# Somatic depression in the picture

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# Chapter 1

## Introduction

Depression is very common among patients with chronic somatic diseases.[1-3] A large amount of research consistently demonstrates the coexistence of depression in a whole range of somatic diseases, including diabetes, heart disease, cancer, pulmonary disease, kidney disease, and more. It is estimated that up to one-third of patients with a serious medical condition have symptoms of depression, which is two- to three times more than for age and sex-matched primary care patients.[3] Comorbid depression is associated with a poorer overall quality of life,[4] higher somatic symptom burden,[5] higher disease severity,[6] treatment non-adherence,[7] and increased risk of disease progression and mortality.[8-10]

For many decades, studies have investigated the mechanisms underlying the relation between depression and somatic diseases in order to explain the high comorbidity. An intuitive explanation may be that suffering from a disabling chronic disease is an understandable risk factor that can trigger depression in vulnerable persons. However, longitudinal studies have shown that depression conversely increases the risk for the onset of a chronic disease.[11-13] A growing body of evidence suggests that physiological mechanisms may mediate the relation between depression and somatic diseases.[14,15] In addition, some researchers have questioned the causal relationship, and regard depression in the context of a somatic disease (at least partly) as a marker for somatic disease severity.[16] Clearly, the proposed bidirectional association between depression and somatic illnesses appears to be multifactorial and complex. Despite extensive research on this topic, the etiology of depression associated with somatic diseases is still not well understood. In this dissertation some specific issues will be addressed in order to contribute to the understanding of the high comorbidity between somatic diseases and depression, and its associated poor medical prognosis.

In the next part of the introduction, depression and the somatic diseases addressed in this dissertation will be introduced. This is followed by an overview of pathways that can lead to somatic depression (i.e., comorbidity of depression and somatic disease). At the end, the specific aims and research questions that are covered in the subsequent chapters are formulated.

## Depression

Depression is one of the strongest contributors to the global burden of disease.[17] It is estimated that about 7% of the general population suffers from a major depressive disorder in a period of a year.[18] Depression is characterized by symptoms such as depressed mood, loss of interest or pleasure in activities, sleep problems, fatigue, and concentration problems. In this dissertation the term depression will refer both to the presence of depressive symptoms and to a depressive disorder. The severity of depressive symptoms is commonly assessed by questionnaires, such as the Beck Depression Inventory (BDI).[19] A cut-off score is often used to determine the presence of depression. The presence of a depressive disorder

is usually assessed by a diagnostic interview, in which a psychiatric diagnosis is defined according to the Diagnostic and Statistical Manual of Mental disorders (DSM).

## Somatic diseases in this dissertation

Although depression is associated with a broader spectrum of somatic diseases, this dissertation focuses on depression in the context of four of the most common and burdensome conditions that are related to the development of vascular pathology: i.e. hypertension, diabetes, coronary artery disease (CAD), and chronic kidney disease (CKD). Hypertension, diabetes, and CAD are in the top 10 leading causes of death in the world; together they accounted for 18% of the global deaths in 2012 (http://www.who.int/mediacentre/factsheets/fs310/en/). Meanwhile, CKD is also increasingly recognized as a global public health problem.[20] Of interest, these four chronic conditions are interrelated and driven by reciprocal relationships.[21] Hypertension and diabetes are important causes for both cardiovascular disease (CVD) and CKD. At the same time, CKD and CVD are major risk factors for hypertension, as well as for each other.[21] Some other important shared risk factors are older age, male, genetics and unhealthy lifestyle habits, such as smoking, high fat diet, and low physical activity.[22] Via damage to blood vessel walls (leading to atherosclerosis) and metabolic imbalances, these risk factors can consequently lead to the development of clinical vascular and metabolic diseases including hypertension, diabetes, CAD, and CKD. Throughout this dissertation 'somatic disease' will refer to this group of disorders.



## Pathways to the comorbidity of depression and somatic disease

The etiology of depression associated with somatic disease is still poorly understood.[23] Many potential pathways have been proposed to underlie the comorbidity between depression and somatic disease and its associated poor medical prognosis. To date, no single conclusive explanation exists and it is unlikely that one single etiological model could account for the complex association between depression and somatic disease. Also, the combinations of pathways that underlie the comorbidity may differ between patients. The potential pathways to comorbidity are reviewed below (see also Figure 1).

### *Psychological pathway*

The psychological consequences of a disabling somatic condition may trigger the onset of depression in vulnerable individuals. There are several reasons why a somatic disease may result in psychological distress. To begin with, an acute medical event, such as a heart attack or receiving a diagnosis of a major

chronic disease, is a substantial life event.[24] In addition, a diagnosis of a chronic disease often has major consequences for someone's well-being, as it is often accompanied by fundamental changes in daily life and future perspectives. For example, individuals become dependent on medication and diet prescriptions. Due to declined health, they may be not be able to pursue their normal activities, they may experience changed social roles or interpersonal relationships, (are worried to) lose their jobs, and may become socially isolated, which all can lead to psychological problems.[25-28] Although a diagnosis of a chronic somatic disease goes along with many limitations and uncertainties, not all patients who are diagnosed with a somatic disease develop psychological problems. Personality, coping style, the degree of medical symptom burden and complications, and (lack of) social support are important predictors for the onset of depression in patients with somatic disease.[29,25,30] Support for this "psychological" pathway comes from studies that report only increased odds of depression in patients with diagnosed diabetes, but not in newly screen-detected diabetes.[31,32] Apparently, only patients who are aware of their diabetes are at increased risk for the development of depressive symptoms.

***Biological pathway***

In addition to the psychological burden of a somatic disease, biological mechanisms may underlie the comorbidity of somatic disease and depression. Both depression and somatic disease are associated with pathophysiological changes. Such pathophysiological changes caused by either of the two can increase the risk of the other.

*Depression leading to somatic disease*

Longitudinal research has shown that individuals with depression are at increased risk of developing somatic disease[11-13] compared to individuals without depression. Stress physiology is one potential aspect of depression that may account for this increased risk. Evidence from both animal and human studies have shown that stress is related to cardiovascular changes such as increased blood pressure, increased heart rate, and acute myocardial infarction.[1,14,15,33] The central nervous system is suggested to be an important mediator in this relation. Neuroimaging research has shown that specific brain regions are activated by stress, leading to an increase in sympathetic and hypothalamus pituitary adrenal (HPA) axis activity, which causes elevated levels of cortisol, catecholamines, and pro-inflammatory cytokines.[34,35] Chronic activation of these systems can lead to metabolic and cardiovascular changes, including increased insulin resistance, decreased heart rate variability, increased heart rate and blood pressure, and platelet activation.[33,36-38] These changes are thought to accelerate the atherosclerotic process and thereby increase the risk for the development of cardiovascular diseases. In turn, stress physiology may directly affect brain structures involved in

cardiovascular processes, such as heart rate and vasomotor regulation, leading to a perpetuation of the cycle.[15,39-41]

*Somatic disease leading to depression*

The biology associated with somatic disease is also suggested to increase the risk for depression. Both structural brain alterations and depression are common in patients with vascular disease. Therefore, abnormal brain structure is a candidate mediator for the relation between vascular disease and subsequent depression. The vascular depression hypothesis is one of the leading theories on the etiology of late-onset depression.[42] It states that vascular pathology may lead to structural brain changes, which may result in depression if brain structures involved in mood regulation (i.e. fronto-subcortical networks) are disrupted.[42,43] Longitudinal and cross-sectional studies in the elderly and in patients with a recent stroke have shown that the presence of white matter lesions (WMLs) was associated with (incident) depression.[44-47] Additionally, it has been suggested that reduced gray matter volumes within the frontal and limbic areas play a role in the pathophysiology of depression later in life.[48] Another potential biological pathway linking somatic disease to depression is inflammation. Somatic disease is associated with chronically increased levels of inflammatory cytokines (e.g. interleukins and tumor necrosis factor) that can act on the brain to induce depressive symptoms.[49]

### *Behavioral pathway*

Behavioral factors associated with depression can contribute to the increased risk for somatic disease. Depressed patients show more adverse health behaviors: they smoke more often, are less physically active, and eat less healthily, thereby increasing their risk for metabolic and cardiovascular diseases.[37,50,51] In addition, depressed patients are less likely to undergo medical procedures[52] and to adhere to medication prescriptions and lifestyle advices.[7,37,53] These unhealthy behaviors pose them at a higher risk for disease progression and adverse prognosis. Evidence for this comes from the Heart and Soul study, which showed that lifestyle factors, especially physical exercise, explained almost half of the association between depression and new cardiovascular events in stable coronary artery disease (CAD) patients.[54] Therefore, behavioral interventions that focus on lifestyle and physical activity may be beneficial for depressed patients. Cardiac rehabilitation and exercise therapies have been demonstrated effective in improving depressive symptoms as well as medical prognosis,[55,56] which supports the theory of a behavioral pathway.

### *Non-causal pathways*

Besides potential causal psychological, biological and behavioral pathways, non-causal factors also have to be taken into account when studying the association

between somatic disease and depression. Two important issues are the substantial overlap of symptoms between somatic disease and depression, and the possibility of a shared predisposition to both somatic disease and depression.

*Symptom overlap*

One difficulty in studying the etiology of somatic depression is that some symptoms resulting from the somatic pathophysiology overlap with depressive symptoms (e.g. fatigue, sleeping problems, and concentration problems).[57] This raises the question whether depressive symptoms may in part be a reflection of the somatic disease.[16] If this holds true, patients with more severe disease consequently may have more (somatic) symptoms and are therefore more likely to report "depressive" symptoms. In that case, the subsequent risk of poor prognosis that is attributed to depression may actually be due to somatic disease severity. In line with this, depression was found to be significantly related to disease severity markers, such as left ventricular ejection fraction[6,58] and blood glucose levels.[59] In addition, specifically somatic depressive symptoms (e.g. fatigue, changes in appetite and weight, and sleeping problems), but not cognitive/affective depressive symptoms (e.g. depressed mood, loss of interest, feelings of guilt) were reported to be related to disease severity markers and poor medical prognosis. This suggests that somatic depressive symptoms may be physiological consequences of somatic disease.[23,60-63] Nevertheless, most studies that adjusted for disease severity markers, observed that these markers explained only part of the association between depression and medical prognosis.[10,58,64] Therefore, additional factors are suggested to cause the association. However, as there is no unequivocal definition of disease severity, the possibility of imprecise or unmeasured confounding remains.[65]

*Shared predisposition*

The relation between depression and somatic disease may also be explained by shared risk factors. For instance, stress may give rise to both depression and somatic disease via independent pathways. It is also possible that genetic factors that contribute to depression may partly overlap with those for somatic disease. Support for this comes from twin studies that suggested a shared genetic pathway between depression and microvascular dysfunction[66] and decreased heart rate variability.[67] Furthermore, besides its proposed role in depression, serotonin has also been found to stimulate vascular smooth muscle proliferation and platelet aggregation.[68] Moreover, polymorphism of the serotonin transporter gene has been associated with increased risk of MI.[69] Nevertheless, it remains unclear whether mutual vulnerability factors or a direct causal relation between depression and somatic disease underlie these observations.

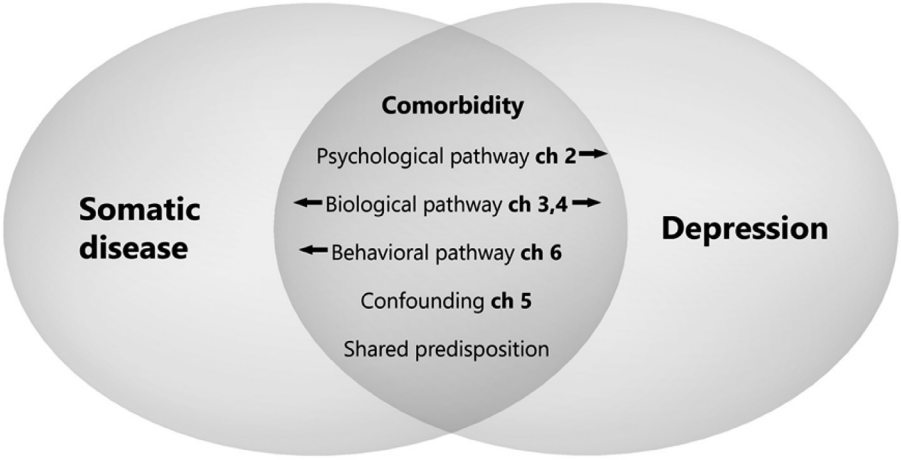


**Figure 1:** Overview of potential pathways leading to comorbidity of depression and somatic disease



## The aims of this dissertation

Although a large body of research indicates a relation between depression and somatic disease, the underlying mechanisms are still not well understood. The consequences for quality of life, medical costs, and medical prognosis endorse further research on the mechanisms behind the association between somatic disease and depression. The broad aim of this dissertation is to contribute to a better understanding of the association between depression and somatic disease. For this purpose several aspects of the pathways described in this introduction will be examined in the subsequent chapters. A better understanding of underlying pathways may enhance the identification of patients who are at risk for somatic depression and may ultimately lead to better intervention possibilities. Below, unresolved issues and the related research topics of the subsequent chapters are introduced.

***Psychological pathway: psychopathology in diagnosed and undiagnosed diabetes***
In order to investigate whether psychopathology is related to the psychological consequences of a disease, large population studies are needed. Research in patients with diabetes suggests that odds of depression are only increased when people are aware of their diabetes.[31,32] However, these results are mostly based on small population studies investigating odds for elevated depressive symptoms in both diagnosed and undiagnosed diabetes, without adjusting for disease

severity markers. Adjusting for disease severity markers is important, because underlying disease may be more severe in diagnosed compared to undiagnosed cases.[59,70-72] In ***chapter 2***, the large population study LifeLines was used to directly compare diagnosed and undiagnosed (i.e., detected during the baseline-visit of the LifeLines study) diabetes for the odds of depressive and anxiety disorders in 90,686 participants, while adjusting for the severity indicators HbA1c and diabetes-related somatic comorbidity.

***Biological pathway: brain structure in early and advanced vascular disease***

Multiple biological factors have been indicated in the association between depression and somatic disease, e.g. inflammation, hypothalamus-pituitary-adrenal (HPA) axis dysregulation and autonomic dysfunction.[1,14,15,33] The brain plays an important role in the regulation of hormonal and autonomic processes. Nevertheless, regional brain morphology in areas of emotional and autonomic regulation as a shared biological link between depression and somatic disease has rarely been studied. Depression and somatic disease have both been associated with abnormal brain morphology in for example the hippocampus, anterior cingulate cortex, orbitofrontal cortex, and inferior frontal gyrus, in studies examining these conditions independently. Brain morphology has rarely been examined in a sample of patients with comorbid depression and somatic disease.

Although no conclusions regarding causality can be drawn from cross-sectional studies, studies in both early and advanced disease might lead to a clearer understanding of the temporal sequence and the potential underlying pathophysiological pathways. Therefore, we performed two cross-sectional MRI studies, in early and in advanced somatic disease (respectively, hypertension and end-stages of CKD), in order to investigate structural brain abnormalities as a potential biological pathway in the relation between depression and somatic disease. ***Chapter 3*** reports on the independent and interactive associations of depressive disorder (N=152) and hypertension (N=82) with regional brain volumes in one sample, using data of the neuroimaging sample (N=285) of the Netherlands study of Depression and Anxiety (NESDA).

Investigating brain structure in patients with depression in the context of advanced vascular disease is especially useful to examine the vascular depression hypothesis.[42,43] To date, the vascular depression hypothesis has mostly been examined in the elderly and in stroke patients.[46-48] Although both depression and structural brain damage are common in patients with advanced CKD, no studies have yet examined the relation between depression and brain structure in the context of CKD. In ***chapter 4***, we evaluated whether white matter hyper-intensities and decreased gray matter volumes in the brains of patients with advanced CKD were particularly located in areas of mood-regulation. In subsequent exploratory analyses, comparing CKD patients with and without depressive symptoms, we examined whether regional brain abnormalities were pronounced for those with

depressive symptoms. For this purpose, we collected MRI data of 24 patients with advanced CKD and 24 controls in the Depression In the Picture (DIP) study.

***Non-causal pathway: the confounding role of prognostic factors***

Many studies examined the confounding role of somatic disease severity in the relation with depression and prognosis following acute MI. However, results have been rather inconsistent on whether depression is still a significant predictor for prognosis after adjusting for this potential confounder.[58] One important problem regarding this is the difficulty in measuring cardiac disease severity. There is no unequivocal definition of disease severity, and different markers are thus used across studies (e.g. left ventricular ejection fraction, previous MI, heart failure, arrhythmia, blood pressure and diabetes). In ***chapter 5***, the relation between post-MI depression and cardiovascular prognosis is studied in 494 MI patients, while adjusting for a well validated composite prognostic measure for prognosis of MI patients, namely the Global Registry of Acute Coronary Events (GRACE) risk score.[73] In a secondary analysis, we examined the association between this prognostic measure with somatic/affective and cognitive/affective depressive symptoms separately, because somatic/affective depressive symptoms have been found to be more strongly related to somatic disease severity markers and are stronger predictors of adverse medical outcome than cognitive/affective symptoms.[60,61] For this study, data from the Depression after Myocardial Infarction (DepreMI) study was used.

***Behavioral pathway: cardiac rehabilitation, depression, and mortality risk***

The beneficial effects of cardiac rehabilitation may not be homogeneous among depressed and non-depressed MI patients. Depressed patients are less likely to adhere to the recommendations offered for cardiac rehabilitation.[74] If patients with depressive symptoms profit less from cardiac rehabilitation programs than those without, this could explain the association of post-MI depression with poor cardiovascular prognosis. On the other hand, patients with depressive symptoms could show a relatively greater degree of mortality reduction than patients without depressive symptoms, because they have higher pre-treatment mortality risks and consequently there is more to gain. No studies have directly evaluated whether depressed and non-depressed MI patients benefit differently from cardiac rehabilitation with regard to long term prognosis. In ***chapter 6***, we directly compared the association of cardiac rehabilitation with all-cause mortality for patients with and without depressive symptoms. For this purpose, we used a combined sample of the DepreMI and the Myocardial Infarction and Depression Intervention Trial (MIND-IT), consisting of 2,198 MI patients.

Finally, in ***chapter 7*** the main findings will be summarized and integrated in a broader perspective. In addition, methodological considerations, future directions, and clinical implications will be discussed.

# References

1. Evans DL, Charney DS, Lewis L, et al. Mood disorders in the medically ill: Scientific review and recommendations. *Biol Psychiatry*. 2005;58(3):175-189.

2. Huang CQ, Dong BR, Lu ZC, Yue JR, Liu QX. Chronic diseases and risk for depression in old age: A meta-analysis of published literature. *Ageing Res Rev.* 2010;9(2):131-141.

3. Katon WJ. Epidemiology and treatment of depression in patients with chronic medical illness. *Dialogues Clin Neurosci.* 2011;13(1):7-23.

4. 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(2):215-221.

5. Katon W, Lin EH, Kroenke K. The association of depression and anxiety with medical symptom burden in patients with chronic medical illness. *Gen Hosp Psychiatry.* 2007;29(2):147-155.

6. van Melle JP, de Jonge P, Ormel J, et al. Relationship between left ventricular dysfunction and depression following myocardial infarction: Data from the MIND-IT. *Eur Heart J.* 2005;26(24):2650-2656.

7. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: Meta-analysis of the effects of anxiety and depression on patient adherence. *Arch Intern Med.* 2000;160(14):2101-2107.

8. Cuijpers P, Vogelzangs N, Twisk J, Kleiboer A, Li J, Penninx BW. Comprehensive meta-analysis of excess mortality in depression in the general community versus patients with specific illnesses. *Am J Psychiatry.* 2014;171(4):453-462.

9. Hedayati SS, Minhajuddin AT, Afshar M, Toto RD, Trivedi MH, Rush AJ. Association between major depressive episodes in patients with chronic kidney disease and initiation of dialysis, hospitalization, or death. *JAMA.* 2010;303(19):1946-1953.

10. Meijer A, Conradi HJ, Bos EH, Thombs BD, van Melle JP, de Jonge P. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: A meta-analysis of 25 years of research. *Gen Hosp Psychiatry.* 2011;33(3):203-216.

11. Meng L, Chen D, Yang Y, Zheng Y, Hui R. Depression increases the risk of hypertension incidence: A meta-analysis of prospective cohort studies. *J Hypertens.* 2012;30(5):842-851.

12. Mezuk B, Eaton WW, Albrecht S, Golden SH. Depression and type 2 diabetes over the lifespan: A meta-analysis. *Diabetes Care.* 2008;31(12):2383-2390.

13. Van der Kooy K, van Hout H, Marwijk H, Marten H, Stehouwer C, Beekman A. Depression and the risk for cardiovascular diseases: Systematic review and meta analysis. *Int J Geriatr Psychiatry.* 2007;22(7):613-626.

14. de Jonge P, Rosmalen JG, Kema IP, et al. Psychophysiological biomarkers explaining the association between depression and prognosis in coronary artery patients: A critical review of the literature. *Neurosci Biobehav Rev.* 2010;35(1):84-90.

15. Grippo AJ, Johnson AK. Biological mechanisms in the relationship between depression and heart disease. *Neurosci Biobehav Rev.* 2002;26(8):941-962.

16. Meijer A, Zuidersma M, de Jonge P. Depression as a non-causal variable risk marker in coronary heart disease. *BMC Med.* 2013;11:130-7015-11-130.

17. Murray CJ, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: A systematic analysis for the global burden of disease study 2010. *Lancet.* 2012;380(9859):2197-2223.

18. 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. *Arch Gen Psychiatry.* 2005;62(6):617-627.

19. Beck AT, Steer RA, Ball R, Ranieri W. Comparison of beck depression inventories -IA and -II in psychiatric outpatients. *J Pers Assess.* 1996;67(3):588-597.

20. Levey AS, Atkins R, Coresh J, et al. Chronic kidney disease as a global public health problem: Approaches and initiatives - a position statement from kidney disease improving global outcomes. *Kidney Int.* 2007;72(3):247-259.

21. Couser WG, Remuzzi G, Mendis S, Tonelli M. The contribution of chronic kidney disease to the global burden of major noncommunicable diseases. *Kidney Int.* 2011;80(12):1258-1270.

22. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med.* 2006;3(11):e442.

23. Ormel J, de Jonge P. Unipolar depression and the progression of coronary artery disease: Toward an integrative model. *Psychother Psychosom.* 2011;80(5):264-274.

24. Maercker A, Einsle F, Kollner V. Adjustment disorders as stress response syndromes: A new diagnostic concept and its exploration in a medical sample. *Psychopathology.* 2007;40(3):135-146.

25. Hare DL, Toukhsati SR, Johansson P, Jaarsma T. Depression and cardiovascular disease: A clinical review. *Eur Heart J.* 2014;35(21):1365-1372.

26. Mezuk B, Johnson-Lawrence V, Lee H, et al. Is ignorance bliss? depression, antidepressants, and the diagnosis of prediabetes and type 2 diabetes. *Health Psychol.* 2013;32(3):254-263.

27. Pearce MJ, Pereira K, Davis E. The psychological impact of diabetes: A practical guide for the nurse practitioner. *J Am Assoc Nurse Pract.* 2013;25(11):578-583.

28. Talbot F, Nouwen A. A review of the relationship between depression and diabetes in adults: Is there a link? *Diabetes Care*. 2000;23(10):1556-1562.

29. de Groot M, Anderson R, Freedland KE, Clouse RE, Lustman PJ. Association of depression and diabetes complications: A meta-analysis. *Psychosom Med*. 2001;63(4):619-630.

30. Chan R, Steel Z, Brooks R, et al. Psychosocial risk and protective factors for depression in the dialysis population: A systematic review and meta-regression analysis. *J Psychosom Res*. 2011;71(5):300-310.

31. Nouwen A, Nefs G, Caramlau I, et al. Prevalence of depression in individuals with impaired glucose metabolism or undiagnosed diabetes: A systematic review and meta-analysis of the european depression in diabetes (EDID) research consortium. *Diabetes Care*. 2011;34(3):752-762.

32. Mezuk B, Chen Y, Yu C, et al. Depression, anxiety, and prevalent diabetes in the chinese population: Findings from the china kadoorie biobank of 0.5million people. *J Psychosom Res*. 2013;75(6):511-517.

33. McEwen BS. Protective and damaging effects of stress mediators: Central role of the brain. *Dialogues Clin Neurosci*. 2006;8(4):367-381.

34. Thayer JF, Lane RD. The role of vagal function in the risk for cardiovascular disease and mortality. *Biol Psychol*. 2007;74(2):224-242.

35. Gianaros PJ, Sheu LK, Matthews KA, Jennings JR, Manuck SB, Hariri AR. Individual differences in stressor-evoked blood pressure reactivity vary with activation, volume, and functional connectivity of the amygdala. *J Neurosci.* 2008;28(4):990-999.

36. Musselman DL, Betan E, Larsen H, Phillips LS. Relationship of depression to diabetes types 1 and 2: Epidemiology, biology, and treatment. *Biol Psychiatry*. 2003;54(3):317-329.

37. Myers V, Gerber Y, Benyamini Y, Goldbourt U, Drory Y. Post-myocardial infarction depression: Increased hospital admissions and reduced adoption of secondary prevention measures--a longitudinal study. *J Psychosom Res*. 2012;72(1):5-10.

38. Champaneri S, Wand GS, Malhotra SS, Casagrande SS, Golden SH. Biological basis of depression in adults with diabetes. *Curr Diab Rep*. 2010;10(6):396-405.

39. Baune BT, Stuart M, Gilmour A, et al. The relationship between subtypes of depression and cardiovascular disease: A systematic review of biological models. *Transl Psychiatry*. 2012;2:e92.

40. Brotman DJ, Golden SH, Wittstein IS. The cardiovascular toll of stress. *Lancet*. 2007;370(9592):1089-1100.

41. Harrison NA, Cooper E, Voon V, Miles K, Critchley HD. Central autonomic network mediates cardiovascular responses to acute inflammation: Relevance to increased cardiovascular risk in depression? *Brain Behav Immun*. 2013;31:189-196.

42. Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Charlson M. 'Vascular depression' hypothesis. *Arch Gen Psychiatry*. 1997;54(10):915-922.

43. Krishnan KR, Taylor WD, McQuoid DR, et al. Clinical characteristics of magnetic resonance imaging-defined subcortical ischemic depression. *Biol Psychiatry*. 2004;55(4):390-397.

44. van Sloten TT, Sigurdsson S, van Buchem MA, et al. Cerebral small vessel disease and association with higher incidence of depressive symptoms in a general elderly population: The AGES-Reykjavik study. *Am J Psychiatry*. 2015:appiajp201414050578.

45. Pavlovic AM, Pekmezovic T, Zidverc Trajkovic J, et al. Baseline characteristic of patients presenting with lacunar stroke and cerebral small vessel disease may predict future development of depression. *Int J Geriatr Psychiatry*. 2015.

46. Wang L, Leonards CO, Sterzer P, Ebinger M. White matter lesions and depression: A systematic review and meta-analysis. *J Psychiatr Res.* 2014;56:56-64.

47. Herrmann LL, Le Masurier M, Ebmeier KP. White matter hyperintensities in late life depression: A systematic review. *J Neurol Neurosurg Psychiatry*. 2008;79(6):619-624.

48. Sexton CE, Mackay CE, Ebmeier KP. A systematic review and meta-analysis of magnetic resonance imaging studies in late-life depression. *Am J Geriatr Psychiatry*. 2013;21(2):184-195.

49. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: When the immune system subjugates the brain. *Nat Rev Neurosci.* 2008;9(1):46-56.

50. Doyle F, Rohde D, Rutkowska A, Morgan K, Cousins G, McGee H. Systematic review and meta-analysis of the impact of depression on subsequent smoking cessation in patients with coronary heart disease: 1990 to 2013. *Psychosom Med*. 2014;76(1):44-57.

51. Strine TW, Mokdad AH, Dube SR, et al. The association of depression and anxiety with obesity and unhealthy behaviors among community-dwelling US adults. *Gen Hosp Psychiatry*. 2008;30(2):127-137.

52. Druss BG, Bradford DW, Rosenheck RA, Radford MJ, Krumholz HM. Mental disorders and use of cardiovascular procedures after myocardial infarction. *JAMA*. 2000;283(4):506-511.

53. Gonzalez JS, Peyrot M, McCarl LA, et al. Depression and diabetes treatment nonadherence: A meta-analysis. *Diabetes Care*. 2008;31(12):2398-2403.

54. Whooley MA, de Jonge P, Vittinghoff E, et al. Depressive symptoms, health behaviors, and risk of cardiovascular events in patients with coronary heart disease. *JAMA*. 2008;300(20):2379-2388.

55. Peterson JC, Charlson ME, Wells MT, Altemus M. Depression, coronary artery disease, and physical activity: How much exercise is enough? *Clin Ther*. 2014;36(11):1518-1530.

56. Blumenthal JA, Sherwood A, Babyak MA, et al. Exercise and pharmacological treatment of depressive symptoms in patients with coronary heart disease: Results from the UPBEAT (understanding the prognostic benefits of exercise and antidepressant therapy) study. *J Am Coll Cardiol*. 2012;60(12):1053-1063.

57. Murtagh FE, Addington-Hall JM, Edmonds PM, et al. Symptoms in advanced renal disease: A cross-sectional survey of symptom prevalence in stage 5 chronic kidney disease managed without dialysis. *J Palliat Med*. 2007;10(6):1266-1276.

58. 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(23):2763-2774.

59. Lustman PJ, Anderson RJ, Freedland KE, de Groot M, Carney RM, Clouse RE. Depression and poor glycemic control: A meta-analytic review of the literature. *Diabetes Care*. 2000;23(7):934-942.

60. de Jonge P, Ormel J, van den Brink RH, et al. Symptom dimensions of depression following myocardial infarction and their relationship with somatic health status and cardiovascular prognosis. *Am J Psychiatry*. 2006;163(1):138-144.

61. Roest AM, Thombs BD, Grace SL, Stewart DE, Abbey SE, de Jonge P. Somatic/affective symptoms, but not cognitive/affective symptoms, of depression after acute coronary syndrome are associated with 12-month all-cause mortality. *J Affect Disord*. 2011;131(1-3):158-163.

62. Smolderen KG, Spertus JA, Reid KJ, et al. The association of cognitive and somatic depressive symptoms with depression recognition and outcomes after myocardial infarction. *Circ Cardiovasc Qual Outcomes*. 2009;2(4):328-337.

63. de Miranda Azevedo R, Roest AM, Hoen PW, de Jonge P. Cognitive/affective and somatic/affective symptoms of depression in patients with heart disease and their association with cardiovascular prognosis: A meta-analysis. *Psychol Med*. 2014;44(13):2689-2703.

64. Meijer A, Conradi HJ, Bos EH, et al. Adjusted prognostic association of depression following myocardial infarction with mortality and cardiovascular events: Individual patient data meta-analysis. *Br J Psychiatry*. 2013;203(2):90-102.

65. Christenfeld NJ, Sloan RP, Carroll D, Greenland S. Risk factors, confounding, and the illusion of statistical control. *Psychosom Med*. 2004;66(6):868-875.

66. Vaccarino V, Votaw J, Faber T, et al. Major depression and coronary flow reserve detected by positron emission tomography. *Arch Intern Med*. 2009;169(18):1668-1676.

67. Su S, Lampert R, Lee F, et al. Common genes contribute to depressive symptoms and heart rate variability: The twins heart study. *Twin Res Hum Genet*. 2010;13(1):1-9.

68. Mulle JG, Vaccarino V. Cardiovascular disease, psychosocial factors, and genetics: The case of depression. *Prog Cardiovasc Dis*. 2013;55(6):557-562.

69. Fumeron F, Betoulle D, Nicaud V, et al. Serotonin transporter gene polymorphism and myocardial infarction: Etude cas-temoins de l'infarctus du myocarde (ECTIM). *Circulation*. 2002;105(25):2943-2945.

70. Melin EO, Thunander M, Svensson R, Landin-Olsson M, Thulesius HO. Depression, obesity, and smoking were independently associated with inadequate glycemic control in patients with type 1 diabetes. *Eur J Endocrinol*. 2013;168(6):861-869.

71. Ciechanowski PS, Katon WJ, Russo JE, Hirsch IB. The relationship of depressive symptoms to symptom reporting, self-care and glucose control in diabetes. *Gen Hosp Psychiatry*. 2003;25(4):246-252.

72. Pouwer F, Beekman AT, Nijpels G, et al. Rates and risks for co-morbid depression in patients with type 2 diabetes mellitus: Results from a community-based study. *Diabetologia*. 2003;46(7):892-898.

73. Fox KA, Eagle KA, Gore JM, Steg PG, Anderson FA, GRACE and GRACE2 Investigators. The global registry of acute coronary events, 1999 to 2009--GRACE. *Heart*. 2010;96(14):1095-1101.

74. Jaarsma T, Lesman-Leegte I, Hillege HL, et al. Depression and the usefulness of a disease management program in heart failure: Insights from the COACH (coordinating study evaluating outcomes of advising and counseling in heart failure) study. *J Am Coll Cardiol*. 2010;55(17):1837-1843.