ESC European Society of Cardiology

European Heart Journal (2020) **41**, 1687–1696
doi:10.1093/eurheartj/ehy913

ESC REPORT

Depression and coronary heart disease: 2018 position paper of the ESC working group on coronary pathophysiology and microcirculation

Viola Vaccarino[1,2], Lina Badimon[3], J. Douglas Bremner[4,5,6], Edina Cenko[7], Judit Cubedo[3], Maria Dorobantu[8], Dirk J. Duncker[9], Akos Koller[10,11], Olivia Manfrini[7], Davor Milicic[12], Teresa Padro[3], Axel R. Pries[13], Arshed A. Quyyumi[2], Dimitris Tousoulis[14], Danijela Trifunovic[15,16], Zorana Vasiljevic[16], Cor de Wit[17], and Raffaele Bugiardini[7]*

ESC Scientific Document Group Reviewers: Patrizio Lancellotti[18,19] and António Vaz Carneiro[20]

[1]Department of Epidemiology, Rollins School of Public Health, Emory University, 1518 Clifton Road Northeast, Atlanta, GA, 30322, USA; [2]Department of Medicine (Cardiology), Emory University School of Medicine, 1518 Clifton Road Northeast, Atlanta, GA, 30322, USA; [3]Cardiovascular Program (ICCC), IR-Hospital de la Santa Creu i Sant Pau. CiberCV-Institute Carlos III. Autonomous University of Barcelona, C/ Sant Antoni Maria Claret, 167, 08025, Barcelona, Spain; [4]Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, 12 Executive Park Drive Northeast, Atlanta, GA, 30329, USA; [5]Department of Radiology, Emory University School of Medicine, 1364 Clifton Road Northeast, Atlanta, GA, 30322, USA; [6]Atlanta Veterans Administration Medical Center, 670 Clairmont Road, Decatur, GA, 30033, USA; [7]Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Via Giuseppe Massarenti 9, 40138, Bologna, Italy; [8]Cardiology Department, University of Medicine and Pharmacy 'Carol Davila' of Bucharest, Emergency Clinical Hospital of Bucharest, Calea Floreasca 8, Sector 1, Bucuresti, 014461, Romania; [9]Division of Experimental Cardiology, Department of Cardiology, Thoraxcenter, Cardiovascular Research Institute COEUR, Erasmus MC, University Medical Center, Rotterdam, Dr. Molewaterplein 40, 3015 GD, Rotterdam, The Netherlands; [10]Institute of Natural Sciences, University of Physical Education, Alkotas street, 44, 1123, Budapest, Hungary; [11]Department of Physiology, New York Medical College, Valhalla, NY, 10595, USA; [12]Department for Cardiovascular Diseases, University Hospital Center Zagreb, University of Zagreb, Kispaticeva 12, HR-10000, Zagreb, Croatia; [13]Department of Physiology, Charitè-University Medicine, Thielallee 71, D-14195, Berlin, Germany; [14]First Department of Cardiology, Hippokration Hospital, University of Athens Medical School, Vasilissis Sofias 114, TK 115 28, Athens, Greece; [15]Department of Cardiology, University Clinical Center of Serbia, Pasterova 2, 11000, Belgrade, Serbia; [16]School of Medicine, University of Belgrade, Dr Subotica 8, 11000, Belgrade, Serbia; [17]Institut für Physiologie, Universität zu Lübeck and Deutsches Zentrumfür Herz-Kreislauf-Forschung (DZHK), Ratzeburger Allee 160, 23538, Lübeck, Germany; [18]GIGA Cardiovascular Sciences, Departments of Cardiology, Heart Valve Clinic, CHU Sart Tilman, University of Liège Hospital, Liège, Belgium; [19]Anthea Hospital, Gruppo Villa Maria Care and Research, VIA C. Rosalba, 35/37, Bari, Italy; and [20]Preventive Medicine and Public Health Institute, Center for Evidence Based Medicine, Faculty of Medicine, University of Lisbon, Av. Prof. Egas Moniz, 1649-028, Lisbon, Portugal

Received 30 July 2018; revised 25 October 2018; editorial decision 28 December 2018; accepted 3 January 2019; online publish-ahead-of-print 28 January 2019

Introduction

Major depression is a highly prevalent condition, affecting approximately 10% of the population.[1] It is also a growing global problem,[2] and has been consistently associated with increased risk of coronary heart disease (CHD).[3] It is therefore not surprising that depression is highly comorbid with CHD, being two to three times more common among patients with CHD than in the general population. The prevalence of depression is 15–30% in patients with CHD,[4] and is approximately twice as high in women than men, especially affecting young women in the aftermath of acute myocardial infarction (MI).[5]

Depression as a risk factor for CHD has been characterized from mild depressive symptoms to a clinical diagnosis of major depression. As defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), clinical depression, or major depression, is characterized by depressed mood or anhedonia (loss of interest or pleasure) for at least 2 weeks accompanied by significant functional impairment and additional somatic or cognitive symptoms.[6] Most epidemiological studies of depression and incidence of CHD have used depressive symptom scales, and have frequently demonstrated a dose–response pattern, with higher levels of depressive symptoms being associated with higher risk.[3]

The exact mechanisms linking depression to increased CHD risk are complex and multifactorial, and still incompletely understood.[7] Although adverse lifestyle behaviours and traditional CHD risk factors, such as smoking and sedentary lifestyle, largely contribute to the risk, they do not explain it entirely. In CHD patients, depression is

* Corresponding author. Tel/Fax: +39 051 347 290, Email: raffaele.bugiardini@unibo.it

also associated with severity of functional impairment, lower adherence to therapy and lower participation in cardiac rehabilitation. Whether and to what extent these factors explain the relationship between depression and CHD deserves future study. The present paper summarizes key aspects in our current knowledge linking depression and CHD within the intersecting fields of neuroscience, cardiovascular physiology, and behavioural medicine, with the objective of bringing attention to this area and stimulating interdisciplinary research, clinical awareness, and improved care.

Epidemiological aspects

Depression and coronary heart disease

Many studies have shown a relationship between major depression, or depressive symptoms, and CHD.[3,8,9] This literature has been summarized by a number of meta-analyses,[8–10] all providing evidence for an association between clinical depression (or depressive symptoms) and CHD. This link is seen in individuals initially free of CHD and in a variety of CHD patient populations, including patients with acute coronary syndromes (ACS), heart failure, stable CHD, and post-coronary bypass surgery. However, individual studies have produced heterogeneous risk estimates and have varied in their ability to adjust for other factors such as smoking, physical inactivity, other risk factors, and severity of CHD. Indeed, depression is associated with several CHD risk factors and health behaviours as described above. In statistical models that adjust for these risk factors, depression usually remains an independent risk factor for CHD, suggesting a biological relationship between these two disease states that remains in part unexplained by an increase in traditional risk factors or lifestyle behaviours.

In one of the relatively recent meta-analyses, which included 30 prospective cohort studies of individuals initially free of CHD, depression was associated with a 30% increased risk of future coronary events.[9] The association remained significant in the group of studies that adjusted for socio-demographic factors and lifestyle behaviours.[8] In community samples and in general practice clinics, the rate of depression is about, 10%[11] but it goes up to about 15–30% in patients with CHD.[11,12]

Studies have also suggested that specific subtypes of depression may be more strongly associated with CHD risk than others. For instance, patients with a new-onset of depression after ACS, with treatment resistant depression, or with somatic depressive symptoms as opposed to cognitive symptoms, are all at increased risk of developing adverse CHD outcomes. However, there is no clear consensus on whether these different phenotypes carry variations in risk.[13]

Gender differences

Among women, depression is approximately twice as prevalent as in men and has shown some of the most robust associations with CHD.[14] Depression in women is also on average more severe than in men and has an earlier age of onset. Women with CHD similarly have twice the rates of depression as men with CHD.[15–17] The condition is especially common in young women who have survived a MI[15,16,18]; about half of women younger than 60 years with a previous MI have a history of major depression.[16–18] Of note, young women are more likely to die MI than men.[19] Depression is linked to early life adversities and psychological trauma, which tend to be more common in girls than boys and may result in chronic dysregulation of neurohormonal stress systems. This may begin at an early age, setting the stage for an increase in cardiovascular risk in women many years before CHD becomes manifest.[5]

Among women, depression increases their risk for CHD between 30% and two-fold depending on depression measures and CHD endpoints.[20,21] Two follow-up studies of young community samples (<40 years old) found that the impact of depression on CHD risk was higher among women than men.[22,23] In the Third National Health and Nutrition Examination Survey (NHANES III), a history of major depression or suicide attempt was associated with almost 15-fold increased risk of ischaemic heart disease among women, and 3.5 in men.[22] In the prospective Community Mental Health Epidemiology Study of Washington County, MD, women younger than 40 years with depression had a six-fold increased risk of CHD compared with women of the same age without depression, while depression was not associated with CHD in men or older individuals.[23] Even among patients referred for coronary angiography, depression is more predictive of adverse cardiovascular outcomes in young women than in other groups.[24] After an acute MI, however, depression seems to affect prognosis to a similar extent in women and men.[25] Overall, the evidence suggests that depression is more closely associated with CHD for women than for men, with the strongest effects for younger women.

Clinical and prognostic considerations

Depression as a prognostic factor in acute coronary syndromes

Despite some heterogeneity of findings, the bulk of the evidence supports the notion that depression after ACS is a risk factor for all-cause and cardiac mortality, as well as for composite outcomes including mortality or non-fatal cardiac events.[4] Among patients hospitalized for ACS, the increased risk occurs regardless of whether depression pre-dated the ACS event or developed subsequently,[4,26,27] although some evidence suggests that that depressive episodes that develop soon after an ACS may carry a higher risk than episodes that begin before the event.[28–30] Depression is also a major determinant of unplanned rehospitalizations within 30 days after a hospital discharge for MI.[31]

Some studies have found that the somatic symptoms of depression may carry a high risk than cognitive symptoms.[32–34] Depressive episodes that do not respond to standard treatments have also been identified as high-risk subtypes.[35] However, evidence suggests that recognition and treatment of depression improves prognosis. In a previous study, patients with depression that was recognized or treated during an MI hospitalization or at discharge had similar 1-year mortality than those without depression, while a higher mortality was confined to patients with untreated depression.[36] These data are important since depression in ACS patients is frequently under-recognized and untreated.[33,37,38]

Patients with comorbid depression and CHD have lower adherence to treatments and lifestyle changes; for example, they are significantly less likely to adhere to medication regimens[39,40] and to follow lifestyle recommendations (e.g. smoking cessation, exercise) and practice self-management (e.g. weight monitoring in heart failure).[41] They

are also less likely to participate in cardiac rehabilitation programmes, and more likely to drop out of these programmes.[39,42,43] Improvement in depression is associated with better self-reported adherence to medications and secondary prevention lifestyle.[44,45]

During the first year post-MI the presence of depression is associated with about 40% higher healthcare costs, including outpatient care and hospital readmissions.[46] In addition, the presence of major depression in the past 12 months can affect societal costs indirectly through work absence.[47] For all the above reasons, major depression has been proposed as a risk factor for adverse medical outcomes in patients with ACS.[4] The application of collaborative care interventions for depression in CHD populations has emerged as a promising healthcare model to reduce the societal impact of this common comorbidity.[48,49]

Depression and quality of life

In the setting of CHD, depression is the strongest predictor of quality of life (QoL).[50] Depression has a greater impact on QoL than symptoms related to the severity of cardiac disease, such as functional impairment or dyspnoea in patients with heart failure, and angina or exercise capacity in patients with stable CHD.[26,44,51,52] After a MI, depressive symptoms are associated with more physical limitations and worse QoL.[26,53] In patients with systolic dysfunction, depression is a major determinant of QoL, whereas cardiac indicators of severity of the disease (i.e. NT-proBNP and left ventricular ejection fraction) are not related to QoL.[51] A change in depressive symptoms is the strongest predictor of 1-year health-related QoL in this population, even after accounting for functional status and clinical variables.[54]

Depression and chest pain

Epidemiological evidence suggests a close relationship between depression and angina, with these two clinical entities frequently co-existing. Presence of depression is associated with increased reporting of shortness of breath and/or chest pain symptoms in patients with established CHD.[55] Not only is depression associated with everyday life angina independently of CHD severity, but it is a stronger predictor of angina than severity of coronary artery disease or other traditional risk indicators.[56] Depression post-MI predicts new angina during follow-up,[26] and improvement in depression leads to improvement in angina symptoms. A cause and effect relationship between depression and angina, however, is difficult prove. Over-reporting of chest pain in depressed patients could be related to alterations in pain perception. Furthermore, patients with chronic pain, including angina, may develop depressive symptoms as a consequence of their symptom burden or disability.[57] Evidence also suggests that chest pain and depression share common neurohormonal pathways[57] and a common genetic background,[58] which could explain their co-existence. The links between depression and chest pain are summarized in *Figure 1*.

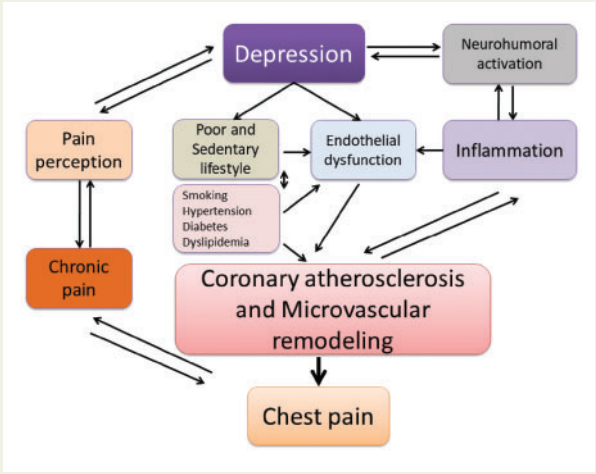

Figure 1 Common links between depression and chest pain in coronary heart disease.

Depression, atrial fibrillation, and ventricular arrhythmias

Atrial fibrillation (AF) can profoundly affect patients' QoL and long-term outcome, and depression, which has been associated with AF, may worsen the symptoms and clinical course of this condition.[59–63] Depression is associated with increased inflammatory and adrenergic activity and reduced heart rate variability (HRV), which is the normal beat-to-beat variability of heart rate. These factors can shorten atrial refractory periods, trigger AF, and foster a substrate that perpetuates AF, suggesting a mechanism for the observed association of depression with AF.[59,63,64]

Depression has been associated with an almost three-fold increase in the odds of the reoccurrence of AF after successful electric cardioversion,[65] and negative emotions have been shown to trigger AF episodes in persons with paroxysmal AF.[66] Furthermore, negative life events like the death of a partner have been associated with transiently increased risk of AF.[67] The opposite pathway may also be true, however, as AF can have substantial impact on the risk or worsening of depression.[62,68] Thus, AF can cause depression and anxiety in patients, and depression and anxiety, in turn, may create an environment that is conducive for the initiation and perpetuation of AF.[68]

Individuals with depression, as well as those exposed to various forms of chronic and acute psychological distress, have also an increased risk of developing ventricular arrhythmias and sudden cardiac arrest, a finding reported both in initially CHD-free populations and in patients with CHD.[69–72] Yet, whether treating depression would affect cardiac arrhythmias still remains an open question.

Mechanisms linking depression to coronary heart disease

Neurobiological aspects of relevance to coronary heart disease

The well-documented association between depression and CHD has prompted a search for underlying mechanisms. One possibility is that changes in neurobiology in depressed patients alter cardiovascular function and structure.[73–75] Additionally, because of the known link between stressful exposures and depression,[76] dysregulation of stress-response pathways may contribute to CHD in vulnerable individuals. Thus, neurobiological mechanisms associated with stress and depression may be relevant for CHD risk. These mechanisms include changes in sympathetic nervous system and neurohormonal function as well as alterations in central brain function.[77,78]

Neuroendocrine pathways

Acute and chronic stress exposure can lead to altered neurochemical function, such as disruptions in the synthesis or activity of norepinephrine, dopamine, or serotonin,[79] which, in turn, may influence mood and cardiovascular risk.[80,81] Endocrine changes associated with depression include alterations in corticotropin-releasing factor (CRF),[82] dysregulated adrenocorticotropic hormone (ACTH) responses to CRF,[83] enhanced adrenal responses to ACTH,[83] and elevated circulating cortisol levels.[84] Several of these changes may affect the immune system leading to excessive secretion of cytokines such as interleukin (IL)-1, IL-6, and tumour necrosis factor (TNF)-α. Enhanced inflammation is common in mood disorders and cardiovascular disease and thus might play a role in the association of these conditions.

Brain systems and cardiovascular physiology

Brain areas that likely play a role in cardiovascular regulation based on imaging studies include those involved in stress and memory that have also been shown to be altered in patients with major depression. These include the amygdala, hippocampus, medial prefrontal cortex, and anterior cingulate (part of the prefrontal cortex).[85–87] Structural and functional magnetic resonance imaging (MRI) studies have shown changes in hippocampal structure and function in depression.[88–108] Moreover, MRI data have demonstrated that acute psychological stressors may reduce baroreflex sensitivity by increasing the functional connectivity of a discrete area of the anterior insula with both the cingulate cortex and the amygdala.[109] Asymmetric sympathetic inputs from these brain areas to the heart may increase the risk of ventricular arrhythmias.[110] Studies have shown that asymmetric brain responses to stress result in pro-arrhythmic sympathetic inputs to the heart.[111] In a recent study,[112] amygdalar activity measured by 18F-fluorodexoyglucose positron emission tomography independently predicted cardiovascular disease events, providing further evidence of brain mechanisms through which emotional stress can lead to cardiovascular disease.

Subjects who exhibit a larger cardiovascular reactivity and acute mental stress are at risk for hypertension and other cardiovascular risk indicators.[113] There is an association between increased blood pressure and heart rate during mental stress and activation in the right insula, cerebellum, and anterior cingulate.[114] Furthermore, myocardial ischaemia provoked by acute psychological stress in CHD patients has been associated with increased activation of the anterior cingualate.[115] Studies have also implicated the insula and the somatosensory cortex in peripheral autonomic function.[116] These studies, as a whole, suggest that brain regulatory systems are implicated in CHD pathophysiology, and imply that disruption of these systems may contribute to the observed associations of stress and depression with CHD risk.

Depression and mental stress

Brain areas involved in stress may modulate peripheral vascular and autonomic function,[115,117] which may mediate the effects of stress acting through the brain to cause myocardial ischaemia in patients with CHD. Mental stress, which can be studied in the laboratory, can induce myocardial ischaemia in susceptible patients with CHD,[73,118,119] and this phenomenon has been linked to depression.[120,121] Such observations suggest that some individuals with CHD, especially those with depression, may experience stress-induced myocardial ischaemia on a daily basis, even in the absence of symptoms,[74,122–124] possibly through a mechanism of increased coronary or peripheral vasoconstriction due to sympathetic nervous system stimulation during emotional stress.[125,126] This phenomenon may be especially pronounced among women.[5,127,128]

Depression and autonomic dysfunction

In part as a consequence of neurobiological alterations described above, chronic dysregulation of autonomic function (*Figure 2*), characterized by an imbalance between the sympathetic and parasympathetic systems, is thought to be a key mechanism linking depression to CHD risk and adverse cardiovascular outcomes.[7] Sympathetic hyperactivity and parasympathetic withdrawal may lower the threshold for myocardial ischaemia and ventricular arrhythmias, and potentially pre-dispose to sudden cardiac death. Data from animal models suggest that depression is associated with cardiovascular and autonomic imbalance, characterized by elevated heart rate, reduced HRV,[129] and elevated cardiac sympathetic tone.[130,131]

Most studies of patients with CHD have found lower HRV and higher heart rate in patients with depression compared with those without depression, together with other indicators of cardiac autonomic dysregulation including decreased baroreceptor sensitivity, increased QT interval variability (reflecting abnormal ventricular repolarization) and increased heart rate turbulence.[3,7] Heart rate variability is probably the most widely used method to assess cardiac autonomic function in humans. Lower HRV, reflecting cardiac autonomic imbalance, predicts mortality after MI,[132,133] and morbidity and mortality in the general population and among patients with stable CHD.[134,135] However, the association between depression and reduced HRV (or other measures of autonomic dysregulation) is not entirely consistent across all studies.[136–138] Part of the effect may be driven by antidepressant medications.[136,137,139,140] Furthermore, the link between depression and HRV is likely bidirectional,[140] and depression and HRV may also share a genetic substrate, suggesting shared neurobiological alterations pre-disposing to both depression and autonomic dysfunction.[141]

Depression and inflammation

Another hypothesized mechanism for the increased risk of CHD associated with depression is chronic inflammation (*Figure 2*), which is a known risk factor for development of atherosclerosis and CHD.[142] Depression has been associated with a sustained state of inflammation and increased concentrations of inflammatory molecules, including C-reactive protein and various cytokines, such as TNF-α, IL-1β, and IL-6[143,144] with known adverse effects on the heart and circulation.[145,146] Depression has been also associated with elevated markers of oxidative stress,[147,148] which is involved in the initiation, progression, and complications of atherosclerosis. Nevertheless, the direction of the association between depression and inflammation and/or oxidative stress remains unclear. Some studies suggested that depression drives the inflammatory state rather than the reverse,[149,150] while others supported the opposite pathway of inflammation predicting depression.[151–153] In fact, inflammation has been considered a potential aetiological factor and treatment target for clinically depressed patients.[144] It also remains unclear to what

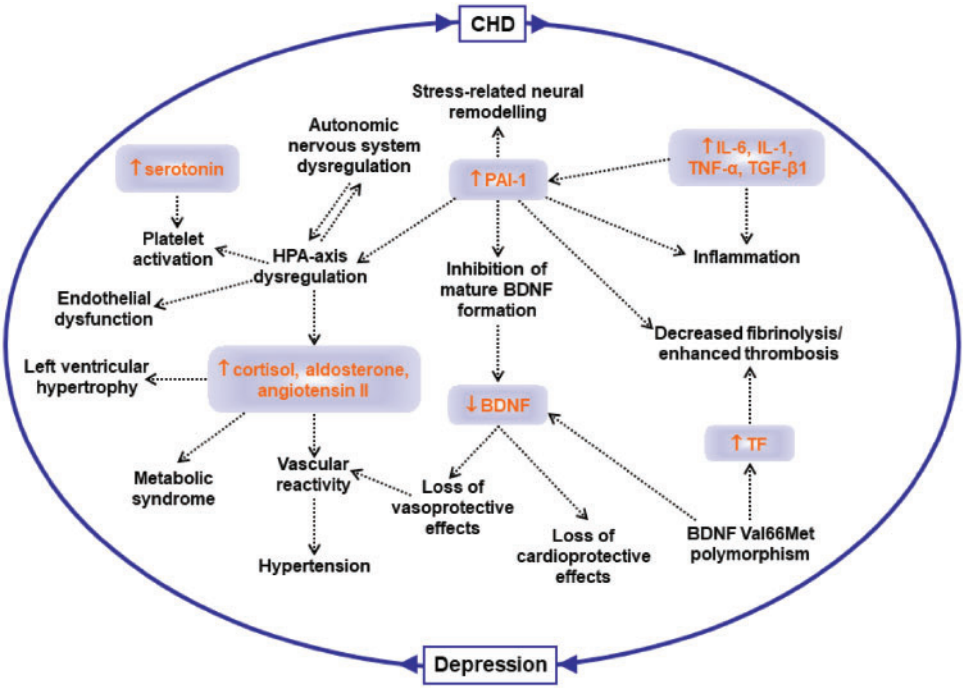

Figure 2 Links between depression, autonomic dysregulation, inflammation, endothelial dysfunction, and thrombosis. BDNF, brain-derived neurotrophic factor; CHD, coronary heart disease; HPA, hypothalamic–pituitary–adrenal axis; IL, interleukin; PAI, plasminogen activator inhibitor; TGF, transforming growth factor; TNF, tumour necrosis factor.

degree inflammation is the result of depression-related co-morbidities and risk factors, such as smoking, obesity, diabetes, and physical inactivity.[142,143,150,154–157] Finally, as for autonomic function, depression and inflammation could share a pathophysiological pathway, such as common genetic precursors or shared behavioural or environmental risk factors.[158,159]

Depression and endothelial dysfunction

Various studies support an inverse correlation between depressed mood and endothelial function, as measured by flow-mediated dilation (FMD).[160–162] The relationship between depression and endothelial dysfunction (*Figure 2*) is likely due to reduced endothelium-derived nitric oxide (NO),[163] as shown by lower FMD of brachial arteries and reduced NO bioavailability in subcutaneous micro-vessels in patients with depressed mood.[161,164,165] Animal models of human depression are useful to gain deeper understanding of underlying mechanisms. One such model is the so-called 'unpredictable chronic mild stress (UCMS)' rat model.[166] Due to activation of neuroendocrine and immune systems the level of TNF-α is elevated in the UCMS rats. The endothelium dependent vasomotor response to carbachol is substantially reduced, whereas the direct NO donor, sodium nitroprusside, or the non-NO dependent agonist, papaverine, elicit similar dilation in vessels of UCMS and control rats.[166] The reduced NO-dependent response is likely due to lower expression of endothelial NO synthase (eNOS). Higher levels of cortisol and increased inflammation in depression can down-regulate eNOS expression and NO production.[167,168] In addition to the NO system, other endothelial mechanisms may play a role, for example, the arachidonic acid pathway with production of constrictor prostanoids.[169] There is also evidence from experimental models that reduction in endothelium-dependent hyperpolarization is an important mechanism underlying the reduced endothelial function in the microcirculation. Endothelin is a powerful vasoconstrictor, and its levels are higher in patients with depression.[170,171] The metabolic syndrome is associated with depression[172] and can contribute to the development of vascular endothelial dysfunction.[156] It is also likely that the effects of depression on the endothelium are due to upstream alterations of autonomic system circuits related to stress. Psychological stress evokes autonomic, hemodynamic, and metabolic changes that may contribute to endothelial dysfunction. Indeed, acute mental stress in the laboratory induces transient endothelial dysfunction, as measured by FMD, which lasts up to 4 h.[173] This effect may be mediated through sympathetic activation,[174] and may have implications for patients with increased sympathetic outflow including those with depression.

Platelet activation and thrombosis

Increased platelet activation and thrombosis represent another pathological mechanism for the association between depression and CHD. Several studies have shown increased platelet activity in major depression.[175–179] Of note, plasminogen activator inhibitor (PAI)-1, an anti-fibrinolytic factor, may also play a pivotal role,[155] as increased

PAI-1 levels have been reported in major depression.[180,181] PAI-1 may also affect hypothalamic–pituitary–adrenal (HPA) axis function and cardiovascular risk factors such as metabolic syndrome and hypertension (*Figure 2*). Furthermore, PAI-1 inhibits the formation of mature brain-derived neurotrophic factor (BDNF), and decreased BDNF levels have been described as a potential link between thrombosis and depression.[182] These data extend a growing body of evidence linking increased PAI-1 concentration with major depression. Furthermore, they provide support for the vascular hypothesis of depression which has been implicated in the two-way association between CHD and depression.[183,184] This hypothesis postulates that deficits in perfusion caused by small-vessel disease (which could be a result of hypercoagulability) induce structural and functional changes in the white matter, which, in turn, may affect brain function and mood.[185]

Health behaviours and cardiometabolic risk factors

Although positive behaviour changes for CHD primary and secondary prevention is recommended,[186] a sizeable proportion of patients do not make any changes.[187] One factor that may shape individuals' responses to a health behaviour change is their emotional state, such as the presence of depression. Prior studies have extensively documented the association of depression with adverse health behaviours, including smoking,[188] excessive drinking,[189] physical inactivity, and overeating.[190–192] For example, depression is associated with an increased risk of becoming a smoker, with an increased rate of daily smoking, and with a lower probability of quitting smoking.[193–196] Depression is also associated with overweight and obesity, and with approximately 40% higher risk of developing Type 2 diabetes.[197–204] Some of these associations appear bidirectional.[205,206] Obesity and other cardiometabolic risk factors have been linked to increased oxidative stress, inflammation, and microvascular dysfunction,[156,207,208] which lend further support for a central role of inflammation and microvascular disease as possible links between cardiometabolic disturbances, depression and CHD (*Figure 2*).[209–212]

Depression, CHD, and genetic vulnerability

Genetic studies can be instructive in clarifying the association between depression and CHD. The heritability of depression, or the proportion of the variance due to genetic factors, is estimated to be 37%,[213] and individuals with a first-degree relative with depression have an almost three-fold higher risk for depression themselves, compared to others from the general population.[213] This has led to genome-wide association studies aimed at the identification of common genetic variants that contribute to the risk of depression. Despite comprehensive efforts, no consistent genetic variation has yet been identified.[214] These surprising results may be due to the heterogeneity of the depression phenotype, and the co-existence of depression and CHD may contribute to this heterogeneity.[215]

It is also possible that there is a core biological pathway that leads to both depression and CHD, as suggested by twin studies showing a common genetic vulnerability between these two phenotypes.[212,216] Additional work has suggested shared, genetically influenced biological pathways underlying the association between depression and CHD that involve autonomic function,[217] inflammation,[218,219] and the serotoninergic system.[158] Patients with depression also show distinct patterns of DNA methylation that are also associated with an increase in inflammatory markers, suggesting epigenetics as another pathway by which core biological changes may lead to both disorders.[220]

All these observations point to common genetic pathways involving neuroendocrine, immune and inflammatory systems that, when disrupted, may simultaneously increase the risk for both depression and CHD. Thus, genetically predisposed individuals could be at risk for both depression and CHD.

Telomere length and depression

Telomeres, the caps at the end of DNA strands, shorten with each cell division and have been proposed to reflect biological age. Studies have shown a relationship between shortened telomere length and risk for CHD.[221–223] Results from studies examining the association between telomere length and depression have been conflicting. Some studies have reported an association,[224,225] whereas other studies have shown no association.[226,227] A study[227] on a sample of more than 67 000 individuals from the Danish general population found that those who attended the hospital for depression treatment had shorter telomere length compared with those who did not attend hospital for depression or use antidepressant medication. However, a large part of this association was explained by confounders such as age, gender, lifestyle factors, and chronic disease. Furthermore, shorter telomere length was not prospectively associated with increased risk of depression and a Mendelian randomization approach showed no causal relationship with depression. This suggests that shortening of telomere length *per se* does not increase risk of depression.

Evaluation of depression in coronary heart disease patients

Recognition and screening

Recognition of depression is an important part of the management of patients with CHD. Depressive symptoms are highly prevalent in this population and can affect patients' well-being and QoL. They can also influence treatment adherence, including fidelity to taking medications as prescribed, cooperating with follow-up care, and making risk factor and lifestyle changes needed to enhance recovery. In spite of this, depression is often unrecognized and untreated in CHD patients. Barriers to recognition of depression include lack of mental health expertise and training in cardiology practices, and the perception that this is not part of the treatment mission. Additionally, many symptoms of psychological distress are easily confused with physical disease, for example, fatigue, weight loss, poor appetite, or trouble sleeping.

There is no consensus on whether screening for and treatment of emotional problems, such as depression, should become a routine part of the cardiology practice. This is related to the fact that there is little evidence one way or another whether screening for and treating these problems will translate into better QoL or improved prognosis.[4] The few studies of interventions for psychiatric disorders in patients with CHD that have been performed have shown only modest improvements in psychological status and no clear evidence of an improvement in cardiac outcomes.[3,228] Nevertheless, psychological

interventions such stress management, individual, or group counselling, and support for self-care and pharmacotherapy, are recommended for patients with CHD and comorbid depression. This is because these interventions can help promote modifications in standard risk factors, encourage lifestyle changes, and mitigate distress when added to standard cardiac rehabilitation or as part of a coordinated care management approach.[48]

Current clinical guidelines in the USA only mention depression as a psychosocial factor that is reasonable for the non-mental health clinician to recognize if patients have access to adequate care support systems (class of recommendation IIa, level of evidence B). These guidelines further state that treatment of depression may be reasonable for its clinical benefits other than improving CHD outcomes (class IIb, level of evidence C).[229] In contrast, the European guidelines, while noting limitations for depression screening, recognize the importance of a comprehensive approach for the detection of psychosocial risk factors, using at least a preliminary assessment with a short series of yes/no questions and recommend a multimodal behavioural intervention approach integrating health education, physical activity, and psychological therapy (class Ia, level of evidence A).[186] In the case of clinically significant symptoms of depression or other psychosocial factors, the European guidelines recommend consideration of interventions such as psychotherapy, medication, or collaborative care (class IIa, level of evidence A). These treatments are reviewed in more detail in the following sections of this paper.

Assessment of depression

Several reliable and valid instruments have been developed for the assessment of depression. The standard for research in the field at least in the USA is the Structured Clinical Interview for the DSM-5 (SCID) interview.[230] This interview requires training and must be administered by someone with clinical experience or with close supervision by a mental health professional. It permits diagnosis based on DSM-5 criteria of major depression and related disorders, including dysthymia and bipolar disorder. Assessment of severity of depressive symptoms can be performed with the Hamilton Depression Scale, a reliable and valid measure of depressive symptoms based on a clinician interview.[231] A score of greater than 9 is indicative of moderate to severe depression.[232] Both of these instruments, however, rely on a mental health clinician to administer, which is not usually practical in busy cardiology clinics. An alternative that can be self-administered by patients with CHD is the Beck Depression Inventory. This is a reliable and valid assessment that can be used to screen for the presence of depression, although it does not provide a diagnosis.[233] If suicidal ideation is a concern, the Sheehan Suicidality Tracking Index is another self-report instrument that can be employed. A score greater than 0 indicates the need for further timely follow-up by a mental health clinician.[234]

Management of depression in patients with coronary heart disease

A number of interventions can be useful for CHD patients with depression. Psychotherapy helps people with depression understand the behaviours, emotions, and ideas that contribute to depression, regain a sense of control and pleasure in life, and learn coping skills.[235] Psychodynamic therapy is based on the assumption that a person is depressed because of unresolved, generally unconscious conflicts, often stemming from childhood. Interpersonal therapy focuses on patient's behaviours and interactions with family and friends. The primary goal of this therapy is to improve communication skills and increase self-esteem during a short period of time. Cognitive behavioural therapy (CBT) involves examining thought patterns that can be negative and self-defeating, and going over the basis of such thoughts and how they contribute to negative emotions. Other therapies useful for depression include stress management and stress reduction techniques such as deep breathing, progressive muscle relaxation, yoga, meditation, and mindfulness-based stress reduction. These interventions can be provided in group format or individually by trained personnel. Psychotherapy has been shown to be equally effective for depression as medications, and some people, especially with early life stress issues, may not respond to medication without psychotherapy.

The Enhanced Recovery in Coronary Heart Disease Patients (ENRICHD) trial could not demonstrate a benefit for CBT, with medication intervention for severe depression, for the improvement of cardiac outcomes in depressed or socially isolated patients with CHD.[236] The effects of the intervention on depression, however, were modest, and patients who responded to treatment did have a better outcome than those who did not respond.[13] Unanswered questions, therefore, remain on whether treatment of depression may improve CHD outcomes.

Antidepressant medications

Antidepressant medications (*Table 1*) are a useful tool for the treatment of depression in patients with CHD, especially those with moderate-to-severe depression.[237,238] Antidepressants act on the serotonin, dopamine, and norepinephrine systems and other neurotransmitter circuits in the brain.

Tricyclic antidepressants

Tricyclics represent the first class of medications found to work for the treatment of depression. Tricyclics increase norepinephrine and serotonin levels in the synapse. These medications have been associated with a lengthening of the PR interval, QRS duration, and QT interval, and a flattening of the T wave on the electrocardiogram (*Table 1*). Likely because of these effects, tricyclics have been linked to malignant ventricular arrhythmias and sudden cardiac death. For patients who suffer a cardiac event while being treated with a tricyclic or who develop a lengthening of the QT interval, abrupt withdrawal from the tricyclic medication can be associated with an increased risk of arrhythmias. Therefore, these medications should be tapered slowly over a period of time. For all of these reasons' tricyclics should be avoided in patients with CHD, especially those with pre-existing cardiac conduction defects, congestive heart failure, or recent MI, and elderly patients.

Selective serotonin reuptake inhibitors

The selective serotonin reuptake inhibitors (SSRIs) block the transporter that brings the serotonin back from the synapse into the

Table 1 Pharmacological management of depression in patients with coronary heart disease

Drug classification/ generic name	Indication	Cardiovascular adverse effects	Other adverse effects
Selective serotonin reuptake inhibitors			
Fluoxetine Sertraline Paroxetine Fluvoxamine Citalopram Escitalopram	• Agents of choice in CHD • Sertraline: agent of choice in post-MI patients • Citalopram: should be used with caution in patients at high risk of QTc prolongation or Torsades de Pointes such as those with congestive heart failure, recent MI, bradyarrhythmias hypokalaemia or hypomagnesaemia, congenital long QT syndrome.	• Fewer to no anticholinergic and cardiac effects • Concomitant use with aspirin and other antiplatelet/anticoagulation treatment may increase risk bleeding especially in the elderly • Citalopram is associated with dose-related QTc interval prolongation	Nausea, diarrhoea, headache, insomnia, agitation, loss of libido, delayed ejaculation, and erectile dysfunction
Tricyclic antidepressants			
Imipramine Doxepine Amoxapine Nortriptyline Amitriptyline	• Avoid in CHD, conduction defects, congestive heart failure, and elderly • Contraindicated in post-MI patients	• Increase heart rate • Prolongation of the PR interval, QRS duration and QTc interval, and a flattening of the T wave on the electrocardiogram • Orthostatic hypotension • Abrupt withdraw may associated with increased risk of arrythmias	Anticholinergic effects: dry mouth, constipation, memory problems, confusion, blurred vision, sexual dysfunction, and decreased urination, and memory impairment especially in the elderly
Serotonin-norepinephrine reuptake inhibitors			
Desvenlafaxine Duloxetine Levomilnacipran Milnacipran Venlafaxine	• Venlafaxine: avoid in patients at high risk of malignant ventricular arrhythmias or with uncontrolled hypertension	• Fewer to no cardiac effects • Have been associated with a dose dependent increase in blood pressure and heart rate • Regular blood pressure monitoring • Venlafaxine: Minor degree of QTc prolongation	Dizziness, constipation, dry mouth, headache, changes in sleep, or more rarely a serotonin syndrome, with restlessness, shivering, and sweating
Antidepressants with novel mechanisms of action			
Buproprion	• Smoking cessation in CHD patients	• Possible increases in blood pressure • Minor degree of QTc prolongation	Weight loss, restlessness, high doses can rarely cause seizures
Mirtazapine	• Use with caution in CHD and post-MI patients	• Mild orthostatic hypotension • Minor degree of QTc prolongation	Sweating and shivering, tiredness, strange dreams, dyslipidemia, weight gain, anxiety, and agitation
Trazodone	• Use with caution in CHD, patients with atrioventricular conductions blocks or other conduction disorders and post-MI patients	• Orthostatic hypotension • Minor to low degree of QTc prolongation	Rarely, it can cause priapism

CHD, coronary heart disease; MI, myocardial infarction; QTc: corrected QT interval.

neuron (*Table 1*). Because of their different mechanism of action, they have fewer to no anticholinergic and cardiac effects. Therefore, they are first line of treatment for CHD patients.

The SSRIs have only modest efficacy over placebo,[239,240] and about 80% of the improvement is due to placebo response. They show their greatest effect on patients with severe depression.[238] Antidepressants without sexual dysfunction side effects can be given instead of an SSRI in case this is an issue, for example, bupropion. The SSRIs stopped suddenly can result in a potent withdrawal syndrome, including agitation, nervousness, and sometimes suicidal thoughts. Patients on aspirin or other antiplatelet/anticoagulation treatment can have an increase in bleeding risk with SSRIs.

Studies of SSRIs have found them to be safe and effective for patients with CHD, although their effects on improving cardiac outcomes are unclear. Some data suggest that patients whose depression improves with SSRIs, typically those with severe depression, may have better cardiac outcomes.[13] However, some data suggest that SSRIs, like tricyclics, when used long-term may increase the risk of cardiac events and death.[21,241] These events are rare, however, and a proper risk-benefit evaluation should be performed case by case.

Serotonin and norepinephrine dual reuptake inhibitors

The latest group of antidepressants has dual reuptake inhibition for serotonin and norepinephrine (*Table 1*). These drugs are moderately more effective than the SSRIs for the treatment of depression, although they can have more side effects. Venlafaxine has been associated with a dose-dependent increase in blood pressure, which is of particular concern for CHD patients, especially those with pre-existing hypertension. In addition, venlafaxine seems to carry the greatest risk of suicidality amongst all of the antidepressants, with a three-fold increased risk of attempted or completed suicides.

Antidepressants with novel mechanisms of action

Some drugs act on various neurotransmitter systems or have poorly understood mechanisms of action (*Table 1*). Buproprion primarily acts on dopamine systems and is used for both depression and smoking cessation. Mirtazapine is a quatrocyclic antidepressant that has actions on a number of different receptor systems. It blocks pre-synaptic noradrenergic alpha-2 receptors with associated enhancement of norepinephrine release. Mirtazapine also increases serotonin release. It can be associated with mild orthostatic hypotension and anticholinergic side effects. Trazodone is a safe and effective antidepressant that can also be an effective non-addicting sleep aid.

Electroconvulsive therapy

Electroconvulsive therapy (ECT) is used as a last resort for the treatment of depression in patients who have had multiple failed trials of psychotherapy and medication. Electroconvulsive therapy has an 80% overall response rate, and contrary to popular belief, is a safe procedure. Although ECT causes profound hemodynamic changes, including bradycardia (up to frank asystole which may last for a few seconds), tachycardia and hypertension, these effects are transient and typically resolve within 20 min. Possible complications include persistent hypertension, arrhythmias, asystole lasting more than 5 s, ischaemia, and heart failure. Older age and pre-existing cardiovascular diseases, including hypertension, CHD, congestive heart failure, aortic stenosis, implanted cardiac devices, and AF, have been associated with increased complication rates. However, most complications remain minor and transient, and the vast majority of patients can safely complete treatment. The procedure should be delayed in patients who are haemodynamically unstable or have new-onset or uncontrolled hypertension. In patients with stable CHD and controlled hypertension, medications can be continued through the morning of the procedure. Electroconvulsive therapy appears safe in patients with an implantable cardioverter defibrillator with detection mode turned off during ECT and continuous electrocardiographic monitoring and life resuscitation equipment on hand. Pacemakers should be tested before and after ECT and the magnet should be placed at the patient bedside.

Exercise

Exercise has been consistently found to be efficacious for the treatment of depression, at least equivalent to the effects of SSRIs or psychotherapy.[242,243] Aerobic exercise seems to work best; therefore, aerobic exercise at a dose consistent with public health recommendations for CHD prevention is an effective treatment for mild-to-moderate depression. Exercise may also complement the effects of antidepressant medications in depressed patients who do not have a complete response to medications. Finally, in patients with CHD, cardiac rehabilitation is highly effective in improving mental health, including depression, as well as physical health outcomes including subsequent CHD events and mortality.[244] Cardiac rehab enhanced by stress management training has been shown to be effective in reducing stress and improving medical outcomes compared with standard cardiac rehabilitation.[245]

Summary of management considerations

There are several treatments options for the CHD patient with depression, from medications to various forms of psychotherapy, to exercise and stress management approaches. Although treatment of depression has not been shown to improve cardiovascular outcomes in CHD patients, depression should still be addressed if severe enough, in order to promote patient wellness and QoL. Tricyclics should be avoided in this patient population.

Concluding remarks

Converging evidence from both experimental and epidemiological studies indicates that there is a bidirectional association between depression and CHD. Depression is very common in patients with CHD and is an independent risk factor for poorer CHD outcomes. The underlying mechanisms linking depression and worse CHD outcomes are complex and potentially multifactorial. Further research is necessary to elucidate them. Nonetheless, there is growing consensus for considering depression as a modifiable prognostic factor for CHD, and for the need of improved efforts towards better recognition and management of this problem in the clinical practice of cardiology.[3,4] Whether effective and safe treatment of depression may improve CHD outcomes, and whether specific patient subgroups may benefit more from such treatments, require further evaluation.

Recommendations

- Clinicians should be aware of the high prevalence of depression in CHD patients. Screening for depression is recommended if patients have access to adequate care support systems
- Patients with positive screening results should be referred to a qualified health care provider in the management of depression
- Non-pharmacologic interventions such as exercise and psychotherapy should be considered as additional treatment options for CHD patients

- Harmonization of care between healthcare providers is essential in patients with combined CHD and depression

Author notes

ESC Committee for Practice Guidelines: Stephan Windecker (Chairperson), Switzerland; Victor Aboyans, France; Stefan Agewall, Norway; Emanuele Barbato, Belgium; Hector Bueno, Spain; Antonio Coca, Spain; Jean-Philippe Collet, France; Ioan Mircea Coman, Romania; Victoria Delgado, Netherlands; Donna Fitzsimons, UK; Oliver Gaemperli, Switzerland; Gerhard Hindricks, Germany; Bernard Iung, France; Peter Juni, Canada; Hugo Katus, Germany; Jujani Knuuti, Finland; Patrizio Lancellotti, Belgium; Christophe Leclerq, France; Theresa McDonagh, UK; Massimo Francesco Piepoli, FESC, Italy; Piotr Ponikowski, Poland; Dimitrios Richter, Greece; Marco Roffi, Switzerland; Evgeny Shlyakhto, Russia; Iain Simpson, UK; Michel Sousa Uva, Portugal; Jose Luis Zamorano (past CPG Chairperson), Spain; Veronica Dean (Head of Practice Guidelines Department) ESC, France.

Conflict of interest: none declared.

References

1. Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication (NCS-R). *Arch Gen Psychiatry* 2005;**62**:617–627.
2. Whiteford HA, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE, Charlson FJ, Norman RE, Flaxman AD, Johns N, Burstein R, Murray CJ, Vos T. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. *Lancet* 2013;**382**:1575–1586.
3. Carney RM, Freedland KE. Depression and coronary heart disease. *Nat Rev Cardiol* 2017;**14**:145–155.
4. Lichtman JH, Froelicher ES, Blumenthal JA, Carney RM, Doering LV, Frasure-Smith N, Freedland KE, Jaffe AS, Leifheit-Limson EC, Sheps DS, Vaccarino V, Wulsin L.; American Heart Association Statistics Committee of the Council on Epidemiology and Prevention and the Council on Cardiovascular and Stroke Nursing. 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**:1350–1369.
5. Vaccarino V, Bremner JD. Behavioral, emotional and neurobiological determinants of coronary heart disease risk in women. *Neurosci Biobehav Rev* 2017;**74**:297–309.
6. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Association; 2013.
7. Penninx BW. Depression and cardiovascular disease: epidemiological evidence on their linking mechanisms. *Neurosci Biobehav Rev* 2017;**74**:277–286.
8. 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**:203–216.
9. Gan Y, Gong Y, Tong X, Sun H, Cong Y, Dong X, Wang Y, Xu X, Yin X, Deng J, Li L, Cao S, Lu Z. Depression and the risk of coronary heart disease: a meta-analysis of prospective cohort studies. *BMC Psychiatry* 2014;**14**:371.
10. Nicholson A, Kuper H, Hemingway H. Depression as an aetiologic 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**:2763–2774.
11. Cassano P, Fava M. Depression and public health: an overview. *J Psychosom Res* 2002;**53**:849–857.
12. Ziegelstein RC. Depression in patients recovering from a myocardial infarction. *JAMA* 2001;**286**:1621–1627.
13. Freedland KE, Carney RM. Depression as a risk factor for adverse outcomes in coronary heart disease. *BMC Med* 2013;**11**:131.
14. Vaccarino V. Psychosocial risk factors in women: Special reference to depression and posttraumatic stress disorder. In: K Orth-Gomer, V Vaccarino, N Schneiderman, HC Deter, eds. *Psychosocial Stress and Cardiovascular Disease in Women: Concepts, Findings and Future Perspectives*. Switzerland: Springer International Publishing; 2015, pp. 63–86.
15. Mallik S, Spertus JA, Reid KJ, Krumholz HM, Rumsfeld JS, Weintraub WS, Agarwal P, Santra M, Bidyasar S, Lichtman JH, Wenger NK, Vaccarino V; PREMIER Registry Investigators. Depressive symptoms after acute myocardial infarction: evidence for highest rates in younger women. *Arch Intern Med* 2006;**166**:876–883.
16. Vaccarino V, Shah AJ, Rooks C, Ibeanu I, Nye JA, Pimple P, Salerno A, D'Marco L, Karohl C, Bremner JD, Raggi P. Sex differences in mental stress-induced myocardial ischemia in young survivors of an acute myocardial infarction. *Psychosom Med* 2014;**76**:171–180.
17. Smolderen KG, Strait KM, Dreyer RP, D'Onofrio G, Zhou S, Lichtman JH, Geda M, Bueno H, Beltrame J, Safdar B, Krumholz HM, Spertus JA. Depressive symptoms in younger women and men with acute myocardial infarction: insights from the VIRGO study. *J Am Heart Assoc* 2015;**4**:e001424.
18. Vaccarino V, Sullivan S, Hammadah M, Wilmot K, Al Mheid I, Ramadan R, Elon L, Pimple PM, Garcia EV, Nye J, Shah AJ, Alkhoder A, Levantsevych O, Gay H, Obideen M, Huang M, Lewis TT, Bremner JD, Quyyumi AA, Raggi P. Mental stress-induced-myocardial ischemia in young patients with recent myocardial infarction: sex differences and mechanisms. *Circulation* 2018;**137**:794–805.
19. Cenko E, Yoon J, Kedev S, Stankovic G, Vasiljevic Z, Krljanac G, Kalpak O, Ricci B, Milicic D, Manfrini O, van der Schaar M, Badimon L, Bugiardini R. Sex differences in outcomes after STEMI: effect modification by treatment strategy and age. *JAMA Intern Med* 2018;**178**:632–639.
20. Wassertheil-Smoller S, Shumaker S, Ockene J, Talavera GA, Greenland P, Cochrane B, Robbins J, Aragaki A, Dunbar-Jacob J. Depression and cardiovascular sequelae in postmenopausal women. The Women's Health Initiative (WHI). *Arch Intern Med* 2004;**164**:289–298.
21. Whang W, Kubzansky LD, Kawachi I, Rexrode KM, Kroenke CH, Glynn RJ, Garan H, Albert CM. Depression and risk of sudden cardiac death and coronary heart disease in women: results from the Nurses' Health Study. *J Am Coll Cardiol* 2009;**53**:950–958.
22. Shah AJ, Veledar E, Hong Y, Bremner JD, Vaccarino V. Depression and history of attempted suicide as risk factors for heart disease mortality in young individuals. *Arch Gen Psychiatry* 2011;**68**:1135–1142.
23. Wyman L, Crum RM, Celentano D. Depressed mood and cause-specific mortality: a 40-year general community assessment. *Ann Epidemiol* 2012;**22**:638–643.
24. Shah AJ, Ghasemzadeh N, Zaragoza-Macias E, Patel R, Eapen DJ, Neeland IJ, Pimple PM, Zafari AM, Quyyumi AA, Vaccarino V. Sex and age differences in the association of depression with obstructive coronary artery disease and adverse cardiovascular events. *J Am Heart Assoc* 2014;**3**:e000741.
25. Parashar S, Rumsfeld JS, Reid KJ, Buchanan D, Dawood N, Khizer S, Lichtman J, Vaccarino V; PREMIER Registry Investigators. Impact of depression on sex differences in outcome after myocardial infarction. *Circ Cardiovasc Qual Outcomes* 2009;**2**:33–40.
26. Parashar S, Rumsfeld JS, Spertus JA, Reid KJ, Wenger NK, Krumholz HM, Amin A, Weintraub WS, Lichtman J, Dawood N, Vaccarino V. Time course of depression and outcome of myocardial infarction. *Arch Intern Med* 2006;**166**:2035–2043.
27. Leung YW, Flora DB, Gravely S, Irvine J, Carney RM, Grace SL. The impact of premorbid and postmorbid depression onset on mortality and cardiac morbidity among patients with coronary heart disease: meta-analysis. *Psychosom Med* 2012;**74**:786–801.
28. Spijkerman T, de Jonge P, van den Brink RH, Jansen JH, May JF, Crijns HJ, Ormel J. Depression following myocardial infarction: first-ever versus ongoing and recurrent episodes. *Gen Hosp Psychiatry* 2005;**27**:411–417.
29. Carney RM, Freedland KE, Steinmeyer B, Blumenthal JA, de Jonge P, Davidson KW, Czajkowski SM, Jaffe AS. History of depression and survival after acute myocardial infarction. *Psychosom Med* 2009;**71**:253–259.
30. de Jonge P, van den Brink RH, Spijkerman TA, Ormel J. Only incident depressive episodes after myocardial infarction are associated with new cardiovascular events. *J Am Coll Cardiol* 2006;**48**:2204–2208.
31. Hess CN, Wang TY, McCoy LA, Messenger JC, Effron MB, Zettler ME, Henry TD, Peterson ED, Fonarow GC. Unplanned inpatient and observation rehospitalizations after acute myocardial infarction: insights from the treatment with adenosine diphosphate receptor inhibitors: longitudinal assessment of treatment patterns and events after acute coronary syndrome (TRANSLATE-ACS) study. *Circulation* 2016;**133**:493–501.
32. Martens EJ, Hoen PW, Mittelhaeuser M, de Jonge P, Denollet J. Symptom dimensions of post-myocardial infarction depression, disease severity and cardiac prognosis. *Psychol Med* 2010;**40**:807–814.
33. Smolderen KG, Spertus JA, Reid KJ, Buchanan DM, Krumholz HM, Denollet J, Vaccarino V, Chan PS. The association of cognitive and somatic depressive symptoms with depression recognition and outcomes after myocardial infarction. *Circ Cardiovasc Qual Outcomes* 2009;**2**:328–337.

34. de Jonge P, Ormel J, van den Brink RH, van Melle JP, Spijkerman TA, Kuijper A, van Veldhuisen DJ, van den Berg MP, Honig A, Crijns HJ, Schene AH. Symptom dimensions of depression following myocardial infarction and their relationship with somatic health status and cardiovascular prognosis. *Am J Psychiatry* 2006; **163**:138–144.
35. Carney RM, Freedland KE. Treatment-resistant depression and mortality after acute coronary syndrome. *Am J Psychiatry* 2009;**166**:410–417.
36. Smolderen KG, Buchanan DM, Gosch K, Whooley M, Chan PS, Vaccarino V, Parashar S, Shah AJ, Ho PM, Spertus JA. Depression treatment and 1-year mortality after acute myocardial infarction: insights from the TRIUMPH registry (Translational Research Investigating Underlying Disparities in Acute Myocardial Infarction Patients' Health Status). *Circulation* 2017;**135**:1681–1689.
37. Huffman JC, Smith FA, Blais MA, Beiser ME, Januzzi JL, Fricchione GL. Recognition and treatment of depression and anxiety in patients with acute myocardial infarction. *Am J Cardiol* 2006;**98**:319–324.
38. Cepoiu M, McCusker J, Cole MG, Sewitch M, Belzile E, Ciampi A. Recognition of depression by non-psychiatric physicians—a systematic literature review and meta-analysis. *J Gen Intern Med* 2008;**23**:25–36.
39. Gehi A, Haas D, Pipkin S, Whooley MA. Depression and medication adherence in outpatients with coronary heart disease: findings from the Heart and Soul Study. *Arch Intern Med* 2005;**165**:2508–2513.
40. Benner JS, Glynn RJ, Mogun H, Neumann PJ, Weinstein MC, Avorn J. Long-term persistence in use of statin therapy in elderly patients. *JAMA* 2002;**288**:455–461.
41. Rumsfeld JS, Ho PM. Depression and cardiovascular disease: a call for recognition. *Circulation* 2005;**111**:250–253.
42. Swardfager W, Herrmann N, Marzolini S, Saleem M, Farber SB, Kiss A, Oh PI, Lanctôt KL. Major depressive disorder predicts completion, adherence, and outcomes in cardiac rehabilitation: a prospective cohort study of 195 patients with coronary artery disease. *J Clin Psychiatry* 2011;**72**:1181–1188.
43. Blumenthal JA, Williams RS, Wallace AG, Williams RB, Needles TL. Physiological and psychological variables predict compliance to prescribed exercise therapy in patients recovering from myocardial infarction. *Psychosom Med* 1982;**44**:519–527.
44. Hare DL, Toukhsati SR, Johansson P, Jaarsma T. Depression and cardiovascular disease: a clinical review. *Eur Heart J* 2014;**35**:1365–1372.
45. Bauer LK, Caro MA, Beach SR, Mastromauro CA, Lenihan E, Januzzi JL, Huffman JC. Effects of depression and anxiety improvement on adherence to medication and health behaviors in recently hospitalized cardiac patients. *Am J Cardiol* 2012;**109**:1266–1271.
46. Frasure-Smith N, Lespérance F, Gravel G, Masson A, Juneau M, Talajic M, Bourassa MG. Depression and health-care costs during the first year following myocardial infarction. *J Psychosom Res* 2000;**48**:471–478.
47. Stein MB, Cox BJ, Afifi TO, Belik SL, Sareen J. Does co-morbid depressive illness magnify the impact of chronic physical illness? A population-based perspective. *Psychol Med* 2006;**36**:587–596.
48. Katon WJ, Lin EH, Von Korff M, Ciechanowski P, Ludman EJ, Young B, Peterson D, Rutter CM, McGregor M, McCulloch D. Collaborative care for patients with depression and chronic illnesses. *N Engl J Med* 2010;**363**:2611–2620.
49. Tully PJ, Baumeister H. Collaborative care for the treatment of comorbid depression and coronary heart disease: a systematic review and meta-analysis protocol. *Syst Rev* 2014;**3**:127.
50. Lane D, Carroll D, Ring C, Beevers DG, Lip GY. Effects of depression and anxiety on mortality and quality-of-life 4 months after myocardial infarction. *J Psychosom Res* 2000;**49**:229–238.
51. Müller-Tasch T, Peters-Klimm F, Schellberg D, Holzapfel N, Barth A, Jünger J, Szecsenyi J, Herzog W. Depression is a major determinant of quality of life in patients with chronic systolic heart failure in general practice. *J Card Fail* 2007; **13**:818–824.
52. Ruo B, Rumsfeld JS, Hlatky MA, Liu H, Browner WS, Whooley MA. Depressive symptoms and health-related quality of life: the Heart and Soul Study. *JAMA* 2003;**290**:215–221.
53. Dickens CM, McGowan L, Percival C, Tomenson B, Cotter L, Heagerty A, Creed FH. Contribution of depression and anxiety to impaired health-related quality of life following first myocardial infarction. *Br J Psychiatry* 2006;**189**: 367–372.
54. Dekker RL, Lennie TA, Albert NM, Rayens MK, Chung ML, Wu JR, Song EK, Moser DK. Depressive symptom trajectory predicts 1-year health-related quality of life in patients with heart failure. *J Card Fail* 2011;**17**:755–763.
55. Barnett LA, Prior JA, Kadam UT, Jordan KP. Chest pain and shortness of breath in cardiovascular disease: a prospective cohort study in UK primary care. *BMJ Open* 2017;**7**:e015857.
56. Hayek SS, Ko YA, Awad M, Del Mar Soto A, Ahmed H, Patel K, Yuan M, Maddox S, Gray B, Hajjari J, Sperling L, Shah A, Vaccarino V, Quyyumi AA. Depression and chest pain in patients with coronary artery disease. *Int J Cardiol* 2017;**230**:420–426.
57. Frasure-Smith N, Lespérance F, Irwin MR, Talajic M, Pollock BG. The relationships among heart rate variability, inflammatory markers and depression in coronary heart disease patients. *Brain Behav Immun* 2009;**23**:1140–1147.
58. van Hecke O, Hocking LJ, Torrance N, Campbell A, Padmanabhan S, Porteous DJ, McIntosh AM, Burri AV, Tanaka H, Williams FM, Smith BH. Chronic pain, depression and cardiovascular disease linked through a shared genetic predisposition: analysis of a family-based cohort and twin study. *PLoS One* 2017;**12**: e0170653.
59. McCabe PJ. Psychological distress in patients diagnosed with atrial fibrillation. The state of the science. *J Cardiovasc Nurs* 2010;**25**:40–51.
60. Andersson T, Magnuson A, Bryngelsson IL, Frøbert O, Henriksson KM, Edvardsson N, Poçi D. All-cause mortality in 272, 186 patients hospitalized with incident atrial fibrillation 1995-2008: a Swedish nationwide long-term case-control study. *Eur Heart J* 2013;**34**:1061–1067.
61. von Eisenhart Rothe A, Hutt F, Baumert J, Breithardt G, Goette A, Kirchhof P, Ladwig KH. Depressed mood amplifies heart-related symptoms in persistent and paroxysmal atrial fibrillation patients: a longitudinal analysis–data from the German Competence Network on Atrial Fibrillation. *Europace* 2015;**17**: 1354–1362.
62. Akintade BF, Chapa D, Friedmann E, Thomas SA. The influence of depression and anxiety symptoms on health-related quality of life in patients with atrial fibrillation and atrial flutter. *J Cardiovasc Nurs* 2015;**30**:66–73.
63. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener H-C, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P; ESC Scientific Document Group. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;**37**:2893–2962.
64. Phillips KP. Role of inflammation in initiation and perpetuation of atrial fibrillation: a systematic review of the published data. *J Atr Fibrillation* 2013;**6**:935.
65. Lange HW, Herrmann-Lingen C. Depressive symptoms predict recurrence of atrial fibrillation after cardioversion. *J Psychosom Res* 2007;**63**:509–513.
66. Lampert R, Jamner L, Burg M, Dziura J, Brandt C, Liu H, Li F, Donovan T, Soufer R. Triggering of symptomatic atrial fibrillation by negative emotion. *J Am Coll Cardiol* 2014;**64**:1533–1534.
67. Graff S, Fenger-Grøn M, Christensen B, Pedersen HS, Christensen J, Li J, Vestergaard M. Long-term risk of atrial fibrillation after the death of a partner. *Open Heart* 2016;**3**:e000367.
68. Patel D, Mc Conkey ND, Sohaney R, Mc Neil A, Jedrzejczyk A, Armaganijan L. A systematic review of depression and anxiety in patients with atrial fibrillation: the mind-heart link. *Cardiovasc Psychiatry Neurol* 2013;**2013**:1.
69. Dimsdale JE. Psychological stress and cardiovascular disease. *J Am Coll Cardiol* 2008;**51**:1237–1246.
70. Lampert R. Mental stress and ventricular arrhythmias. *Curr Cardiol Rep* 2016;**18**: 118.
71. Peacock J, Whang W. Psychological distress and arrhythmia: risk prediction and potential modifiers. *Prog Cardiovasc Dis* 2013;**55**:582–589.
72. Liang JJ, Huang CX, Yang B, Huang H, Wan J, Tang YH, Zhao QY. Depressive symptoms and risk factors in Chinese patients with premature ventricular contractions without structural heart disease. *Clin Cardiol* 2009;**32**:E11–E17.
73. Burg MM, Soufer R. Psychological stress and induced ischemic syndromes. *Curr Cardiovasc Risk Rep* 2014;**8**:377.
74. Soufer R. Neurocardiac interaction during stress-induced myocardial ischemia: how does the brain cope?. *Circulation* 2004;**110**:1710–1713.
75. Vaccarino V, Bremner JD. Traumatic stress is heartbreaking. *Biol Psychiatry* 2013; **74**:790–792.
76. Kendler KS, Thornton LM, Gardner CO. Stressful life events and previous episodes in the etiology of major depression in women: an evaluation of the "kindling" hypothesis. *Am J Psychiatry* 2000;**157**:1243–1251.
77. Veith RC, Lewis N, Linares OA, Barnes RF, Raskind MA, Villacres EC, Murburg MM, Ashleigh EA, Castillo S, Peskind ER. Sympathetic nervous system activity in major depression. Basal and desipramine-induced alterations in plasma norepinephrine kinetics. *Arch Gen Psychiatry* 1994;**51**:411–422.
78. Carney RM, Freedland KE, Veith RC, Cryer PE, Skala JA, Lynch T, Jaffe AS. Major depression, heart rate, and plasma norepinephrine in patients with coronary heart disease. *Biol Psychiatry* 1999;**45**:458–463.
79. Adell A, Trullas R, Gelpi E. Time course of changes in serotonin and noradrenaline in rat brain after predictable or unpredictable shock. *Brain Res* 1988;**459**: 54–59.
80. Knardahl S, Sanders BJ, Johnson AK. Effects of adrenal demedullation on stress-induced hypertension and cardiovascular responses to acute stress. *Acta Physiol Scand* 1988;**133**:477–483.

81. Corbalan R, Verrier R, Lown B. Psychological stress and ventricular arrhythmias during myocardial infarction in the conscious dog. *Am J Cardiol* 1974;**34**: 692–696.
82. van Praag HM. The cognitive paradox in posttraumatic stress disorder: a hypothesis. *Prog Neuropsychopharmacol Biol Psychiatry* 2004;**28**:923–935.
83. Froger N, Palazzo E, Boni C, Hanoun N, Saurini F, Joubert C, Dutriez CI, Enache M, Maccari S, Barden N, Cohen-Salmon C, Hamon M, Lanfumey L. Neurochemical and behavioral alterations in glucocorticoid receptor-impaired transgenic mice after chronic mild stress. *J Neurosci* 2004;**24**:2787–2796.
84. Weber B, Lewicka S, Deuschle M, Colla M, Vecsei P, Heuser I. Increased diurnal plasma concentrations of cortisone in depressed patients. *J Clin Endocrinol Metab* 2000;**85**:1133–1136.
85. Smith GS, Eyler LT. Structural neuroimaging in geriatric psychiatry. *Am J Geriatr Psychiatry* 2006;**14**:809–811.
86. Bremner JD. Changes in brain volume in major depression. *Depression: Mind and Body* 2005;**2**:38–46.
87. Kumar A, Gupta RC, Albert Thomas M, Alger J, Wyckoff N, Hwang S. Biophysical changes in normal-appearing white matter and subcortical nuclei in late-life major depression detected using magnetization transfer. *Psychiatry Res* 2004;**130**:131–140.
88. Bremner JD, Narayan M, Anderson ER, Staib LH, Miller HL, Charney DS. Hippocampal volume reduction in major depression. *Am J Psychiatry* 2000;**157**: 115–118.
89. Vythilingam M, Heim C, Newport J, Miller AH, Anderson E, Bronen R, Brummer M, Staib L, Vermetten E, Charney DS, Nemeroff CB, Bremner JD. Childhood trauma associated with smaller hippocampal volume in women with major depression. *Am J Psychiatry* 2002;**159**:2072–2080.
90. Mervaala E, Föhr J, Könönen M, Valkonen-Korhonen M, Vainio P, Partanen K, Partanen J, Tiihonen J, Viinamäki H, Karjalainen AK, Lehtonen J. Quantitative MRI of the hippocampus and amygdala in severe depression. *Psychol Med* 2000; **30**:117–125.
91. Bremner JD, Vythilingam M, Vermetten E, Vaccarino V, Charney DS. Deficits in hippocampal and anterior cingulate functioning during verbal declarative memory encoding in midlife major depression. *Am J Psychiatry* 2004;**161**:637–645.
92. Bremner JD, Vythilingam M, Vermetten E, Nazeer A, Adil J, Khan S, Staib LH, Charney DS. Reduced volume of orbitofrontal cortex in major depression. *Biol Psychiatry* 2002;**51**:273–279.
93. Kumar A, Bilker W, Lavretsky H, Gottlieb G. Volumetric asymmetries in late-onset mood disorders: an attenuation of frontal asymmetry with depression severity. *Psychiatry Res* 2000;**100**:41–47.
94. Ballmaier M, Toga AW, Blanton RE, Sowell ER, Lavretsky H, Peterson J, Pham D, Kumar A. Anterior cingulate, gyrus rectus, and orbitofrontal abnormalities in elderly depressed patients: an MRI-based parcellation of the prefrontal cortex. *Am J Psychiatry* 2004;**161**:99–108.
95. Lacerda AL, Keshavan MS, Hardan AY, Yorbik O, Brambilla P, Sassi RB, Nicoletti M, Mallinger AG, Frank E, Kupfer DJ, Soares JC. Anatomic evaluation of the orbitofrontal cortex in major depressive disorder. *Biol Psychiatry* 2004;**55**: 353–358.
96. Greenwald BS, Kramer-Ginsberg E, Krishnan KR, Ashtari M, Auerbach C, Patel M. Neuroanatomic localization of magnetic resonance imaging signal hyperintensities in geriatric depression. *Stroke* 1998;**29**:613–617.
97. Hickie I, Scott E, Wilhelm K, Brodaty H. Subcortical hyperintensities on magnetic resonance imaging in patients with severe depression–a longitudinal evaluation. *Biol Psychiatry* 1997.;**42**:367–374.
98. Lenze E, Cross D, McKeel D, Neuman RJ, Sheline YI. White matter hyperintensities and gray matter lesions in physically healthy depressed subjects. *Am J Psychiatry* 1999;**156**:1602–1607.
99. Austin MP, Dougall N, Ross M, Murray C, O'Carroll RE, Moffoot A, Ebmeier KP, Goodwin GM. Single photon emission tomography with 99mTc-exametazime in major depression and the pattern of brain activity underlying the psychotic/neurotic continuum. *J Affect Disord* 1992;**26**:31–43.
100. Biver F, Goldman S, Delvenne V, Luxen A, De Maertelaer V, Hubain P, Mendlewicz J, Lotstra F. Frontal and parietal metabolic disturbances in unipolar depression. *Biol Psychiatry* 1994;**36**:381–388.
101. Mayberg HS, Brannan SK, Mahurin RK, Jerabek PA, Brickman JS, Tekell JL, Silva JA, McGinnis S, Glass TG, Martin CC, Fox PT. Cingulate function in depression: a potential predictor of treatment response. *Neuroreport* 1997;**8**:1057–1061.
102. Drevets WC, Price JL, Simpson JR, Todd RD, Reich T, Vannier M, Raichle ME. Subgenual prefrontal cortex abnormalities in mood disorders. *Nature* 1997;**386**: 824–827.
103. George MS, Ketter TA, Parekh PI, Rosinsky N, Ring HA, Pazzaglia PJ, Marangell LB, Callahan AM, Post RM. Blunted left cingulate activation in mood disorder subjects during a response interference task (the Stroop). *J Neuropsychiatry Clin Neurosci* 1997;**9**:55–63.
104. Bremner JD, Innis RB, Salomon RM, Staib LH, Ng CK, Miller HL, Bronen RA, Krystal JH, Duncan J, Rich D, Price LH, Malison R, Dey H, Soufer R, Charney DS. Positron emission tomography measurement of cerebral metabolic correlates of tryptophan depletion-induced depressive relapse. *Arch Gen Psychiatry* 1997;**54**:364–374.
105. Bremner JD, Vythilingam M, Ng CK, Vermetten E, Nazeer A, Oren DA, Berman RM, Charney DS. Regional brain metabolic correlates of alpha-methylparatyrosine-induced depressive symptoms: implications for the neural circuitry of depression. *JAMA* 2003;**289**:3125–3134.
106. Smith GS, Reynolds CF, Houck PR, Dew MA, Ma Y, Mulsant BH, Pollock BG. Glucose metabolic response to total sleep deprivation, recovery sleep, and acute antidepressant treatment as functional neuroanatomic correlates of treatment outcome in geriatric depression. *Am J Geriatr Psychiatry* 2002;**10**: 561–567.
107. Mayberg HS, Brannan SK, Tekell JL, Silva JA, Mahurin RK, McGinnis S, Jerabek PA. Regional metabolic effects of fluoxetine in major depression: serial changes and relationship to clinical response. *Biol Psychiatry* 2000;**48**:830–843.
108. Goodwin GM, Austin M-P, Dougall N, Ross M, Murray C, O'Caroll RE, Moffoot A, Prentice N, Ebmeier KP. State changes in brain activity shown by the uptake of 99mTc-exametazime with single photon emission tomography in major depression before and after treatment. *J Affect Disord* 1993;**29**:243–253.
109. Gianaros PJ, Onyewuenyi IC, Sheu LK, Christie IC, Critchley HD. Brain systems for baroreflex suppression during stress in humans. *Hum Brain Mapp* 2012;**33**: 1700–1716.
110. Lane RD, Jennings JR. Hemispheric asymmetry, autonomic asymmetry and the problem of sudden cardiac death. In: RJ Davidson, K Hugdahl, eds. *Brain Asymmetry*. Cambridge, MA: MIT Press; 1995, pp. 271–304.
111. Critchley HD, Taggart P, Sutton PM, Holdright DR, Batchvarov V, Hnatkova K, Malik M, Dolan RJ. Mental stress and sudden cardiac death: asymmetric midbrain activity as a linking mechanism. *Brain* 2004;**128**:75–85.
112. Tawakol A, Ishai A, Takx RA, Figueroa AL, Ali A, Kaiser Y, Truong QA, Solomon CJ, Calcagno C, Mani V, Tang CY, Mulder WJ, Murrough JW, Hoffmann U, Nahrendorf M, Shin LM, Fayad ZA, Pitman RK. Relation between resting amygdalar activity and cardiovascular events: a longitudinal and cohort study. *Lancet* 2017;**389**:834–845.
113. Chida Y, Steptoe A. Greater cardiovascular responses to laboratory mental stress are associated with poor subsequent cardiovascular risk status: a meta-analysis of prospective evidence. *Hypertension* 2010;**55**:1026–1032.
114. Critchley HD, Corfield DR, Chandler MP, Mathias CJ, Dolan RJ. Cerebral correlates of autonomic cardiovascular arousal: a functional neuroimaging investigation in humans. *J Physiol* 2000;**523** Pt 1:259–270.
115. Bremner JD, Campanella C, Khan Z, Shah M, Hammadah M, Wilmot K, Al Mheid I, Lima BB, Garcia EV, Nye J, Ward L, Kutner MH, Raggi P, Pearce BD, Shah AJ, Quyyumi AA, Vaccarino V. Brain correlates of mental stress-induced myocardial ischemia. *Psychosom Med* 2018;**80**:515–525.
116. Critchley HD, Mathias CJ, Dolan RJ. Neuroanatomical basis for first- and second-order representations of bodily states. *Nat Neurosci* 2001;**4**:207–212.
117. Thayer JF, Hansen AL, Saus-Rose E, Johnsen BH. Heart rate variability, prefrontal neural function, and cognitive performance: the neurovisceral integration perspective on self-regulation, adaptation, and health. *Ann Behav Med* 2009;**37**: 141–153.
118. Wei J, Rooks C, Ramadan R, Shah AJ, Bremner JD, Quyyumi AA, Kutner M, Vaccarino V. Meta-analysis of mental stress-induced myocardial ischemia and subsequent cardiac events in patients with coronary artery disease. *Am J Cardiol* 2014;**114**:187–192.
119. Arri SS, Ryan M, Redwood SR, Marber MS. Mental stress-induced myocardial ischaemia. *Heart* 2016;**102**:472–480.
120. Wei J, Pimple P, Shah AJ, Rooks C, Bremner JD, Nye JA, Ibeanu I, Murrah N, Shallenberger L, Raggi P, Vaccarino V. Depressive symptoms are associated with mental stress-induced myocardial ischemia after acute myocardial infarction. *PLoS One* 2014;**9**:e102986.
121. Burg MM, Meadows J, Shimbo D, Davidson KW, Schwartz JE, Soufer R. Confluence of depression and acute psychological stress among patients with stable coronary heart disease: effects on myocardial perfusion. *J Am Heart Assoc* 2014;**3**:e000898.
122. Arrighi JA, Burg M, Cohen IS, Soufer R. Simultaneous assessment of myocardial perfusion and function during mental stress in patients with chronic coronary artery disease. *J Nucl Cardiol* 2003;**10**:267–274.
123. Stone PH, Krantz DS, McMahon RP, Goldberg AD, Becker LC, Chaitman BR, Taylor HA, Cohen JD, Freedland KE, Bertolet BD, Coughlan C, Pepine CJ, Kaufmann PG, Sheps DS. Relationship among mental stress-induced ischemia and ischemia during daily life and during exercise: the Psychophysiologic Investigations of Myocardial Ischemia (PIMI) study. *J Am Coll Cardiol* 1999;**33**: 1476–1484.

124. Ramachandruni S, Fillingim RB, McGorray SP, Schmalfuss CM, Cooper GR, Schofield RS, Sheps DS. Mental stress provokes ischemia in coronary artery disease subjects without exercise- or adenosine-induced ischemia. *J Am Coll Cardiol* 2006;**47**:987–991.
125. Ramadan R, Sheps D, Esteves F, Zafari AM, Bremner JD, Vaccarino V, Quyyumi AA. Myocardial ischemia during mental stress: role of coronary artery disease burden and vasomotion. *J Am Heart Assoc* 2013;**2**:e000321.
126. Hammadah M, Alkhoder A, Al Mheid I, Wilmot K, Isakadze N, Abdulhadi N, Chou D, Obideen M, O'Neal WT, Sullivan S, Tahhan AS, Kelli HM, Ramadan R, Pimple P, Sandesara P, Shah AJ, Ward L, Ko YA, Sun Y, Uphoff I, Pearce B, Garcia EV, Kutner M, Bremner JD, Esteves F, Sheps DS, Raggi P, Vaccarino V, Quyyumi AA. Hemodynamic, catecholamine, vasomotor and vascular responses: determinants of myocardial ischemia during mental stress. *Int J Cardiol* 2017;**243**:47–53.
127. Sullivan S, Hammadah M, Al Mheid I, Wilmot K, Ramadan R, Alkhoder A, Isakadze N, Shah A, Levantsevych O, Pimple PM, Kutner M, Ward L, Garcia EV, Nye J, Mehta PK, Lewis TT, Bremner JD, Raggi P, Quyyumi AA, Vaccarino V. Sex differences in hemodynamic and microvascular mechanisms of myocardial ischemia induced by mental stress. *Arterioscler Thromb Vasc Biol* 2018;**38**:473–480.
128. Pimple P, Hammadah M, Wilmot K, Ramadan R, Al Mheid I, Levantsevych O, Sullivan S, Garcia EV, Nye J, Shah AJ, Ward L, Mehta P, Raggi P, Bremner JD, Quyyumi AA, Vaccarino V. Chest pain and mental stress-induced myocardial ischemia: sex differences. *Am J Med* 2018;**131**:540–547.e1.
129. Jangpangi D, Mondal S, Bandhu R, Kataria D, Gandhi A. Alteration of heart rate variability in patients of depression. *J Clin Diagn Res* 2016;**10**:CM04–CM06.
130. Grippo AJ, Beltz TG, Johnson AK. Behavioral and cardiovascular changes in the chronic mild stress model of depression. *Physiol Behav* 2003;**78**:703–710.
131. Shi S, Liang J, Liu T, Yuan X, Ruan B, Sun L, Tang Y, Yang B, Hu D, Huang C. Depression increases sympathetic activity and exacerbates myocardial remodeling after myocardial infarction: evidence from an animal experiment. *PLoS One* 2014;**9**:e101734.
132. Xhyheri B, Manfrini O, Mazzolini M, Pizzi C, Bugiardini R. Heart rate variability today. *Prog Cardiovasc Dis* 2012;**55**:321–331.
133. Manfrini O, Pizzi C, Trerè D, Fontana F, Bugiardini R. Parasympathetic failure and risk of subsequent coronary events in unstable angina and non-ST-segment elevation myocardial infarction. *Eur Heart J* 2003;**24**:1560–1566.
134. Dekker JM, Crow RS, Folsom AR, Hannan PJ, Liao D, Swenne CA, Schouten EG. Low heart rate variability in a 2-minute rhythm strip predicts risk of coronary heart disease and mortality from several causes: the ARIC Study. Atherosclerosis Risk In Communities. *Circulation* 2000;**102**:1239–1244.
135. Manfrini O, Pizzi C, Viecca M, Bugiardini R. Abnormalities of cardiac autonomic nervous activity correlate with expansive coronary artery remodeling. *Atherosclerosis* 2008;**197**:183–189.
136. Kemp AH, Brunoni AR, Santos IS, Nunes MA, Dantas EM, Carvalho de Figueiredo R, Pereira AC, Ribeiro AL, Mill JG, Andreão RV, Thayer JF, Benseñor IM, Lotufo PA. Effects of depression, anxiety, comorbidity, and antidepressants on resting-state heart rate and its variability: an ELSA-Brasil cohort baseline study. *Am J Psychiatry* 2014;**171**:1328–1334.
137. Licht CM, Naarding P, Penninx BW, van der Mast RC, de Geus EJ, Comijs H. The association between depressive disorder and cardiac autonomic control in adults 60 years and older. *Psychosom Med* 2015;**77**:279–291.
138. Gehi A, Mangano D, Pipkin S, Browner WS, Whooley MA. Depression and heart rate variability in patients with stable coronary heart disease: findings from the Heart and Soul Study. *Arch Gen Psychiatry* 2005;**62**:661.
139. Licht CM, de Geus EJ, van Dyck R, Penninx BW. Longitudinal evidence for unfavorable effects of antidepressants on heart rate variability. *Biol Psychiatry* 2010;**68**:861–868.
140. Huang M, Shah A, Su S, Goldberg J, Lampert RJ, Levantsevych OM, Shallenberger L, Pimple P, Bremner JD, Vaccarino V. Association of depressive symptoms and heart rate variability in vietnam war-era twins: a longitudinal twin difference study. *JAMA Psychiatry* 2018;**75**:705–712.
141. Vaccarino V, Lampert R, Bremner JD, Lee F, Su S, Maisano C, Murrah NV, Jones L, Jawed F, Afzal N, Ashraf A, Goldberg J. Depressive symptoms and heart rate variability: evidence for a shared genetic substrate in a study of twins. *Psychosom Med* 2008;**70**:628–636.
142. Mason JC, Libby P. Cardiovascular disease in patients with chronic inflammation: mechanisms underlying premature cardiovascular events in rheumatologic conditions. *Eur Heart J* 2015;**36**:482–9c.
143. Raedler TJ. Inflammatory mechanisms in major depressive disorder. *Curr Opin Psychiatry* 2011;**24**:519–525.
144. Miller AH, Raison CL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. *Nat Rev Immunol* 2016;**16**:22–34.
145. Das UN. Free radicals, cytokines and nitric oxide in cardiac failure and myocardial infarction. *Mol Cell Biochem* 2000;**215**:145–152.
146. Francis J, Chu Y, Johnson AK, Weiss RM, Felder RB. Acute myocardial infarction induces hypothalamic cytokine synthesis. *Am J Physiol Heart Circ Physiol* 2004;**286**:H2264–H2271.
147. Black CN, Bot M, Scheffer PG, Cuijpers P, Penninx BW. Is depression associated with increased oxidative stress? A systematic review and meta-analysis. *Psychoneuroendocrinology* 2015;**51**:164–175.
148. Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, Lanctôt KL. A meta-analysis of cytokines in major depression. *Biol Psychiatry* 2010;**67**:446–457.
149. Miller GE, Freedland KE, Carney RM, Stetler CA, Banks WA. Pathways linking depression, adiposity, and inflammatory markers in healthy young adults. *Brain Behav Immun* 2003;**17**:276–285.
150. Copeland WE, Shanahan L, Worthman C, Angold A, Costello EJ. Cumulative depression episodes predict later C-reactive protein levels: a prospective analysis. *Biol Psychiatry* 2012;**71**:15–21.
151. Khandaker GM, Pearson RM, Zammit S, Lewis G, Jones PB. Association of serum interleukin 6 and C-reactive protein in childhood with depression and psychosis in young adult life: a population-based longitudinal study. *JAMA Psychiatry* 2014;**71**:1121–1128.
152. Valkanova V, Ebmeier KP, Allan CL. CRP, IL-6 and depression: a systematic review and meta-analysis of longitudinal studies. *J Affect Disord* 2013;**150**:736–744.
153. Zalli A, Jovanova O, Hoogendijk WJ, Tiemeier H, Carvalho LA. Low-grade inflammation predicts persistence of depressive symptoms. *Psychopharmacology (Berl)* 2016;**233**:1669–1678.
154. Nemeroff CB, Goldschmidt-Clermont PJ. Heartache and heartbreak–the link between depression and cardiovascular disease. *Nat Rev Cardiol* 2012;**9**:526–539.
155. Savoy C, Van Lieshout RJ, Steiner M. Is plasminogen activator inhibitor-1 a physiological bottleneck bridging major depressive disorder and cardiovascular disease?. *Acta Physiol (Oxf)* 2017;**219**:715–727.
156. Badimon L, Bugiardini R, Cenko E, Cubedo J, Dorobantu M, Duncker DJ, Estruch R, Milicic D, Tousoulis D, Vasiljevic Z, Vilahur G, De Wit C, Koller A. Position paper of the European Society of Cardiology-working group of coronary pathophysiology and microcirculation: obesity and heart disease. *Eur Heart J* 2017;**38**:1951–1958.
157. Libby P. Inflammation in atherosclerosis. *Arterioscler Thromb Vasc Bio* 2012;**32**:2045–2051.
158. Su S, Zhao J, Bremner JD, Miller AH, Tang W, Bouzyk M, Snieder H, Novik O, Afzal N, Goldberg J, Vaccarino V. Serotonin transporter gene, depressive symptoms, and interleukin-6. *Circ Cardiovasc Genet* 2009;**2**:614–620.
159. Bufalino C, Hepgul N, Aguglia E, Pariante CM. The role of immune genes in the association between depression and inflammation: a review of recent clinical studies. *Brain Behav Immun* 2013;**31**:31–47.
160. Broadley AJ, Korszun A, Jones CJ, Frenneaux MP. Arterial endothelial function is impaired in treated depression. *Heart* 2002;**88**:521–523.
161. Rajagopalan S, Brook R, Rubenfire M, Pitt E, Young E, Pitt B. Abnormal brachial artery flow-mediated vasodilation in young adults with major depression. *Am J Cardiol* 2001;**88**:196–198, A7.
162. Sherwood A, Hinderliter AL, Watkins LL, Waugh RA, Blumenthal JA. Impaired endothelial function in coronary heart disease patients with depressive symptomatology. *J Am Coll Cardiol* 2005;**46**:656–659.
163. Pries AR, Badimon L, Bugiardini R, Camici PG, Dorobantu M, Duncker DJ, Escaned J, Koller A, Piek JJ, de Wit C. Coronary vascular regulation, remodelling, and collateralization: mechanisms and clinical implications on behalf of the working group on coronary pathophysiology and microcirculation. *Eur Heart J* 2015;**36**:3134–3146.
164. Cooper DC, Tomfohr LM, Milic MS, Natarajan L, Bardwell WA, Ziegler MG, Dimsdale JE. Depressed mood and flow-mediated dilation: a systematic review and meta-analysis. *Psychosom Med* 2011;**73**:360–369.
165. Greenstein AS, Paranthaman R, Burns A, Jackson A, Malik RA, Baldwin RC, Heagerty AM. Cerebrovascular damage in late-life depression is associated with structural and functional abnormalities of subcutaneous small arteries. *Hypertension* 2010;**56**:734–740.
166. Demirtaş T, Utkan T, Karson A, Yazır Y, Bayramgürler D, Gacar N. The link between unpredictable chronic mild stress model for depression and vascular inflammation? *Inflammation* 2014;**37**:1432–1438.
167. Wallerath T, Witte K, Schäfer SC, Schwarz PM, Prellwitz W, Wohlfart P, Kleinert H, Lehr HA, Lemmer B, Förstermann U. Down-regulation of the expression of endothelial NO synthase is likely to contribute to glucocorticoid-mediated hypertension. *Proc Natl Acad Sci USA* 1999;**96**:13357–13362.
168. Le Mellédo JM, Mahil N, Baker GB. Nitric oxide: a key player in the relation between cardiovascular disease and major depressive disorder? *J Psychiatry Neurosci* 2004;**29**:414–416.
169. Yui K, Imataka G, Nakamura H, Ohara N, Naito Y. Eicosanoids derived from arachidonic acid and their family prostaglandins and cyclooxygenase in psychiatric disorders. *Curr Neuropharmacol* 2015;**13**:776–785.

170. Bouzinova EV, Wiborg O, Aalkjaer C, Matchkov VV. Role of peripheral vascular resistance for the association between major depression and cardiovascular disease. *J Cardiovasc Pharmacol* 2015;**65**:299–307.
171. Burg MM, Martens EJ, Collins D, Soufer R. Depression predicts elevated endothelin-1 in patients with coronary artery disease. *Psychosom Med* 2011;**73**:2–6.
172. Huffman JC, Celano CM, Beach SR, Motiwala SR, Januzzi JL. Depression and cardiac disease: epidemiology, mechanisms, and diagnosis. *Cardiovasc Psychiatry Neurol* 2013;**2013**:1.
173. Ghiadoni L, Donald AE, Cropley M, Mullen MJ, Oakley G, Taylor M, O'Connor G, Betteridge J, Klein N, Steptoe A, Deanfield JE. Mental stress induces transient endothelial dysfunction in humans. *Circulation* 2000;**102**:2473–2478.
174. Hijmering ML, Stroes ES, Olijhoek J, Hutten BA, Blankestijn PJ, Rabelink TJ. Sympathetic activation markedly reduces endothelium-dependent, flow-mediated vasodilation. *J Am Coll Cardiol* 2002;**39**:683–688.
175. Laghrissi-Thode F, Wagner WR, Pollock BG, Johnson PC, Finkel MS. Elevated platelet factor 4 and beta-thromboglobulin plasma levels in depressed patients with ischemic heart disease. *Biol Psychiatry* 1997;**42**:290–295.
176. Sanner JE, Frazier L. The role of serotonin in depression and clotting in the coronary artery disease population. *J Cardiovasc Nurs* 2011;**26**:423–429.
177. Zafar MU, Paz-Yepes M, Shimbo D, Vilahur G, Burg MM, Chaplin W, Fuster V, Davidson KW, Badimon JJ. Anxiety is a better predictor of platelet reactivity in coronary artery disease patients than depression. *Eur Heart J* 2010;**31**:1573–1582.
178. Serebruany VL, Glassman AH, Malinin AI, Nemeroff CB, Musselman DL, van Zyl LT, Finkel MS, Krishnan KRR, Gaffney M, Harrison W, Califf RM, O'Connor CM; Group SAHARTS. Platelet/endothelial biomarkers in depressed patients treated with the selective serotonin reuptake inhibitor sertraline after acute coronary events: the sertraline anti-depressant heart attack randomized trial (SADHART) platelet substudy. *Circulation* 2003;**108**:939–944.
179. Pollock BG, Laghrissi-Thode F, Wagner WR. Evaluation of platelet activation in depressed patients with ischemic heart disease after paroxetine or nortriptyline treatment. *J Clin Psychopharmacol* 2000;**20**:137–140.
180. Lahlou-Laforet K, Alhenc-Gelas M, Pornin M, Bydlowski S, Seigneur E, Benetos A, Kierzin JM, Scarabin PY, Ducimetiere P, Aiach M, Guize L, Consoli SM. Relation of depressive mood to plasminogen activator inhibitor, tissue plasminogen activator, and fibrinogen levels in patients with versus without coronary heart disease. *Am J Cardiol* 2006;**97**:1287–1291.
181. Geiser F, Meier C, Wegener I, Imbierowicz K, Conrad R, Liedtke R, Oldenburg J, Harbrecht U. Association between anxiety and factors of coagulation and fibrinolysis. *Psychother Psychosom* 2008;**77**:377–383.
182. Amadio P, Colombo GI, Tarantino E, Gianellini S, Ieraci A, Brioschi M, Banfi C, Werba JP, Parolari A, Lee FS, Tremoli E, Barbieri SS. BDNFVal66met polymorphism: a potential bridge between depression and thrombosis. *Eur Heart J* 2017;**38**:1426–1435.
183. Alexopoulos GS. The vascular depression hypothesis: 10 years later. *Biol Psychiatry* 2006;**60**:1304–1305.
184. Newberg AR, Davydow DS, Lee HB. Cerebrovascular disease basis of depression: post-stroke depression and vascular depression. *Int Rev Psychiatry* 2006;**18**:433–441.
185. Taylor WD, Aizenstein HJ, Alexopoulos GS. The vascular depression hypothesis: mechanisms linking vascular disease with depression. *Mol Psychiatry* 2013;**18**:963–974.
186. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corrà U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs FDR, Løchen ML, Löllgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, van der Worp HB, van Dis I, Verschuren WMM, Binno S; ESC Scientific Document Group. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016;**37**:2315–2381.
187. McBride CM, Puleo E, Pollak KI, Clipp EC, Woolford S, Emmons KM. Understanding the role of cancer worry in creating a "teachable moment" for multiple risk factor reduction. *Soc Sci Med* 2008;**66**:790–800.
188. Mykletun A, Overland S, Aarø LE, Liabø HM, Stewart R. Smoking in relation to anxiety and depression: evidence from a large population survey: the HUNT study. *Eur Psychiatry* 2008;**23**:77–84.
189. Levola J, Holopainen A, Aalto M. Depression and heavy drinking occasions: a cross-sectional general population study. *Addict Behav* 2011;**36**:375–380.
190. Ferrer-Garcia M, Pla-Sanjuanelo J, Dakanalis A, Vilalta-Abella F, Riva G, Fernandez-Aranda F, Sánchez I, Ribas-Sabaté J, Andreu-Gracia A, Escandón-Nagel N, Gomez-Tricio O, Tena V, Gutiérrez-Maldonado J. Eating behavior style predicts craving and anxiety experienced in food-related virtual environments by patients with eating disorders and healthy controls. *Appetite* 2017;**117**:284–293.
191. Bruch H. Psychological aspects of overeating and obesity. *Psychosomatics* 1964;**5**:269–274.
192. van Strien T, Herman CP, Verheijden MW. Eating style, overeating and weight gain. A prospective 2-year follow-up study in a representative Dutch sample. *Appetite* 2012;**59**:782–789.
193. Breslau N, Peterson EL, Schultz LR, Chilcoat HD, Andreski P. Major depression and stages of smoking. A longitudinal investigation. *Arch Gen Psychiatry* 1998;**55**:161–166.
194. Fergusson DM, Goodwin RD, Horwood LJ. Major depression and cigarette smoking: results of a 21-year longitudinal study. *Psychol Med* 2003;**33**:1357–1367.
195. Anda RF, Williamson DF, Escobedo LG, Mast EE, Giovino GA, Remington PL. Depression and the dynamics of smoking. A national perspective. *JAMA* 1990;**264**:1541–1545.
196. Hall SM, Muñoz RF, Reus VI, Sees KL. Nicotine, negative affect, and depression. *J Consult Clin Psychol* 1993;**61**:761–767.
197. Petri E, Bacci O, Barbuti M, Pacchiarotti I, Azorin JM, Angst J, Bowden CL, Mosolov S, Vieta E, Young AH, Perugi G; BRIDGE-II-Mix Study Group. Obesity in patients with major depression is related to bipolarity and mixed features: evidence from the BRIDGE-II-Mix study. *Bipolar Disord* 2017;**19**:458–464.
198. Mason TB, Lewis RJ. Profiles of binge eating: the interaction of depressive symptoms, eating styles, and body mass index. *Eat Disord* 2014;**22**:450–460.
199. Lee JH, Park SK, Ryoo JH, Oh CM, Mansur RB, Alfonsi JE, Cha DS, Lee Y, McIntyre RS, Jung JY. The association between insulin resistance and depression in the Korean general population. *J Affect Disord* 2017;**208**:553–559.
200. Pine DS, Goldstein RB, Wolk S, Weissman MM. The association between childhood depression and adulthood body mass index. *Pediatrics* 2001;**107**:1049–1056.
201. Goodman E, Whitaker RC. A prospective study of the role of depression in the development and persistence of adolescent obesity. *Pediatrics* 2002;**110**:497–504.
202. Kawakami N, Takatsuka N, Shimizu H, Ishibashi H. Depressive symptoms and occurrence of type 2 diabetes among Japanese men. *Diabetes Care* 1999;**22**:1071–1076.
203. Golden SH, Williams JE, Ford DE, Yeh HC, Paton Sanford C, Nieto FJ, Brancati FL; Atherosclerosis Risk in Communities study. Depressive symptoms and the risk of type 2 diabetes: the Atherosclerosis Risk in Communities study. *Diabetes Care* 2004;**27**:429–435.
204. Arroyo C, Hu FB, Ryan LM, Kawachi I, Colditz GA, Speizer FE, Manson J. Depressive symptoms and risk of type 2 diabetes in women. *Diabetes Care* 2004;**27**:129–133.
205. Pan A, Lucas M, Sun Q, van Dam RM, Franco OH, Manson JE, Willett WC, Ascherio A, Hu FB. Bidirectional association between depression and type 2 diabetes mellitus in women. *Arch Intern Med* 2010;**170**:1884–1891.
206. Pan A, Sun Q, Czernichow S, Kivimaki M, Okereke OI, Lucas M, Manson JE, Ascherio A, Hu FB. Bidirectional association between depression and obesity in middle-aged and older women. *Int J Obes (Lond)* 2012;**36**:595–602.
207. Ngo DT, Farb MG, Kikuchi R, Karki S, Tiwari S, Bigornia SJ, Bates DO, LaValley MP, Hamburg NM, Vita JA, Hess DT, Walsh K, Gokce N. Antiangiogenic actions of vascular endothelial growth factor-A165b, an inhibitory isoform of vascular endothelial growth factor-A, in human obesity. *Circulation* 2014;**130**:1072–1080.
208. Sorop O, Olver TD, van de Wouw J, Heinonen I, van Duin RW, Duncker DJ, Merkus D. The microcirculation: a key player in obesity-associated cardiovascular disease. *Cardiovasc Res* 2017;**113**:1035–1045.
209. van Agtmaal MJM, Houben AJHM, Pouwer F, Stehouwer CDA, Schram MT. Association of microvascular dysfunction with late-life depression: a systematic review and meta-analysis. *JAMA Psychiatry* 2017;**74**:729–739.
210. Capuron L, Su S, Miller AH, Bremner JD, Goldberg J, Vogt GJ, Maisano C, Jones L, Murrah NV, Vaccarino V. Depressive symptoms and metabolic syndrome: is inflammation the underlying link? *Biol Psychiatry* 2008;**64**:896–900.
211. Vaccarino V, McClure C, Johnson BD, Sheps DS, Bittner V, Rutledge T, Shaw LJ, Sopko G, Olson MB, Krantz DS, Parashar S, Marroquin OC, Merz CN. Depression, the metabolic syndrome and cardiovascular risk. *Psychosom Med* 2008;**70**:40–48.
212. Vaccarino V, Votaw J, Faber T, Veledar E, Murrah NV, Jones LR, Zhao J, Su S, Goldberg J, Raggi JP, Quyyumi AA, Sheps DS, Bremner JD. Major depression and coronary flow reserve detected by positron emission tomography. *Arch Intern Med* 2009;**169**:1668–1676.
213. Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: review and meta-analysis. *Am J Psychiatry* 2000;**157**:1552–1562.
214. Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium; Ripke S, Wray NR, Lewis CM, Hamilton SP, Weissman MM, Breen G, Byrne EM, Blackwood DH, Boomsma DI, Cichon S, Heath AC, Holsboer F, Lucae S, Madden PA, Martin NG, McGuffin P, Muglia P, Noethen MM, Penninx BP, Pergadia ML, Potash JB, Rietschel M, Lin D, Müller-Myhsok B, Shi J, Steinberg S, Grabe HJ, Lichtenstein P, Magnusson P, Perlis RH, Preisig M,

Smoller JW, Stefansson K, Uher R, Kutalik Z, Tansey KE, Teumer A, Viktorin A, Barnes MR, Bettecken T, Binder EB, Breuer R, Castro VM, Churchill SE, Coryell WH, Craddock N, Craig IW, Czamara D, De Geus EJ, Degenhardt F, Farmer AE, Fava M, Frank J, Gainer VS, Gallagher PJ, Gordon SD, Goryachev S, Gross M, Guipponi M, Henders AK, Herms S, Hickie IB, Hoefels S, Hoogendijk W, Hottenga JJ, Iosifescu DV, Ising M, Jones I, Jones L, Jung-Ying T, Knowles JA, Kohane IS, Kohli MA, Korszun A, Landen M, Lawson WB, Lewis G, Macintyre D, Maier W, Mattheisen M, McGrath PJ, McIntosh A, McLean A, Middeldorp CM, Middleton L, Montgomery GM, Murphy SN, Nauck M, Nolen WA, Nyholt DR, O'Donovan M, Oskarsson H, Pedersen N, Scheftner WA, Schulz A, Schulze TG, Shyn SI, Sigurdsson E, Slager SL, Smit JH, Stefansson H, Steffens M, Thorgeirsson T, Tozzi F, Treutlein J, Uhr M, van den Oord EJ, Van Grootheest G, Völzke H, Weilburg JB, Willemsen G, Zitman FG, Neale B, Daly M, Levinson DF, Sullivan PF. A mega-analysis of genome-wide association studies for major depressive disorder. *Mol Psychiatry* 2013;**18**:497–511.

215. Mulle JG, Vaccarino V. Cardiovascular disease, psychosocial factors, and genetics: the case of depression. *Prog Cardiovasc Dis* 2013;**55**:557–562.
216. Scherrer JF, Xian H, Bucholz KK, Eisen SA, Lyons MJ, Goldberg J, Tsuang M, True WR. A twin study of depression symptoms, hypertension, and heart disease in middle-aged men. *Psychosom Med* 2003;**65**:548–557.
217. Su S, Lampert R, Lee F, Bremner JD, Snieder H, Jones L, Murrah NV, Goldberg J, Vaccarino V. Common genes contribute to depressive symptoms and heart rate variability: the Twins Heart Study. *Twin Res Hum Genet* 2010;**13**:1–9.
218. Vaccarino V, Brennan ML, Miller AH, Bremner JD, Ritchie JC, Lindau F, Veledar E, Su S, Murrah NV, Jones L, Jawed F, Dai J, Goldberg J, Hazen SL. Association of major depressive disorder with serum myeloperoxidase and other markers of inflammation: a twin study. *Biol Psychiatry* 2008;**64**:476–483.
219. Su S, Miller AH, Snieder H, Bremner JD, Ritchie J, Maisano C, Jones L, Murrah NV, Goldberg J, Vaccarino V. Common genetic contributions to depressive symptoms and inflammatory markers in middle-aged men: the Twins Heart Study. *Psychosom Med* 2009;**71**:152–158.
220. Crawford B, Craig Z, Mansell G, White I, Smith A, Spaull S, Imm J, Hannon E, Wood A, Yaghootkar H, Ji Y, Mullins N, Lewis CM, Mill J, Murphy TM; Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium. DNA methylation and inflammation marker profiles associated with a history of depression. *Hum Mol Genet* 2018;**27**:2840–2850.
221. Brouilette SW, Moore JS, McMahon AD, Thompson JR, Ford I, Shepherd J, Packard CJ, Samani NJ; West of Scotland Coronary Prevention Study Group. Telomere length, risk of coronary heart disease, and statin treatment in the West of Scotland Primary Prevention Study: a nested case-control study. *Lancet* 2007;**369**:107–114.
222. Codd V, Nelson CP, Albrecht E, Mangino M, Deelen J, Buxton JL, Hottenga JJ, Fischer K, Esko T, Surakka I, Broer L, Nyholt DR, Mateo Leach I, Salo P, Hägg S, Matthews MK, Palmen J, Norata GD, O'Reilly PF, Saleheen D, Amin N, Balmforth AJ, Beekman M, de Boer RA, Böhringer S, Braund PS, Burton PR, de Craen AJ, Denniff M, Dong Y, Douroudis K, Dubinina E, Eriksson JG, Garlaschelli K, Guo D, Hartikainen AL, Henders AK, Houwing-Duistermaat JJ, Kananen L, Karssen LC, Kettunen J, Klopp N, Lagou V, van Leeuwen EM, Madden PA, Mägi R, Magnusson PK, Männistö S, McCarthy MI, Medland SE, Mihailov E, Montgomery GW, Oostra BA, Palotie A, Peters A, Pollard H, Pouta A, Prokopenko I, Ripatti S, Salomaa V, Suchiman HE, Valdes AM, Verweij N, Viñuela A, Wang X, Wichmann HE, Widen E, Willemsen G, Wright MJ, Xia K, Xiao X, van Veldhuisen DJ, Catapano AL, Tobin MD, Hall AS, Blakemore AI, van Gilst WH, Zhu H, Erdmann J, Reilly MP, Kathiresan S, Schunkert H, Talmud PJ, Pedersen NL, Perola M, Ouwehand W, Kaprio J, Martin NG, van Duijn CM, Hovatta I, Gieger C, Metspalu A, Boomsma DI, Jarvelin MR, Slagboom PE, Thompson JR, Spector TD, van der Harst P, Samani NJ; CARDIoGRAM consortium. Identification of seven loci affecting mean telomere length and their association with disease. *Nat Genet* 2013;**45**:422–427, 427e1-2.
223. Said MA, Eppinga RN, Hagemeijer Y, Verweij N, van der Harst P. Telomere length and risk of cardiovascular disease and cancer. *J Am Coll Cardiol* 2017;**70**:506–507.
224. Wikgren M, Maripuu M, Karlsson T, Nordfjäll K, Bergdahl J, Hultdin J, Del-Favero J, Roos G, Nilsson LG, Adolfsson R, Norrback KF. Short telomeres in depression and the general population are associated with a hypocortisolemic state. *Biol Psychiatry* 2012;**71**:294–300.
225. Karabatsiakis A, Kolassa IT, Kolassa S, Rudolph KL, Dietrich DE. Telomere shortening in leukocyte subpopulations in depression. *BMC Psychiatry* 2014;**14**:192.
226. Shaffer JA, Epel E, Kang MS, Ye S, Schwartz JE, Davidson KW, Kirkland S, Honig LS, Shimbo D. Depressive symptoms are not associated with leukocyte telomere length: findings from the Nova Scotia Health Survey (NSHS95), a population-based study. *PLoS One* 2012;**7**:e48318.
227. Wium-Andersen MK, Ørsted DD, Rode L, Bojesen SE, Nordestgaard BG. Telomere length and depression: prospective cohort study and Mendelian randomisation study in 67 306 individuals. *Br J Psychiatry* 2017;**210**:31–38.
228. Whalley B, Rees K, Davies P, Bennett P, Ebrahim S, Liu Z, West R, Moxham T, Thompson DR, Taylor RS. Psychological interventions for coronary heart disease. *Cochrane Database Syst Rev* 2011;CD002902.
229. Smith SC, Benjamin EJ, Bonow RO, Braun LT, Creager MA, Franklin BA, Gibbons RJ, Grundy SM, Hiratzka LF, Jones DW, Lloyd-Jones DM, Minissian M, Mosca L, Peterson ED, Sacco RL, Spertus J, Stein JH, Taubert KA; World Heart Federation and the Preventive Cardiovascular Nurses Association. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. *Circulation* 2011;**124**:2458–2473.
230. First MB, Williams JBW, Gibbon M. *Structured Clinical Interview for DSMIV-Patient Edition (SCID-P)*. Washington, DC: American Psychiatric Press; 1995.
231. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960;**23**:56–62.
232. Carneiro AM, Fernandes F, Moreno RA. Hamilton depression rating scale and Montgomery-Asberg Depression Rating Scale in depressed and bipolar I patients: psychometric properties in a Brazilian sample. *Health Qual Life Outcomes* 2015;**13**:42.
233. Beck AT, Steer RA, Brown GK. *Manual for the Beck Depression Inventory-II*. San Antonio, TX: Psychological Corporation; 1996.
234. Coric V, Stock EG, Pultz J, Marcus R, Sheehan DV. Sheehan Suicidality Tracking Scale (Sheehan-STS): preliminary results from a multicenter clinical trial in generalized anxiety disorder. *Psychiatry (Edgmont)* 2009;**6**:26–31.
235. Hirschfeld RM. The epidemiology of depression and the evolution of treatment. *J Clin Psychiatry* 2012;**73** Suppl 1:5–9.
236. Berkman LF, Blumenthal J, Burg M, Carney RM, Catellier D, Cowan MJ, Czajkowski SM, DeBusk R, Hosking J, Jaffe A, Kaufmann PG, Mitchell P, Norman J, Powell LH, Raczynski JM, Schneiderman N; Enhancing Recovery in Coronary Heart Disease Patients Investigators (ENRICHD). Effects of treating depression and low perceived social support on clinical events after myocardial infarction: the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) Randomized Trial. *JAMA* 2003;**289**:3106–3116.
237. Davis L, Hamner M, Bremner JD. Pharmacotherapy for PTSD: effects on PTSD symptoms and the brain. In: JD Bremner, ed. *Posttraumatic Stress Disorder: From Neurobiology to Treatment*. Hoboken, NJ: Wiley Blackwell; 2016. p389–412.
238. Fournier JC, DeRubeis RJ, Hollon SD, Dimidjian S, Amsterdam JD, Shelton RC, Fawcett J. Antidepressant drug effects and depression severity: a patient-level meta-analysis. *JAMA* 2010;**303**:47–53.
239. Jakobsen JC, Katakam KK, Schou A, Hellmuth SG, Stallknecht SE, Leth-Møller K, Iversen M, Banke MB, Petersen IJ, Klingenberg SL, Krogh J, Ebert SE, Timm A, Lindschou J, Gluud C. Selective serotonin reuptake inhibitors versus placebo in patients with major depressive disorder. A systematic review with meta-analysis and Trial Sequential Analysis. *BMC Psychiatry* 2017;**17**:58.
240. Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y, Leucht S, Ruhe HG, Turner EH, Higgins JPT, Egger M, Takeshima N, Hayasaka Y, Imai H, Shinohara K, Tajika A, Ioannidis JPA, Geddes JR. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Lancet* 2018;**391**:1357–1366.
241. Weeke P, Jensen A, Folke F, Gislason GH, Olesen JB, Andersson C, Fosbøl EL, Larsen JK, Lippert FK, Nielsen SL, Gerds T, Andersen PK, Kanters JK, Poulsen HE, Pehrson S, Køber L, Torp-Pedersen C. Antidepressant use and risk of out-of-hospital cardiac arrest: a nationwide case-time-control study. *Clin Pharmacol Ther* 2012;**92**:72–79.
242. Kvam S, Kleppe CL, Nordhus IH, Hovland A. Exercise as a treatment for depression: a meta-analysis. *J Affect Disord* 2016;**202**:67–86.
243. Blumenthal JA, Babyak MA, Moore KA, Craighead WE, Herman S, Khatri P, Waugh R, Napolitano MA, Forman LM, Appelbaum M, Doraiswamy PM, Krishnan KR. Effects of exercise training on older patients with major depression. *Arch Intern Med* 1999;**159**:2349–2356.
244. Rutledge T, Redwine LS, Linke SE, Mills PJ. A meta-analysis of mental health treatments and cardiac rehabilitation for improving clinical outcomes and depression among patients with coronary heart disease. *Psychosom Med* 2013;**75**:335–349.
245. Blumenthal JA, Sherwood A, Smith PJ, Watkins L, Mabe S, Kraus WE, Ingle K, Miller P, Hinderliter A. Enhancing cardiac rehabilitation with stress management training: a randomized, clinical efficacy trial. *Circulation* 2016;**133**:1341–1350.