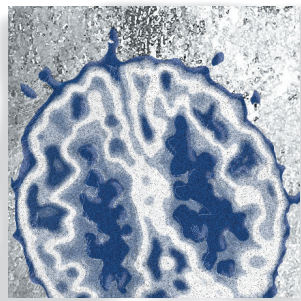


The intriguing relationship between coronary heart disease and mental disorders

Marc De Hert, MD, PhD; Johan Detraux, MPsy; Davy Vancampfort, PhD



Introduction

Cardiovascular diseases (CVDs) are the leading cause of death in almost every region of the world.^{1,4} According to the World Health Organization 2015 statistics, CVDs account for 17.7 million or 31% of all deaths worldwide.⁴ An estimated 7.4 million of these deaths are due to coronary heart disease (CHD).⁴

CHD, also known as ischemic heart disease or coronary artery disease,⁵ is a common term for the buildup

Coronary heart disease (CHD) and mental illness are among the leading causes of morbidity and mortality worldwide. Decades of research has revealed several, and sometimes surprising, links between CHD and mental illness, and has even suggested that both may actually cause one another. However, the precise nature of these links has not yet been clearly established. The goal of this paper, therefore, is to comprehensively review and discuss the state-of-the-art nature of the epidemiological and pathophysiological aspects of the bidirectional links between mental illness and CHD. This review demonstrates that there exists a large body of epidemiological prospective data showing that people with severe mental illness, including schizophrenia, bipolar disorder, and major depressive disorder, as a group, have an increased risk of developing CHD, compared with controls [adjusted hazard ratio (adjHR)=1.54; 95% CI: 1.30-1.82, P<0.0001]. Anxiety symptoms or disorders (Relative Risk (RR)=1.41, 95% CI: 1.23-1.61, P<0.0001), as well as experiences of persistent or intense stress or posttraumatic stress disorder (PTSD) (adjHR=1.27, 95% CI: 1.08-1.49), although to a lesser degree, may also be independently associated with an increased risk of developing CHD. On the other hand, research also indicates that these symptoms/mental diseases are common in patients with CHD and may be associated with a substantial increase in cardiovascular morbidity and mortality. Finally, mental diseases and CHD appear to have a shared etiology, including biological, behavioral, psychological, and genetic mechanisms.

© 2018, AICH – Servier Research Group

Dialogues Clin Neurosci. 2018;20:31-39.

Keywords: anxiety disorder; bipolar disorder; coronary heart disease; depression; epidemiology; mental disorder; pathophysiology; posttraumatic stress disorder; schizophrenia; severe mental illness

Address for correspondence: Dr Marc De Hert, Department of Neurosciences, KU Leuven University Psychiatric Centre, Leuvensesteenweg 517, 3070 Kortenberg, Belgium (email: marc.dehert@upckuleuven.be)

Author affiliations: Department of Neurosciences, KU Leuven University Psychiatric Centre, Kortenberg, Belgium (Marc De Hert, Johan Detraux), Department of Rehabilitation Sciences, KU Leuven University of Leuven, Leuven, Belgium (Davy Vancampfort), KU Leuven University of Leuven, Kortenberg, Belgium (Marc De Hert, Johan Detraux, Davy Vancampfort)

Translational research

of a waxy substance, called plaque, in the heart's arteries, leading to the failure of coronary circulation to supply adequate blood circulation to cardiac muscle and surrounding tissue—a phenomenon that can result in a myocardial infarction (MI).^{5,6} The main risk factors for CHD include dyslipidemia, diabetes, arterial hypertension, obesity, smoking, and a sedentary lifestyle, as well as stress, older age, male gender, and a family history of CHD.⁷

Mental illness is also a major contributor to the global burden of disease.^{2,8-10} For example, more than 300 million people of all ages suffer from depression worldwide and the disease is expected to become the leading cause of worldwide disability by 2030.^{4,11,12} According to a recent meta-analysis, 14.3% of all deaths worldwide, or approximately 8 million deaths each year, are attributable to mental disorders.¹³

An intriguing relationship between mental illness and CHD appears to exist. A higher prevalence of mental diseases in CHD patients has been demonstrated. Conversely, people suffering from a mental disease seem to have an increased risk of CHD. Moreover, common pathophysiological mechanisms may link both diseases. The objective of this article is to elucidate current understanding of the epidemiological and pathophysiological links between mental disorders and CHD.

Epidemiological aspects of the relationship between mental disorders and coronary heart disease

Severe mental illnesses and coronary heart disease

People with severe mental illness (SMI), including schizophrenia, bipolar disorder (BPD) and major depressive disorder (MDD), have an average mortality rate that is 2 to 3 times higher than the general population, corresponding to a 10- to 25-year shortened life expectancy.¹⁴ As in the general population, CVD are the most common cause of death in people with SMI.^{6,14,15} According to the most comprehensive meta-analysis of CVD risk in people with SMI conducted to date, including 3 211 768 patients and 113 383 368 controls, SMI patients, as a group, have a statistically significantly increased risk of CHD versus controls (a 51% higher risk in cross-sectional studies and a 54% higher risk in longitudinal studies).¹⁶ Although people with schizophrenia and MDD (versus controls) were found to be at increased risk for CHD, those with BPD were not (*Table I*). Despite this, BPD was significantly associated with CVD in longitudinal studies. The study also showed that SMI patients are at an increased CVD risk worldwide. CVD risk-reducing interventions in SMI patients are therefore needed with the same ur-

Meta-analytic results of cross-sectional studies		
Disorder	Adjusted odds ratio	95% Confidence Interval (P value)
Schizophrenia	1.52	1.48-1.56 (P<0.001)
Bipolar disorder	0.94	0.79-1.11 (P =0.49)
Major depressive disorder	2.52	1.81-3.52 (P <0.001)
Severe mental illnesses (pooled)	1.51	1.47-1.55 (P <0.001)
Meta-analytic results of longitudinal studies		
Disorder	Adjusted hazard ratio/relative risk	95% Confidence Interval (P value)
Schizophrenia	1.59	1.08-2.35 (P =0.02)
Bipolar disorder	1.16	0.76-1.78 (P =0.49)
Major depressive disorder	1.63	1.33-2.00 (P <0.0001)
Severe mental illnesses (pooled)	1.54	1.30-1.82 (P <0.0001)
Anxiety disorder	1.41	1.23-1.61 (P <0.0001)
Posttraumatic stress disorder	1.27	1.08-1.49 (P <0.05)

Table I. Meta-analytic results of studies on coronary heart disease risk of patients with severe or other mental illnesses.^{16,54,60} Statistically significant results are indicated in bold

gency across all regions of the world, particularly as recent data indicates that the management of physical diseases in the SMI population, despite earlier recommendations,⁶ has been much less successful as hoped.¹⁵

Depression and coronary heart disease

Although the association between depression (defined here as either MDD or significant depressive symptoms with substantial functional impairment) and CHD has been best studied in patients with existing CHD,¹⁷ a bidirectional relationship between both is now well established.^{12,18-20} Moreover, this association may not only involve bidirectional causation but also common pathophysiology (see below).^{18,20}

Depression in patients with existing coronary heart disease

The prevalence of depression is, compared with the general population, significantly higher in patients with CHD.¹² More than one fifth of all patients with CHD are depressed (with the risk of depression highest in the most severe CHD cases), and up to one third of them report elevated depressive symptoms. These are prevalence figures that are at least 4 times greater than in the general population.^{18,21-23} Although the prevalence of depression in established CHD is higher in women than men, depression is more strongly related to a worse cardiac prognosis in men than in women.²⁴

The cardiotoxic effects of depressive symptoms have been consistently observed despite the continual improvement in cardiovascular interventions, medications, and care.²² As a dose-response relationship seems to exist between depressive symptoms and cardiac events in patients with CHD,^{17,22} these patients are at increased risk for recurrent cardiovascular events and mortality.^{22,25} A meta-analysis of over 25 years of research into the relationship between post-MI depression and cardiac prognosis showed that post-MI depression is associated with a 1.6- to 2.7-fold increased risk of impaired outcomes within 24 months.²⁶

Although some studies have found that the association between depression and cardiovascular outcomes does not persist after control of confounding factors, many others (eg, ref 27) have been able to demonstrate an independent contribution of depression, beyond that which may be explained by confounding variables,

such as smoking, physical inactivity, hypertension, obesity, and cardiac disease severity in patients with existing CHD. This finding has led to the American Heart Association's recommendation that depression has to be considered as a risk factor for poor prognosis after acute coronary syndromes (ACS), such as MI.^{17,28} This statement was historic in that it represented the first "psychological" variable to be officially recognized by a major national health organization as a risk factor for vascular outcomes.¹⁷

Depression and the development of coronary heart disease

Although results from older reviews and meta-analyses²⁹⁻³⁴ have been inconsistent, later ones, including more rigorous and prospective data^{16-19,25,35} have shown that depression constitutes an independent (ie, confounder-adjusted) risk factor for CHD morbidity and mortality.^{12,21,36} According to a meta-analysis of 30 prospective cohort studies (N=893 850), individuals with depression, compared with nondepressed persons, experience a significant increased risk of 30% (RR=1.30, 95% CI:1.22-1.40) for CHD.³⁵ Another meta-analysis of prospective cohort studies (N=323 709) has found that depression was associated with a 31% increase in the risk of MI (adjHR=1.31, 95% CI:1.09-1.57) and a 36% increase in the risk of coronary death (adjHR=1.36, 95% CI:1.14-1.63), compared with nondepressed persons.¹⁹

Bipolar disorder and coronary heart disease

The association between BPD and CVD is less commonly recognized⁹ due to fragmentary and contradictory data. Although the most comprehensive meta-analysis of CVD risk in people with SMI did not find an increased risk of CHD in people with BPD,¹⁶ it nevertheless did find that BPD was significantly associated with CVD in longitudinal studies. This is in line with the results of several other reviews and meta-analyses showing that the risk of CVD-related death may be as much as doubled in BPD, compared with the general population.^{37,38} Evidence suggests that individuals diagnosed with BPD may have a 1.5- to 2.5-fold increased risk of CVD.^{9,38,39} Despite these controversial findings, it seems that CVD are responsible for about 35% to 40% of bipolar deaths, and that people with BPD who die from CVD tend to do so earlier than their non-bipolar counterparts.³⁷ Moreover,

Translational research

according to a scientific statement from the American Heart Association, BPD (and MDD) among youth are moderate-risk conditions that predispose to accelerated atherosclerosis and early CHD.⁹

Schizophrenia and coronary heart disease

The preponderance of evidence suggests that patients with schizophrenia or other psychoses are at significantly higher risk for cardiovascular morbidity and mortality than their counterparts in the general population.^{6,14,16,40,41} Although the first systematic review and meta-analysis of cohort studies (N=422 698) confirmed that schizophrenia indeed is significantly associated with an increased risk for CVD, no significant increased risk for CHD (RR=1.20, 95% CI:0.93-1.53) was found.⁴² This is not in line with the results of the above mentioned largest meta-analysis of CVD risk in people with SMI conducted to date.¹⁶ The negative findings of the former meta-analysis could be explained partially by the under-diagnosis rate of CHD among patients with schizophrenia.⁴² A recent study indicated that patients with schizophrenia die 10 years earlier from CVD, including CHD, than people in the general population.⁴³

Anxiety disorders and coronary heart disease

Anxiety symptoms and disorders in patients with existing coronary heart disease

The role of anxiety in CHD risk has been less studied.^{40,44} Although anxiety has been clinically linked with CHD for more than 100 years, the association between these conditions remains to be clarified.^{7,22,45-47}

Findings suggest that anxiety symptoms (commonly referred to as psychological distress)⁴⁸ or disorders (excluding posttraumatic stress disorder, which will be discussed in a separate section) are common in patients with CHD (for example the prevalence of panic disorder in CHD populations can be as high as 22%),⁴⁷ and may be associated with a substantial increase in cardiovascular morbidity and mortality.^{25,40,44-47,49-51} This association holds across the spectrum of anxiety disorders.⁸ Of all anxiety disorder subtypes, generalized anxiety disorder in particular may increase the risk for major adverse cardiac events in CHD patients.^{44,52}

Stewart et al⁵¹ have found that persistent moderate or severe psychological distress assessed over 4 years

was associated with a 2-fold to 4-fold increased risk of cardiovascular mortality in patients with stable CHD over the following 12 years. In contrast, distress which was mild or not persistent was not clearly associated with increased mortality. In a meta-analysis of 10 large prospective cohorts with 68 222 subjects, a dose-related association between psychological distress and cardiovascular (including CHD) mortality was found during a mean follow-up of 8.2 years (with a 22% increased risk of CVD death, HR=1.22, 95% CI:1.14-1.31).⁴⁸ Other research (eg, ref 53) confirms that episodes of psychological distress, which are not permanent, are associated with a lesser increase in risk.

Anxiety symptoms and disorders and the development of coronary heart disease

It seems that anxiety symptoms or disorders may be associated with a mild-to-moderate increased risk of developing CHD.^{25,40,44-47,49-51,54} Three meta-analyses,^{46,49,54} published in the last decade, reinforced the findings of prior studies that anxiety (disorders) can be associated with incident CHD. According to the most recent of these,⁵⁴ anxiety is associated with a 41% higher risk of developing CHD (RR=1.41, 95% CI:1.23-1.61, $P<0.0001$, *Table I*). Phobic anxiety was more strongly associated with incident CHD than general/unspecified anxiety. Another meta-analysis of 20 studies (N = 249 846), assessing the association of anxiety (ie, anxiety, panic, phobia, and worry) with incident CHD, found that initially healthy individuals with high anxiety had a 26% increased risk for incident CHD (HR=1.26, 95% CI:1.15-1.38, $P<0.0001$), independent of demographic variables, biological risk factors, and health behaviors.⁴⁹

Although all these findings are significant, it should be noted that high levels of heterogeneity relating to methodological differences among studies exist and that the risk associated with anxiety probably is not as great as that associated with depression.⁴⁶⁻⁴⁷ Sensitivity analyses have shown that it is likely that the exclusion of depression (which is highly correlated with anxiety) substantially reduces the risk of CHD (or attenuates the relationship between anxiety and poor cardiac outcomes in patients with CHD).^{22,45,46,52} The extent to which depression and anxiety disorders jointly and independently contribute to CHD risk should therefore be clarified.⁵²

Posttraumatic stress disorder and coronary heart disease

Posttraumatic stress disorder in patients with existing coronary heart disease

Sudden cardiac events, followed by an intrusive experience of treatments such as coronary surgery, can be potentially traumatic, leading to the development of posttraumatic stress disorder (PTSD).⁵⁵ According to a recent systematic review, including 150 studies, the prevalence of cardiac disease-induced PTSD shows a large variance (ranging from 0% to 38%), averaging at 4% to 16% depending on the diagnostic tool used.⁵⁵ PTSD symptoms occur in 10% to 25% of patients with ACS.⁵⁶⁻⁵⁷ The prevalence rates of PTSD in cardiac patients seem to be comparable to reports of prevalence rates of lifetime PTSD in the general population, as well as to rates of PTSD among those exposed to other kinds of traumatic events. Thus, while a minority of cardiac patients do develop PTSD symptoms, most experience distress that diminishes over time.^{55,57} Developing clinically significant PTSD symptoms due to ACS doubles the risk (RR=2.00, 95% CI:1.69-2.37) of having recurrent ACS or dying within 1 to 3 years, compared with cardiac patients who do not develop these symptoms.⁵⁸

Posttraumatic stress disorder and the development of coronary heart disease

Evidence is accumulating that experiences of persistent or intense stress and PTSD may be independently associated with an increased risk of developing CHD over a relatively short period.^{22,25,57,59-62} A systematic review and meta-analysis of studies that assessed PTSD in individuals initially free of CHD (N=402 274), found that PTSD was associated with a 27% increased risk for incident CHD or cardiac-specific mortality (HR=1.27, 95% CI:1.08-1.49), after adjustment for numerous confounding variables, including depression (*Table I*).⁶⁰ A prospective cohort study on the impact of combat deployment and PTSD on newly reported CHD among US active duty and reserve forces has found that deployment on combat (versus non-combat) missions was associated with a 63% increased risk of new-onset CHD (adjOD=1.63; 95% CI: 1.11-2.40).⁶² A twin study with 281 pairs, found that the incidence of CHD was

more than double in twins with PTSD (22.6%), compared with those without PTSD (8.9%)($P<0.0001$), over a median follow-up of 13 years. This association remained robust after adjusting for lifestyle factors, other CHD risk factors, MDD, and other psychiatric diagnoses (OR=2.1, 95% CI:1.1-3.9, $P<0.02$).⁶¹

Other mental disorders

Although severity of mental illness may be important in the risk for subsequent CHD, the link between mental disorders and CHD risk probably is not confined to those patients with more chronic or more severe illness. A large-scale Swedish study (N=1 107 524) showed that the association between mental illness and CHD is present across a wide range of mental disorders, including adjustment disorders, personality disorders, alcohol-related disorders, and other substance use disorders, with higher CHD risks ranging from 35% to 92%, compared with those who were not diagnosed with the disorder in question.⁴⁰

Pathophysiological aspects of the relationship between mental disorders and coronary heart disease

Mental disorders and CHD appear to have a shared etiology. The underlying mechanism of how mental disorders contribute to CHD is, however, complex and has not been fully elucidated.^{12,19,61} Plausible pathways for the increased risk of CHD in people with mental disorders fall into several categories: biological, behavioral, psychological, and genetic mechanisms.

Biological mechanisms

Many biological mechanisms have been proposed to be implicated in the association between mental disorders and CHD. Mental disorders have been associated with autonomic nervous system (ANS) dysfunction (diminished heart rate variability, hypertension, increased variability in the QT interval, increased dispersion of the QT and P-wave), hypothalamic-pituitary-adrenal (HPA) axis dysregulation, inflammation, lipid pattern abnormalities, oxidative stress, and increased platelet reactivity. These physiological processes are all involved in the development and progression of CHD.^{9,11,12,17,19,20,44,47,52,57,59-61,63,64}

Translational research

Hypothalamic-pituitary-adrenal axis dysregulation

Elevated cortisol levels as a result of enhanced activity of the HPA axis⁶⁵ are a possible biological mechanism in the link between mental disorders and CHD.^{7,12,17,65} Cortisol participates in the pathophysiological processes that contribute to atherogenesis.²⁰ HPA hyperactivity and elevated cortisol levels have been documented in several mental disorders (ie, depression, anxiety disorders, and schizophrenia).^{12,17,66} However, a relationship between the HPA axis dysregulation and anxiety has not been found in all studies of PTSD, and might be even less robust in studies of other anxiety disorders.⁶⁴

Autonomic nervous system dysfunction

The ANS is divided into the sympathetic and parasympathetic systems that act to control heart rate, blood pressure, vasodilation, and other critical functions. Hyperactivity of the sympathetic system can increase the risk of poor cardiovascular outcomes, including death.⁵⁷ Patients with mental disorders, such as MDD and anxiety disorders, tend to have higher levels of circulating catecholamines, a marker of sympathetic activation, causing increases in heart rate and blood pressure while at the same time decreasing coronary blood flow and increasing systemic vascular resistance.^{7,20,61} These processes may contribute to the excess risk of CHD associated with these disorders.¹² Another marker of ANS dysfunction is decreased heart rate variability (HRV). Decreased HRV, known to be an independent risk factor for cardiac mortality,^{12,18} is observed across several mental disorders, including MDD, schizophrenia and anxiety disorders, and CHD.^{8,11,66-67}

Inflammation

Inflammation might be a shared etiological factor for both mental disorders and CHD.²⁰ The role of inflammation in the development and prognosis of CHD has been described extensively in the cardiovascular literature.²⁰ Studies have demonstrated that inflammation contributes to the development, sustainment, and progression of atherosclerosis.^{12,17,57,68} Inflammation entails endothelial dysfunction (characterized by a loss of vasodilatory and anti-inflammatory factors and a gain of vasoconstrictive and proinflammatory factors), an early pathological event in the development of atherosclerotic CVD.^{7,57,69}

Increased levels of inflammatory biomarkers [including interleukin (IL)-1 and IL-6 and C-reactive protein, (CRP)], predicting CVD and events,⁷⁰ have been demonstrated for MDD, schizophrenia, and BPD.^{17-18,71-75} Data suggests that antidepressant treatment tends to have a normalizing effect on the proinflammatory states seen in depression.^{12,17}

Increased platelet reactivity

Thrombus generation resulting from platelet activation and aggregation is the established main process involved in atherosclerotic vascular diseases, including CHD.^{36,76} Several studies support the hypothesis that MDD is associated with increased platelet reactivity.^{7,18,21} Given the established link between serotonin and depression and the fact that the body's serotonin is almost exclusively stored in platelets along with the fact that increased platelet reactivity is firmly linked to CHD,^{36,76} platelet dysfunction is a logical mechanism linking depression and CHD.^{12,21}

Medication

The use of antipsychotic medication and, to a lesser extent, antidepressants and mood stabilizers, may increase the risk of CHD.^{14,39,63,77} In addition to obesity and other cardio-metabolic-related mechanisms, a direct effect of antipsychotics on cardiovascular risk may exist. For example, ANS dysfunction triggered by schizophrenia may be exacerbated by antipsychotic treatment through blockade of peripheral dopamine receptors, increasing sympathetic activity.¹⁴

Behavioral mechanisms

Evidence suggests that, in addition to biological mechanisms, behavioral mechanisms are substantially involved in the relation between mental disorders and CHD.¹² Depression, schizophrenia, and BPD, as well as other mental disorders such as anxiety disorders have been associated with a range of behaviors that may increase the risk of cardiac morbidity and mortality. More specifically, people with these disorders display generally unhealthy behaviors (high-fat diet, smoking, alcohol or other substance use, lack of physical exercise), which are also well-established risk factors for CHD. Moreover, these patients mostly have poor medication

adherence (to cardioprotective and other prescribed medications), and low adherence to rehabilitation programs.^{8,11,12,17-19,40,44,47,52,57,61}

Psychological mechanisms

The influence of psychological factors on the etiopathogenesis of CHD is unquestionable. Among these factors mainly personality and emotional factors, such as anxiety, depression, and stress play an important role.⁷

Although large clinical trials raise doubts about the influence of Type A personality (including competitiveness and hostility) on CHD risk, some evidence indicates that Type D personality (including negative affectivity and social inhibition) may be associated with plaque vulnerability, after adjustment for other risk factors.⁷⁸ Stress and anxiety cause excess activation of the HPA axis and sympathetic nervous system, leading to higher cortisol and catecholamine levels, respectively. Through these changes they can lead to inflammation, metabolic abnormalities, platelet activation, endothelial dysfunction, hypertension, and insulin resistance, ultimately leading to atherosclerosis and to the development and/or progression of CHD.^{8,11,22,36,44,47,52,57} Depression and impairments in social functioning (lack of family support, solitude) can increase CHD risk in patients with PTSD.^{7,59} Sleep disturbances may further increase CHD risk in these patients.⁵⁹ In individuals with BPD psychological factors such as childhood trauma, stress, and some personality features have been hypothesized to contribute to both CHD in BPD patients and BPD itself.⁶³

Genetic mechanisms

Schizophrenia, MDD, BPD, and cardiometabolic diseases are highly heritable. Genetic factors contribute to 31% to 42% in MDD, 30% to 40% in anxiety disorders, 59% to 85% in BPD, 30% to 60% in CHD, and up to 80% in schizophrenia.^{10,64,79} Twin studies and molecular genetic studies have revealed relatively modest genetic correlations between cardio-metabolic abnormalities, CHD and mental disorders.^{9,20,63} These observations suggest potential pleiotropic effects of a shared gene locus that is associated with mental disorders and cardio-metabolic diseases.¹⁰

Comorbid conditions

The association between mental disorders and CHD is often complicated by comorbid psychiatric conditions.⁵⁷ Several mental disorders, including SMI and anxiety disorders, are correlated with comorbid conditions such as obesity, hypertension, dyslipidemia (elevated triglycerides and decreased high-density lipoprotein [HDL] cholesterol), glucose intolerance or insulin resistance, all known to be associated with an increased risk of CHD. These abnormalities are major characteristics of the metabolic syndrome, that confers a 3- to 6-fold increased risk of mortality due to CHD.^{6-8,19,42,57} Lifestyle and behavioral patterns (smoking, physical inactivity, poor dietary habits), as well as medication can play important roles in the prevalence of the metabolic syndrome in patients with mental disorders.^{6,14}

Conclusion

Efforts to reduce the excess burden of morbidity and mortality among people with mental disorders need to address the problem of CHD, as this is a major contributor to this excess burden. The differential mortality in people with mental disorders not only stems from a number of behavioral and lifestyle factors (or quality of health care and/or lack of access to it),¹⁵ but also from biological factors that seem to be common to both mental and cardio-metabolic diseases. Future studies should therefore address the mechanisms underlying the increased risk of CHD in persons with a mental disorder, as a greater awareness of the relationship between CHD and mental disorders would help to develop more effective prevention and treatment strategies and contribute significantly to a lessening of this global burden. □

Disclosure/Acknowledgments: Dr Marc De Hert, Prof Faculty of Medicine, declares that he has received educational grants from, and has participated in, advisory boards of the Janssen-Cilag company. Johan Detraux, research psychologist at the Z.org KU Leuven - University Psychiatric Centre, Department of Neurosciences, declares that his work for the Belgian Discussion Board on Antipsychotic Treatment, established by Janssen and consisting of Belgian psychiatrists discussing relevant topics on antipsychotic treatment, has been partially supported by the Janssen Academy. Davy Vancampfort has no conflict of interest. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Translational research

REFERENCES

1. Shepard D, VanderZanden A, Moran A, Naghavi M, Murray C, Roth G. Ischemic heart disease worldwide, 1990 to 2013: estimates from the global burden of disease study 2013. *Circ Cardiovasc Qual Outcomes*. 2015;8(4):455-456.
2. Benziger CP, Roth GA, Moran AE. The global burden of disease study and the preventable burden of NCD. *Glob Heart*. 2016;11(4):393-397.
3. Foley JR, Plein S, Greenwood JP. Assessment of stable coronary artery disease by cardiovascular magnetic resonance imaging: current and emerging techniques. *World J Cardiol*. 2017;9(2):92-108.
4. World Health Organization (2017). Cardiovascular diseases (CVDs). Fact sheet, updated May 2017. Available at: <http://www.who.int/mediacentre/factsheets/fs317/en/>. Accessed December 18, 2017.
5. American Heart Association. Available at: http://www.heart.org/HEARTORG/Conditions/HeartAttack/TreatmentofaHeartAttack/Silent-Ischemia-and-Ischemic-Heart-Disease_UCM_434092_Article.jsp#.WZ_pPT-5JaUl. Accessed December 18, 2017.
6. De Hert M, Correll CU, Bobes J, et al. Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care. *World Psychiatry*. 2011;10(1):52-77.
7. Nasifowska-Barud A, Zapolski T, Barud M, Wysokiński A. Overt and covert anxiety as a toxic factor in ischemic heart disease in women: the link between psychological factors and heart disease. *Med Sci Monit*. 2017;23:751-758.
8. Player MS, Peterson LE. Anxiety disorders, hypertension, and cardiovascular risk: a review. *Int J Psychiatry Med*. 2011;41(4):365-377.
9. Goldstein BI, Carnethon MR, Matthews KA, et al. Major depressive disorder and bipolar disorder predispose youth to accelerated atherosclerosis and early cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. 2015;132(10):965-986.
10. Amare AT, Schubert KO, Klingler-Hoffmann M, Cohen-Woods S, Baune BT. The genetic overlap between mood disorders and cardiometabolic diseases: a systematic review of genome wide and candidate gene studies. *Transl Psychiatry*. 2017;7(1):e1007.
11. Stapelberg NJ, Hamilton-Craig I, Neumann DL, Shum DH, McConnell H. Mind and heart: heart rate variability in major depressive disorder and coronary heart disease - a review and recommendations. *Aust N Z J Psychiatry*. 2012;46(10):946-957.
12. Whooley MA, Wong JM. Depression and cardiovascular disorders. *Annu Rev Clin Psychol*. 2013;9:327-354.
13. Walker ER, McGee RE, Druss BG. Mortality in mental disorders and global disease burden implications: a systematic review and meta-analysis. *JAMA Psychiatry*. 2015;72(4):334-341.
14. Correll CU, Detraux J, De Lepeleire J, De Hert M. Effects of antipsychotics, antidepressants and mood stabilizers on risk for physical diseases in people with schizophrenia, depression and bipolar disorder. *World Psychiatry*. 2015;14(2):119-136.
15. De Hert M, Detraux J. Reversing the downward spiral for people with severe mental illness through educational innovations. *World Psychiatry*. 2017;16(1):41-42.
16. Correll CU, Solmi M, Veronese N, et al. Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3 211 768 patients and 113 383 368 controls. *World Psychiatry*. 2017;16(2):163-180.
17. Fiedorowicz JG. Depression and cardiovascular disease: an update on how course of illness may influence risk. *Curr Psychiatry Rep*. 2014;16(10):492.
18. Seligman F, Nemeroff CB. The interface of depression and cardiovascular disease: therapeutic implications. *Ann N Y Acad Sci*. 2015;1345:25-35.
19. Wu Q, Kling JM. Depression and the risk of myocardial infarction and coronary death: a meta-analysis of prospective cohort studies. *Medicine*. 2016;95(6):e2815.
20. Adibfar A, Saleem M, Lancot KL, Herrmann N. Potential biomarkers for depression associated with coronary artery disease: a critical review. *Curr Mol Med*. 2016;16(2):137-164.
21. Williams MS. Platelets and depression in cardiovascular disease: a brief review of the current literature. *World J Psychiatry*. 2012;2(6):114-123.
22. Cohen BE, Edmondson D, Kronish IM. State of the art review: depression, stress, anxiety, and cardiovascular disease. *Am J Hypertens*. 2015;28(11):1295-1302.
23. Ren Y, Yang H, Browning C, Thomas S, Liu M. Performance of screening tools in detecting major depressive disorder among patients with coronary heart disease: a systematic review. *Med Sci Monit*. 2015;21:646-653.
24. Doyle F, McGee H, Conroy R, et al. Systematic review and individual patient data meta-analysis of sex differences in depression and prognosis in persons with myocardial infarction: a MINDMAPS Study. *Psychosom Med*. 2015;77(4):419-428.
25. Scott KM. Depression, anxiety and incident cardiometabolic diseases. *Curr Opin Psychiatry*. 2014;27(4):289-293.
26. Meijer A, Conradi HJ, Bos EH, Thombs BD, van Melle JP, de Jonge P. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis of 25 years of research. *Gen Hosp Psychiatry*. 2011;33(3):203-216.
27. Meijer A, Conradi HJ, Bos EH, et al. Adjusted prognostic association of depression following myocardial infarction with mortality and cardiovascular events: individual patient data meta-analysis. *Br J Psychiatry*. 2013;203(2):90-102.
28. Lichtman JH, Froelicher ES, Blumenthal JA, et al. Depression as a risk factor for poor prognosis among patients with acute coronary syndrome: systematic review and recommendations: a scientific statement from the American Heart Association. *Circulation*. 2014;129(12):1350-1369.
29. Booth-Kewley S, Friedman HS. Psychological predictors of heart disease: a quantitative review. *Psychol Bull*. 1987;101(3):343-362.
30. Rugulies R. Depression as a predictor for coronary heart disease: a review and meta-analysis. *Am J Prev Med*. 2002;23(1):51-61.
31. Wulsin LR, Singal BM. Do depressive symptoms increase the risk for the onset of coronary disease? A systematic quantitative review. *Psychosom Med*. 2003;65(2):201-210.
32. Barth J, Schumacher M, Herrmann-Lingen C. Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. *Psychosom Med*. 2004;66(6):802-813.
33. Nicholson A, Kuper H, Hemingway H. Depression as an aetiological and prognostic factor in coronary heart disease: a meta-analysis of 6362 events among 146 538 participants in 54 observational studies. *Eur Heart J*. 2006;27(23):2763-2774.
34. Van der Kooy K, van Hout H, Marwijk H, Marten H, Stehouwer C, Beekman A. Depression and the risk for cardiovascular diseases: systematic review and meta analysis. *Int J Geriatr Psychiatry*. 2007;22(7):613-626.
35. Gan Y, Gong Y, Tong X, et al. Depression and the risk of coronary heart disease: a meta-analysis of prospective cohort studies. *BMC Psychiatry*. 2014;14:371.
36. Kim DA, McClure WG, Neighoff JB, Vaidya D, Williams MS. Platelet response to serotonin in patients with stable coronary heart disease. *Am J Cardiol*. 2014;114(2):181-186.
37. Miller C, Bauer MS. Excess mortality in bipolar disorders. *Curr Psychiatry Rep*. 2014;16(11):499.
38. Hayes JF, Miles J, Walters K, King M, Osborn DP. A systematic review and meta-analysis of premature mortality in bipolar affective disorder. *Acta Psychiatr Scand*. 2015;131(6):417-425.
39. Crump C, Sundquist K, Winkleby MA, Sundquist J. Comorbidities and mortality in bipolar disorder: a Swedish national cohort study. *JAMA Psychiatry*. 2013;70(9):931-939.
40. Gale CR, Batty GD, Osborn DP, Tynelius P, Rasmussen F. Mental disorders across the adult life course and future coronary heart disease: evidence for general susceptibility. *Circulation*. 2014;129(2):186-193.
41. Hayes JF, Marston L, Walters K, King MB, Osborn DPJ. Mortality gap for people with bipolar disorder and schizophrenia: UK-based cohort study 2000-2014. *Br J Psychiatry*. 2017;211(3):175-181.
42. Fan Z, Wu Y, Shen J, Ji T, Zhan R. Schizophrenia and the risk of cardiovascular diseases: a meta-analysis of thirteen cohort studies. *J Psychiatr Res*. 2013;47(11):1549-1556.
43. Westman J, Eriksson SV, Gissler M, et al. Increased cardiovascular mortality in people with schizophrenia: a 24-year national register study. *Epidemiol Psychiatr Sci*. 2017 Jun 5:1-9.
44. Tully PJ, Cosh SM, Baune BT. A review of the affects of worry and generalized anxiety disorder upon cardiovascular health and coronary heart disease. *Psychol Health Med*. 2013;18(6):627-644.

45. Celano CM, Millstein RA, Bedoya CA, Healy BC, Roest AM, Huffman JC. Association between anxiety and mortality in patients with coronary artery disease: a meta-analysis. *Am Heart J*. 2015;170(6):1105-1115.
46. Tully PJ, Turnbull DA, Beltrame J, et al. Panic disorder and incident coronary heart disease: a systematic review and meta-regression in 1 131 612 persons and 58 111 cardiac events. *Psychol Med*. 2015;45(14):2909-2920.
47. Caldirola D, Schruers KR, Nardi AE, De Berardis D, Fornaro M, Perna G. Is there cardiac risk in panic disorder? An updated systematic review. *J Affect Disord*. 2016;194:38-49.
48. Russ TC, Stamatakis E, Hamer M, Starr JM, Kivimäki M, Batty GD. Association between psychological distress and mortality: individual participant pooled analysis of 10 prospective cohort studies. *BMJ*. 2012;345:e4933.
49. Roest AM, Martens EJ, de Jonge P, Denollet J. Anxiety and risk of incident coronary heart disease: a meta-analysis. *J Am Coll Cardiol*. 2010;56(1):38-46.
50. Thurston RC, Rewak M, Kubzansky LD. An anxious heart: anxiety and the onset of cardiovascular diseases. *Prog Cardiovasc Dis*. 2013;55(6):524-537.
51. Stewart RAH, Colquhoun DM, Marschner SL, et al. Persistent psychological distress and mortality in patients with stable coronary artery disease. *Heart*. 2017;103(23):1860-1866.
52. Tully PJ, Cosh SM, Baumeister H. The anxious heart in whose mind? A systematic review and meta-regression of factors associated with anxiety disorder diagnosis, treatment and morbidity risk in coronary heart disease. *J Psychosom Res*. 2014;77(6):439-448.
53. Rosengren A, Hawken S, Ounpuu S, et al. Association of psychosocial risk factors with risk of acute myocardial infarction in 11 119 cases and 13 648 controls from 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364(9438):953-962.
54. Emdin CA, Odotayo A, Wong CX, Tran H, Hsiao AJ, Hunn BH. Meta-analysis of anxiety as a risk factor for cardiovascular disease. *Am J Cardiol*. 2016;118(4):511-519.
55. Vilchinsky N, Ginzburg K, Fait K, Foa EB. Cardiac-disease-induced PTSD (CDI-PTSD): a systematic review. *Clin Psychol Rev*. 2017;55:92-106.
56. Edmondson D, Rieckmann N, Shaffer JA, et al. Posttraumatic stress due to an acute coronary syndrome increases risk of 42-month major adverse cardiac events and all-cause mortality. *J Psychiatr Res*. 2011;45(12):1621-1626.
57. Levine AB, Levine LM, Levine TB. Posttraumatic stress disorder and cardiometabolic disease. *Cardiology*. 2014;127(1):1-19.
58. Edmondson D, Richardson S, Falzon L, Davidson KW, Mills MA, Neria Y. Posttraumatic stress disorder prevalence and risk of recurrence in acute coronary syndrome patients: a meta-analytic review. *PLoS One*. 2012;7(6):e38915.
59. Edmondson D, Cohen BE. Posttraumatic stress disorder and cardiovascular disease. *Prog Cardiovasc Dis*. 2013;55(6):548-556.
60. Edmondson D, Kronish IM, Shaffer JA, Falzon L, Burg MM. Posttraumatic stress disorder and risk for coronary heart disease: a meta-analytic review. *Am Heart J*. 2013;166(5):806-814.
61. Vaccarino V, Goldberg J, Rooks C, et al. Post-traumatic stress disorder and incidence of coronary heart disease: a twin study. *J Am Coll Cardiol*. 2013;62(11):970-978.
62. Crum-Cianflone NF, Bagnell ME, Schaller E, et al. Impact of combat deployment and posttraumatic stress disorder on newly reported coronary heart disease among US active duty and reserve forces. *Circulation*. 2014;129(18):1813-1820.
63. Marshe VS, Pira S, Mantere O, et al. C-reactive protein and cardiovascular risk in bipolar disorder patients: a systematic review. *Prog Neuropsychopharmacol Biol Psychiatry*. 2017;79(Pt B):442-451.
64. Craske MG, Stein MB, Eley TC, et al. Anxiety disorders. *Nat Rev Dis Primers*. 2017;3:17024.
65. Zorn JV, Schür RR, Boks MP, Kahn RS, Joëls M, Vinkers CH. Cortisol stress reactivity across psychiatric disorders: a systematic review and meta-analysis. *Psychoneuroendocrinology*. 2017;77:25-36.
66. Montaquila JM, Trachik BJ, Bedwell JS. Heart rate variability and vagal tone in schizophrenia: a review. *J Psychiatr Res*. 2015;69:57-66.
67. Moon E, Lee SH, Kim DH, Hwang B. Comparative study of heart rate variability in patients with schizophrenia, bipolar disorder, post-traumatic stress disorder, or major depressive disorder. *Clin Psychopharmacol Neurosci*. 2013;11(3):137-143.
68. Teague H, Mehta NN. The link between inflammatory disorders and coronary heart disease: a look at recent studies and novel drugs in development. *Curr Atheroscler Rep*. 2016;18(1):3.
69. Zehr KR, Walker MK. Omega-3 polyunsaturated fatty acids improve endothelial function in humans at risk for atherosclerosis: A review. *Prostaglandins Other Lipid Mediat*. 2018;134:131-140.
70. Libby P. Inflammation in atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2009;71(2):171-186.
71. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosom Med*. 2009;71(2):171-186.
72. Dowlati Y, Herrmann N, Swardfager W, et al. A meta-analysis of cytokines in major depression. *Biol Psychiatry*. 2010;67(5):446-457.
73. Potvin S, Stip E, Sepehry AA, Gendron A, Bah R, Kouassi E. Inflammatory cytokine alterations in schizophrenia: a systematic quantitative review. *Biol Psychiatry*. 2008;63(8):801-808.
74. Upthegrove R, Manzanares-Teson N, Barnes NM. Cytokine function in medication-naïve first episode psychosis: a systematic review and meta-analysis. *Schizophr Res*. 2014;155(1-3):101-108.
75. Manu P, Correll CU, Wampers M, et al. Markers of inflammation in schizophrenia: association vs. causation. *World Psychiatry*. 2014;13(2):189-192.
76. Spiliopoulos S, Pastromas G. Current status of high on-treatment platelet reactivity in patients with coronary or peripheral arterial disease: mechanisms, evaluation and clinical implications. *World J Cardiol*. 2015;7(12):912-921.
77. Yu ZH, Jiang HY, Shao L, Zhou YY, Shi HY, Ruan B. Use of antipsychotics and risk of myocardial infarction: a systematic review and meta-analysis. *Br J Clin Pharmacol*. 2016;82(3):624-632.
78. Lin P, Li L, Wang Y, et al. Type D personality, but not Type A behavior pattern, is associated with coronary plaque vulnerability. *Psychol Health Med*. 2018;23(2):216-223.
79. Misiak B, Stramecki F, Gawęda Ł, et al. Interactions between variation in candidate genes and environmental factors in the etiology of schizophrenia and bipolar disorder: a systematic review. *Mol Neurobiol*. 2017 Aug 18. doi: 10.1007/s12035-017-0708-y.

La intrigante relación entre enfermedad coronaria y trastornos mentales

La enfermedad coronaria (EC) y los trastornos mentales están entre las principales causas de morbilidad y mortalidad en todo el mundo. Décadas de investigación han revelado varias relaciones, y a veces sorprendentes, entre EC y enfermedad mental e incluso se ha sugerido que ambas pueden ser causa una de la otra. Sin embargo, aún no se ha establecido claramente la naturaleza precisa de estas relaciones. Por lo tanto, el objetivo de este artículo es revisar y discutir de manera comprensible el estado del arte de la naturaleza de los aspectos epidemiológicos y fisiopatológicos de las relaciones bidireccionales entre la enfermedad mental y la EC. Esta revisión demuestra que existe un gran conjunto de datos epidemiológicos prospectivos que encuentran que las personas con enfermedades mentales graves, incluyendo esquizofrenia, trastorno bipolar y trastorno depresivo, como grupo, tienen un riesgo aumentado de desarrollar EC, en comparación con controles [razón de riesgo ajustada (RRa)=1,54; 95% CI: 1,30-1,82; P<0,0001]. Aunque en menor grado, tanto los síntomas ansiosos o trastornos de ansiedad [Riesgo relativo (RR)= 1,41, 95% CI: 1,23-1,61; P<0,0001], como las experiencias de estrés intenso o persistente, o el trastorno por estrés post-traumático (TEPT) (RRa=1,27, 95% CI: 1,08-1,49), también pueden estar asociados de manera independiente con un riesgo aumentado de desarrollar EC. Por otra parte, la investigación también indica que estos síntomas o patologías mentales son comunes en pacientes con EC y pueden estar asociadas con un aumento significativo de la morbilidad y mortalidad cardiovascular. Por último, las enfermedades mentales y la EC parecen tener una etiología compartida, incluyendo mecanismos biológicos, conductuales y psicológicos.

Le lien surprenant entre la maladie coronaire et les troubles mentaux

La maladie coronaire (MC) et la maladie mentale font partie des principales causes de morbidité et de mortalité dans le monde. Des décennies de recherche ont montré plusieurs liens, parfois surprenants, entre les deux et ont même suggéré qu'en fait, l'un pouvait entraîner l'autre et réciproquement. La nature de ces liens n'est cependant pas claire. Cet article a donc pour but d'analyser de façon exhaustive et de discuter les connaissances épidémiologiques et physiopathologiques les plus récentes concernant les liens bidirectionnels entre la maladie mentale et la MC. Dans cet article, de nombreuses données épidémiologiques prospectives montrent que le risque de développer une MC chez les sujets atteints de maladie mentale sévère comme la schizophrénie, les troubles bipolaires et les troubles dépressifs majeurs, en tant que groupe, est augmenté comparé au risque de sujets témoins (Rapport de risque ajusté $HR_{adj} = 1,54$; IC 95 % : 1,3-1,82 $p < 0,0001$). Les troubles ou symptômes anxieux (Risque relatif RR = 1,41 ; IC 95 % : 1,23-1,61 $p < 0,0001$) de même que les expériences de stress intense ou persistant ou les troubles de stress post-traumatique (TSPT) ($HR_{adj} = 1,27$; IC 95 % : 1,08-1,49), bien qu'à un moindre degré, peuvent aussi être associés de façon indépendante à un risque augmenté de développer une MC. D'un autre côté, d'après la recherche, ces symptômes/troubles mentaux sont courants chez les patients atteints de MC et peuvent s'associer à une morbidité et mortalité cardiovasculaires augmentées de façon importante. Enfin, les troubles mentaux et la MC semblent partager des facteurs étiologiques communs, y compris par des mécanismes biologiques, comportementaux, psychologiques et génétiques.