prone behaviour, a psychological concept identified by two cardiologists. Meyer Friedman and Ray Rosenman defined type A, as opposed to type B, as a behaviour pattern in men ‘characterised by intense ambition, competitive ‘drive’, constant preoccupation with occupational ‘deadlines’ and a sense of time urgency’ (p10515). They conducted the Western Collaborative Group Study\(^\text{13, 14}\) that assessed type A/B behaviour and lipid levels in more than 3000 middle-aged men initially free of CHD. Baseline type A behaviour predicted CHD incidence over 8 years, and the predictive value of type A was not accounted for by other cardiac risk factors. In 1981 a review panel of the NHLBI declared ‘type A behaviour... is associated with an increased risk of clinically apparent CHD in employed, middle-aged US citizens’ (p.1200\(^\text{15}\)). Soon after this declaration, contradictory evidence began to appear.\(^\text{13}\) Perhaps most damaging was a long-term analysis from the Western Collaborative Group Study showing that patients with type A behaviour who survived an initial MI had better long-term prognosis than type B.\(^\text{18}\) Today, type A research is rare. However, as originally described, type A behaviour was a composite of several dimensions (e.g., competitiveness, time pressure, hostility/anger), and in the mid-1980s researchers began to examine the cardiac risk associated with these components. The most promising data concern the component of hostility/anger which has weaker links with CHD than shown by the first epidemiological studies of type A. A recent meta-analysis suggests small effect sizes in both apparently healthy subjects (1.19; 95% CI 1.05 to 1.35) and patients with CHD (1.24; 95% CI 1.08 to 1.42).\(^\text{19}\) This level of risk is unlikely to stimulate much enthusiasm for targeting hostility/anger as a major cardiac risk factor.

RECENT TRENDS IN RESEARCH ON DEPRESSION AND CHD

There has not yet been a consensus statement recognising the increased cardiac risk in depressed patients, but an AHA scientific advisory has recommended routine screening in patients with CHD.\(^\text{20}\)

While the value of screening is controversial,\(^\text{21, 22}\) the recent epidemiological literature on depression and CHD remains strong. Nonetheless, our review suggests that the annual number of publications is levelling off. The few treatment studies that have been done have not resulted in large enough changes in depression to make it reasonable to think that current depression treatments would have a clinically important impact on cardiac events. Dismantling of the depression concept is underway, with research focusing on isolating the “cardiotoxic” aspects of depression in patients with CHD. This work is mostly based on re-analyses of existing epidemiological and clinical trial data, and has involved several approaches, including examining prognostic differences between various depression symptom clusters,\(^\text{23, 24}\) comparing cardiac outcomes in patients with first depressions and those with recurrent episodes,\(^\text{25}\) considering the role of depression severity,\(^\text{26}\) and, most recently, evaluating the importance of depression persistence and treatment resistance in predicting cardiac events.\(^\text{27}\) There is no consensus on which, if any of these distinctions, are clinically relevant, but additional research is warranted.

Another line of research assumes that depression is causally linked to CHD, and is attempting to determine the pathophysiological mechanisms. Many cardio-toxic pathways have been suggested,\(^\text{28}\) including depression-related changes in autonomic balance,\(^\text{29}\) platelet reactivity,\(^\text{30}\) inflammation,\(^\text{31}\) and endothelial function.\(^\text{11, 32, 33}\) None of these factors have been shown to be strong enough individual mediators of the association between depression and cardiac events to act as proxy outcomes for prevention trials. Although the complexities are only beginning to be studied, it seems likely that if depression and CHD are causally linked, the explanation is multifactorial. Another possibility is that the influence of depression on CHD is indirect, by making depressed patients more vulnerable to other cardiac risks. For example, there is evidence that depressed patients are less likely to comply with cardiac treatments and modification of cardiac risks,\(^\text{34}\) potentially placing them at higher overall risk. Reduced compliance may not only be because the depressed are less optimistic about the benefit of prescribed drugs or changes in unhealthy behaviour such as inactivity. Impaired executive function, with reduced ability to handle, process and retain new information may have a major role.\(^\text{35}\)

Finding ways to facilitate compliance may provide cardiovascular benefits for depressed patients without improving mood.

IS IT TIME FOR A SURVIVAL TRIAL?

Despite the prevalence of depression and association with negative cardiac prognosis, only one trial was specifically designed to determine whether treating depression alters CHD outcomes. ENRICH-D\(^\text{36}\) was an NHLBI-sponsored, multicentre trial that assessed the potential benefit of 6 months of cognitive behaviour therapy (CBT), plus sertraline (a selective serotonin reuptake inhibitor (SSRI)) if needed, in comparison with usual care in a sample including 1343 depressed patients after a MI. Results were disappointing. Although there was a significantly greater improvement in depression scores (p<0.001) in the CBT group, the treatment had a small effect size. Further, this study was unable to demonstrate that CBT, in comparison with usual care, reduced the combined end point of all-cause mortality and non-fatal MI over 2 years. However, the doctors of patients in the usual-care group were informed that their patients were depressed, and there was a high rate of antidepressant prescription in the usual-care group. In retrospect, the problem may not have been only because of co-intervention in the control group. Depression is a highly heterogeneous condition, and individual response to treatment is difficult to predict. Two antidepressant trials in cardiac patients have also reported only small to medium effect sizes for changing depression.\(^\text{37, 38}\) These trials (SADHART and CREATE) documented the efficacy and safety of sertraline and citalopram (another SSRI) for the acute
treatment of MDD in patients with CHD, but were not powered to examine cardiac event rates.

The situation is somewhat analogous to the status of cholesterol and CHD before the introduction of statins. Is it reasonable to hope for a similar magic bullet for depression? Despite the introduction of many new drugs, there has been no improvement in the efficacy of antidepressant monotherapy in the past 40 years. The current approach for treatment resistance involves combining or switching treatments, but the overall success rate remains less than optimal. Further, assessing the safety of such complex strategies in patients with CHD presents major challenges.

In the past it was often claimed that the ultimate proof of causation can only come from randomised clinical trials in which interventions to reduce or eliminate the potential cause succeed in changing outcomes. However, reasoning about causation and understanding of the pathophysiological pathways underlying CHD have both progressed. While there is ample evidence that statins lower lipid levels and decrease cardiac events, there is some controversy about the extent to which their cardiac benefits, at least partially, reside in other pleiotropic effects, including reducing inflammation and improving endothelial function. Because of the pleiotropic impact of many pharmaceutical agents, drug trials are no longer taken as definitive proof of causality, unless the tested agent is known to affect only the mechanism of interest. There are increasing data suggesting that SSRI antidepressants have pleiotropic effects, including changes in platelet function, and inflammatory markers. Thus, a positive cardiac event trial based on antidepressants would not prove a causal relationship between depression and CHD. It might simply mean that antidepressants have beneficial physiological impacts beyond their impact on depression.

**FUTURE DIRECTIONS: A CAUTIONARY, YET OPTIMISTIC VIEW**

Perhaps what is needed is a more individualised form of treatment for depressed patients based on their other cardiac risks or markers of cardiac pathophysiology, rather than on the phenomenology of depression symptoms per se. We also need to know more about factors contributing to non-compliance with treatment and risk factor modification, and to develop and test interventions to improve overall adherence in at-risk patients, including the depressed. It is often forgotten that depression is different from all the established risk factors for CHD, in that it is defined uniquely in terms of a cluster of symptoms. Improvement in depression, whether based on self-report scales or clinician observations of patient complaints, can come about because of large changes in a few symptoms or smaller changes in all symptoms. Symptom reporting itself is subject to many potential biases and distortions, including memory problems and patients’ desires to give socially acceptable responses and avoid stigma. In this context, it is striking that the relationship between depression and cardiac outcomes has remained robust. However, it also makes it difficult to argue that changes in depression symptoms equate with changes in pathophysiology. As pointed out by the ethicist I McHenry, “Nature refuses to reveal her true causes from the mere control of symptoms” (p.406). He notes that aspirin relieves the symptom of fever, but this tells us little about the causes of the fever. Similarly, changes in depression symptoms may have little to do with the pathophysiological changes posited to explain links between depression and CHD. In fact, although the number of treatment studies is limited, there is little evidence that changes in depression following antidepressant use correlate with changes in platelet function, inflammation or heart rate variability.

In a prescient essay first published in 1975, Sir Michael Marmot discussed the history of approaches to understanding causation in cardiac disease. He reflected on the work of mathematical philosopher Imre Lakatos, who introduced the concept of programmatic research. According to Lakatos, when a theory comes up against a road block, programmatic research dissecting the elements of the theory should lead to new insights and progress. If not, it is time to abandon the theory. We have just started the dissection in depression, and are greatly in need of resources to develop new and stronger treatments for depressed patients, not to improve the strength of our causal inferences so that depression will be declared a cardiac risk factor, but to improve quality of life and protect patients from the pathophysiological and behavioural correlates of depression.

Only time will tell whether depression will follow in the footsteps of type A behaviour, or whether the efforts at isolating and treating its most cardiotoxic elements or behavioural and pathophysiological pathways will succeed. Public resources for clinical research are limited. It is time to stop wasting them in ruminations over whether or not depression is a cardiac risk factor. Although “cardiology—psychiatry turf wars” are now behind us, peaceful coexistence is only a beginning. Increasing the number of strong interdisciplinary research and clinical partnerships is essential to advancing knowledge of the complex web of factors producing and promoting cardiac and psychiatric disease.

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