CARDIOVASCULAR DISEASES AND MENTAL DISORDERS | REVIEW

Cardiovascular Diseases and Mental Disorders: Bidirectional Risk Factors?

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ABSTRACT
Cardiovascular diseases (CVD), their well-established risk factors (CVRF) and mental disorders are common and co-occur more frequently than would be expected by chance. However, potential causal mechanisms underlying their association still need to be elucidated. Several non-mutually exclusive hypotheses have been suggested to explain this association: a) mental disorders could increase vulnerability to CVD through poor health behaviour including smoking, unbalanced diet, sedentary lifestyle or the side effects of psychotropic drugs; b) CVD or their treatment could favour the development of mental disorders; or c) mental disorders and CVD/CVRF could share risk factors such as common metabolic processes or common genes. Disentangling some of these mechanisms will require studying the temporal relationship of the appearance of CVD and mental disorders.

Herein we review the existing epidemiological evidence of an association between these two types of disorders, and describe several mechanisms potentially involved. We will briefly describe the CoLaus/PsyCoLaus study cohort, a population-based in Lausanne, Switzerland designed to address some of these questions.

The Problem
Both cardiovascular diseases (CVD) and mental disorders are major public health issues, which lead to increased disability and mortality. CVD are the worldwide leading cause of death and are responsible for around four million deaths each year in Europe. Mental disorders also demonstrate high lifetime prevalence. For example, the National Comorbidity Survey (NCS), a population-based study in the USA, revealed that as many as 48.7% of the respondents report at least one lifetime disorder, with the most frequent being substance abuse/dependence (35.4%), followed by anxiety (19.2%) and mood disorders (14.7%). Similar figures have been reported in European populations. A recent WHO projection concluded, that by 2030, unipolar depressive disorders and ischemic heart disease will be among the three leading causes of disease burden worldwide.

In addition, there is evidence indicating that CVD and mental disorders co-occur more frequently than would be expected by chance. Similarly, depression can occur from 20% up to 50% of patients after a clinically significant acute stroke, with poststroke depression occurring in up to 30% of the patients. The development of psychiatric symptoms is associated with a poor functional prognosis and a negative impact on the patient’s quality of life. Conversely, in population-based prospective studies, individuals with depression or depressive symptoms have increased cardiovascular morbidity and mortality. However, the large majority of these epidemiological studies rely on depression scales or self-rating questionnaires for depression rather than diagnostic interviews and did not mental disorders such as anxiety and substance use disorders.

As these studies could not or only partially adjust for the presence of CVRF other than depression, the question of whether or not depression is an independent risk factor for CVD is still not resolved. In addition, not only depression but also anxiety symptoms, “worry” and specific anxiety disorders may influence the prognosis in patients with CAD. Potential mechanisms involved in this association of CVD and mental disorders have only been partially elucidated. Several non-mutually exclusive hypotheses have been suggested to explain this association: a) mental disorders could increase vulnerability to CVD; b) CVD or their treatment could favour the development of mental disorders and c) CVD/CVRF could share common pathogenic processes.

The association between mental disorders and CVD
It is well documented that the prevalence of depression is increased among patients with various manifestations of coronary artery diseases (CAD).
Potential mechanisms underlying increased vulnerability to CVD in individuals with mental disorders

Several mechanisms have been postulated, starting with the fact that subjects with mental disorders may display damaging health behaviours. For example, depression and anxiety disorders are associated with poor health behaviour such as smoking or unbalanced diet. In addition, depressed patients are less compliant with medical therapy, which could contribute to an increased risk of CVD in individuals treated for high blood pressure, dyslipidaemia or diabetes.

Furthermore, hormonal factors have also been suggested to play a role. In particular, the hypothalamic-pituitary-adrenocortical axis (HPA) and the sympatho-medullary system are two primary components of the stress response and could mediate the association between depressive or anxiety disorder and the subsequent development of CVD. Administration of corticosteroids induces hypercholesterolemia, hypertiglyceridermia and hypertension leading to endothelial dysfunction.

Therefore, HPA hyperactivity, which has been frequently observed in patients with depression or anxiety disorders, could contribute to increased vulnerability to CVD in these individuals. Similarly, depression and anxiety disorders are associated with dysregulation of the sympathoadrenal system, hence elevated norepinephrine levels, which could contribute to CVD through effects on the heart, blood vessels and platelets. Likewise, decreased parasympathetic tone in depression is associated with decreased heart rate variability, a possible risk factor for arrhythmia and cardiovascular mortality.

Finally, antidepressants drug used for the treatment for mood and anxiety disorders are also suspected to be involved in the occurrence of CVD. Tricyclic in particular have negative effects on the cardiovascular system by in particular by potentially increasing arrhythmias.

Potential mechanisms underlying increased vulnerability to mental disorders in individuals with CVRF/CVD

CVRF such as hypertension, cigarette smoking, hypercholesterolemia and diabetes are risk factors for the incidence of late-onset depression or “vascular depression”, related probably to subcortical brain lesions. Depression could also be a consequence of specific drug treatments for CVRF or CVD. Beta-blockers and in particular propranolol has been shown to be associated with higher frequency of anti-depressant prescription, but this has not been a consistent finding. Moreover, the association between coronary artery disease and in particular myocardial infarction (MI) and depression has frequently been explained by the psychological effect of chronic illness on mood.

However, as the prevalence of depression does not correlate with the degree of cardiac dysfunction, this hypothesis can be questioned. Finally, it has been suggested that CAD may contribute to the development of depression through inflammation, as coronary artery disease is a chronic inflammatory process.

Shared common pathophysiological processes

Several common pathophysiological processes have also been suggested to explain the association between depression and CVD. These include, but not exhaustively: increased pro-inflammatory activity, metabolic abnormalities linked to reduced intake of essential fatty acids, sleep disturbances, migraine and common genetic variants. These mechanisms could either act as common pathophysiological process underlying the development of CVD and mental disorders or an intermediate process within the potentially bi-directional causal relationship between CVD and mental disorders.

Recently, strong attention was drawn to the role of pro-inflammatory cytokines. Experimental studies show that inflammation participates centrally in all stages of the atherosclerotic process from the very early adhesion of monocytes to endothelial cells to atherosclerotic plaque growth progression and rupture. Furthermore, in large-scale epidemiological studies, CRP, tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6) and fibrinogen prospectively predicted cardiovascular events. However, it is not clear whether some of the studied variables such as CRP are only markers of inflammation or mediators of the atherosclerotic disease.

Accumulated evidence also suggests that there is a chronic low-grade inflammatory state in depression as evidenced by increased plasma levels of pro-inflammatory cytokines: TNF-α, interleukin IL-1β, and IL-6 as well as CRP and fibrinogen. Moreover, treatments including the cytokine interferon-α lead to depression in up to 50% of patients. Moreover, CRP has been found to be higher in patients with bipolar-I disorder during acute mania and the depressive phase than in healthy controls. Currently, available data on inflammation markers in depression and in other mental disorders are largely cross-sectional and therefore the direction of the association remains unclear. As inflammation may contribute to the development of CAD and depression, it is possible that genetic variation related to inflammation could underlie both CAD and depression.

Disturbed sleep is another risk factor that could predispose to both mental disorders (in particular mood and anxiety disorders) and CVD or mediate the association between the two types of pathology. Circadian rhythm disturbances were found in both unipolar and bipolar mood disorders, although the direction of causality remains unclear. Moreover, short latency of the first rapid eye movement (REM) sleep period and decreased sleep intensity are potential biological markers of mood disorders, whereas sleep deprivation has an antidepressant effect. Obstructive sleep apnoea (OSA) has been shown to be one of the major risk factors for CVD and metabolic disease, with a four-fold increased risk of fatal cardiovascular events in severe OSA patients. Recent studies also documented an association between poor sleep and increased plasma-levels of IL-6 and the pro-coagulant marker fibrin D-dimer, suggesting a mechanism that may explain the association between disturbed sleep and CVD.

Persistent pain (more than three months) is another clinical characteristic that has shown to be associated with mental disorders and CVD. Indeed several studies documented associations between chronic pain and anxiety or depressive disorders.
A recent study has also demonstrated an association between back pain, coronary heart events and mortality in elderly women. It has been hypothesised that pain could be an intermediate factor contributing to reduced mobility, polypharmacy, obesity/malnutrition or sleep disturbances or a third factor underlying the association between CVRF/CVD and mental disorders. It is also possible that dietary factors such as omega-3 fatty acids affect both depression and heart disease. CAD mortality is positively associated with low plasma levels of omega-3 fatty acids\(^{[19]}\) and omega-3 fatty acids supplementation has been shown to significantly reduce the combined incidence of death, nonfatal MI and stroke.

Similarly, several studies suggest a negative association between high plasma levels of omega-3 fatty acids and the prevalence of major depression, post-partum depression and suicidal ideation\(^{[20]}\). CAD patients with depression also revealed lower plasma levels of omega-3 fatty acids than CAD patients without depression\(^{[21]}\). Regarding the role of genetic variants contributing to these pathologies, to our knowledge there is only twin study that considered depressive symptoms and CAD jointly\(^{[22]}\). It revealed a correlation across heritabilities of 0.42, suggesting that nearly 20% of variability in depressive symptoms and CAD was attributable to common genetic factors. Although there is no genome-wide association (GWAS) or linkage study which jointly included depression and CAD phenotypes, yet, research focusing either on depression or CAD has provided some preliminary evidence of overlapping signals for the two types of pathology suggesting the potential for common candidate genes.

Regarding potential candidate genes, polymorphisms involved in the above processes which could underlie both mental disorders and CVD/CVRF are of particular interest, e.g. polymorphisms related to inflammation, serotonin, the regulation of sleep, the HPA for example. Both mental disorders and CAD are 'complex' traits, meaning that the causal pathways are likely to involve multiple genes of small effect, as well as gene x gene and gene x environment interaction.

**Limitations of existing studies**

Existing studies investigating potential associations between mental disorders and CVD have suffered from methodological limitations including in particular:

1) the use of clinical rather than epidemiological samples
2) the lack of a comparison group
3) the application of psychiatric scales rather than structured diagnostic interviews
4) the assessment of the incidence of CVRF/CVD by self reports rather than clinical and biological information,
5) the lack of simultaneous assessments of both CVD and risk factors for CVD and finally
6) the use of cross-sectional designs which leads to the problematic distinction between cause and consequence. These limitations are likely to account for the large body of conflicting findings and make it difficult to determine the mechanisms underlying associations between mental disorders and CVRF/CVD.

**The CoLaus/PsyCoLaus study**

In order to prospectively study the complex mechanisms underlying the association between mental disorders and CVD or risk factors, we have built the CoLaus/PsyCoLaus cohort study in Lausanne, Switzerland. This cohort is the follow-up of a cross sectional population-based study including 6738 participants aged 35-75 and assessed between 2003 and 2006 for prevalence and determinants of cardiovascular risk factors (CoLaus) and a psychiatric arm including 3719 subjects aged 35-66 years (PsyCoLaus). These studies have been described in detail previously\(^{[23][24]}\). In summary in the CoLaus study all subjects underwent a detailed cardiovascular assessment including the measurement of a large panel of biological plasma markers as well as genotyping using a 500K Affymetrix\(^{*}\) DNA chip.

All subjects in the PsyCoLaus study underwent a comprehensive psychiatric assessment based on a semi-structured diagnostic interview (Diagnostic Interview for Genetic studies: DIGS\(^{[25]}\)). In the current follow-up, which started in 2009 all subjects are re-contacted for a new cardiovascular and psychiatric assessment. In addition to the repetition of measures done at baseline, we are collecting data on serum levels of pro-inflammatory cytokines, sleep disorders, physical activity, diet and cognitive function in elderly subjects. The prospective design together with the combined physical and psychiatric investigation in a population-based sample overcomes most of the limitations of previous research and therefore provides a unique opportunity to study the dynamic interplay between CVD/CVRF and mental disorders.

**CONCLUSIONS**

CVD and mental disorders are prevalent disorders with a major health burden and co-occur more frequently than expected by chance. A better understanding of the mechanistic links underlying these conditions should lead to the development of more specific and efficient strategies of their prevention and treatment.

**REFERENCES**


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