

Review Article

Depression and Cardiovascular Disease: A Bidirectional Link between a Sad Mood and a Broken Heart

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Abstract

Recent studies have shown that the two-way link between depression and heart disease may be more prevalent than ever.

INTRODUCTION

Recent studies have shown that the two-way link between depression and heart disease may be more prevalent than ever [1-3]. Depression is rampant globally. According to the World Health Organization (WHO), more than 264 million individuals suffer from various forms of depression [4]. Depression can lead to suicide and close to 800,000 individuals per year die due to suicide.⁴ Heart disease is even a larger problem. Data from the WHO indicate that 17.3 million people die from cardiovascular disease (CVD) annually and accounts for 31% of all deaths worldwide [5]. Prior evidence has shown a relationship between depression and heart disease. According to 2015 American Heart Association (AHA) scientific statement, the prevalence of CVD among adults with major depressive disorder (MDD) was nearly 3-fold greater than among adults without mood disorders, and adults with CVD and MDD were about 7.5 years younger than adults with CVD who did not have mood disorders [2]. Furthermore, depression is associated with at least 2-fold increase in the risk of mortality or rehospitalization within 3 to 12 months after a heart failure hospitalization [6]. While continued research is being conducted to further study this intriguing relationship, numerous questions remain regarding this link. Is depression a sign of potential heart disease? Is depression an independent risk factor for the development of heart disease? Can depression arise from cardiac disease? Can the treatment of depression reduce cardiac morbidity and mortality? This review will address the two-way relationship between depression and heart disease, and propose future of research in this field.

Evidence that supports a two-way relationship

Several crucial pieces of evidence strongly support the assertion that there is a two-way relationship between depression and heart disease. Not only can depression-like symptoms increase the risk for cardiac diseases, but it has been found that cardiac morbidity can exacerbate previously hidden depression [7]. Depression has been shown to be an independent risk factor that can drastically affect a CVD mortality rate [8]. Multiple studies have shown that depressive symptoms, even of the lowest order, are strongly associated with an increase in the risk of cardiac morbidity and mortality [9-11]. Indeed, depressive symptoms do not have to be indicative of major depression, but can just be of the lowest order that may be representative of low-level depression, such as low self-esteem, fatigue or lack of energy, and insomnia. A study by Holahan et al. [12], involving data from 388 patients with clinical depression and 404 community-matched controls across 10 years, showed that patients with depression had a two-thirds higher likelihood of suffering from CVD sometime in their lives, as compared to controls. In a systematic review and meta-analysis including 80,000 patients from 28 longitudinal studies, it was concluded that major depression seems to be an independent risk factor for the onset of a wide range of CVDs (RR, 2.54; 95%CI, 2.07-3.10); moreover, patients with even the depressive symptoms, but not depressive disorders, also had a significantly increased risk of CVD (RR, 1.39; 95%CI, 1.26-1.54). The mean (range) of follow up among the included studies was 10.9 (3 - 37) years [13].

The reverse relationship has also been suggested to be plausible, as cardiovascular disease can predispose patients to having a higher risk of developing depression in later years, as compared to healthy controls [14]. In the study by Choi et al., 5414 participants over the age of 65 were tested to examine the association between CVD and late-life depression. Results indicated that depressive symptoms were significantly higher one year later among those with CVD events than among those without CVD at baseline. In addition, the severity of depressive symptoms was also significantly higher among those who had a newly diagnosed CVD or episode since baseline than among those who did not [14]. Although there has been no prospective data that proves this link, a sudden CVD diagnosis can often lead to a shock for the patient, and subsequently, a depression in mood and subsequently poor quality of life (QOL). The patients must adapt to this new event and cope with their new diagnosis. This would expectedly lead to much stress in their lives, further contributing to a possible reason for why depression would appear in patients with recently diagnosed CVD. Although most patients adapt quickly to their CVD diagnosis in a few weeks or so, some patients fail to recover from their depression, which can sometimes result in clinical depression.

Gender difference in this relationship

An important question to be answered in the relationship between heart disease and depression is whether a difference in this relationship exists between males and females? Recent data has shown that major depression is twice as common in women compared to men with cardiac disease [15]. This data aligns with emerging evidence that depression is associated with a greater increase in incidence of CVD in women, and that women with CVD experience higher levels of depression than men [16,17]. In addition, prognosis of CVD is worse in females as compared to males [18]. The association between depression and type 2 diabetes is worth commenting. Patients with type 2 diabetes have almost twice the rate of depression relative to those without diabetes (19.1% vs 10.7%) and depression is associated with a 60% increased risk of type 2 diabetes [19]. In addition, women with diabetes have a significantly higher relative risk of fatal coronary heart disease than do men with diabetes [20]. Depressed women with or without CVD at baseline appear to have poorer response to antidepressant therapy, as compared to men, in improving CVD prognosis or reducing CVD risk. Psychological counseling towards depression coupled with behavioral treatment in women after CVD diagnosis negatively affects prognosis, as compared to the largely neutral effects in men [21]. The IMPACT (Improving Mood-Promoting Access to Collaborative Treatment) randomized controlled trial is an 8-year follow-up study of elderly patients with late-life depression who received either usual care or a 12-month collaborative stepped care program comprised of antidepressants and psychotherapy. The IMPACT intervention was associated with a significant CVD risk reduction for men without baseline CVD (70%), though not significant for women (37%) [1]. Further systematic gender studies needs to be conducted on the disparity between men and women in this link; moreover, whether or not treatment of depression makes a different impact on the development and progression of CVD in male vs. female need to be researched

more extensively to better meet the specific needs of men and women suffering from both diseases.

Current challenges

It must be emphasized that the link between cardiac disease and depression is merely an association, rather than a proven, causative relationship. A causal relationship between depression and heart disease is not confirmed, as in multiple interventional trials performed, no reduction in cardiac deaths or CVD has been reported when depression was treated. The more understanding is gained about a potential causal relationship, the better depression and CVD can be diagnosed and treated. However, it is very possible that confounding factors can explain the association between CVD and depression. For example, a person with depression may be more likely noncompliant with medications, staying inside, not performing exercise, obese or using tobacco products.

Treatment of depression, which has been mostly used by researchers to try and determine the effect of depression on CVD, may not be adequate to fully address this link [22]. Although depression therapy could improve depression and depression-like symptoms, this treatment does not necessarily change depression-associated health risk behaviors and confounding variables. Subsequently, the mortality rate among patients with depression is not improved and this presents a considerable challenge to clinicians and researchers.

In general, more randomized clinical trials need to be conducted. Despite the abundance of scientific and medical data on the association between CVD and depression, as well as evidence suggesting that a causal relationship may exist, there is a lack of high-quality clinical and efficacy trials. These randomized controlled trials are necessary to identify a causal link. This limitation hampers physicians' ability to make useful clinical recommendations on how to prevent and treat depression and CVD. The struggle to make conclusions based on limited hypotheses and clinical data is a challenge that must be overcome in order for the link between CVD and depression to be understood fully.

What is the future direction?

These challenges are not likely to deter further research from being done, but to inspire researchers and clinicians to reexamine the direction we are heading. The potential of this association is intriguing. While clinicians need a proved causal relationship for the treatment of depression to result in improved CVD outcomes. It would be interesting if an effective treatment regimen for depression that could significantly reduce the cardiac morbidity and mortality. When treatment efficacy for depression in the clinical research was solely determined by improvement in clinical symptoms, instead of the quality of life (QOL) [23,24] that reflects behavioral changes such as long-term compliance with treatment and healthy lifestyle, little is known about treatment effects on overall health and CVD. While reduction of symptoms has remained the primary focus in the treatment of depression [23], emerging evidence indicate that a significant proportion of what is contributing to QOL is distinct from one's affective states [25-28]. Improvement in one's mood states does not necessarily

translate into changes in determinants of cardiovascular disease [29] or depression-related cardiotoxic pathways [30] such as autonomic balance [31], platelet reactivity [32], inflammation [33], and endothelial function [34]. For instance, CVD patients usually stop smoking right at their diagnosis, but as much as 50% of those who quit smoking resumed within one year [35]. Many patients with depression suffer from poor QOL following improvement in symptom severity and even after achieving remission [36]. Although reduction of depressive symptoms was the largest predictor of improvement in QOL in patients with depression, reducing depressive symptoms alone does not appear to be sufficient for substantial improvement in QOL [37]. Is it time to shift gears and stop keeping reduction of symptoms as the primary focus in the treatment of depression especially in patients with CVD? We must move beyond solely treating the symptoms of depression but also substantially improve QOL through multidisciplinary approach; in the meantime, the QOL rather than mere reduction of affective symptoms should be used to measure treatment success in the clinical research. It is time to stop wasting public research resources in ruminations over whether or not depression is a cardiac risk factor when depression related QOL may be indeed a causal factor in development of CVD or poor CVD prognosis.

Future Directed Therapy (FDT) is the first and only treatment for depression developed based on the understanding that the brain operates in a primarily future-oriented way (<https://www.futuredirectedtherapy.com/>). FDT is intended to teach a set of comprehensive skills necessary to improve one's ability to move toward the future and achieve personal growth and well-being by generating more positive future experiences and thus also enhancing QOL. FDT does not put emphasis on symptom reduction but instead employ the positive psychology strategy of teaching skills for thriving and wellness [37]. Vilhauer et al., used a quasi-experimental design to examine the differences between FDT and cognitive behavioral therapy (CBT) on improving QOL in patients with major depressive disorder. For each group, 22 patients participated in the FDT intervention as opposed to 20 patients completing the CBT intervention. Study findings suggest that those patients treated with FDT demonstrated significant improvements in QOL ($p=0.002$) while those treated in the CBT did not. The magnitude of improvements in depression symptoms, hopelessness and positive future anticipation was significantly larger in the FDT group, although both treatments were effective at improving aforementioned outcome metrics [37]. As a spiritual being, a patient with a sad mood and a broken heart must be treated as a whole; furthermore, researchers should be mindful of the complexity of tangled relationship between depression and CVD, and go beyond the pathophysiological level to focus more on one's well-being over symptoms reduction while conducting future research on this vital subject.

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