Arch Gynecol Obstet (2015) 291:1213–1220
DOI 10.1007/s00404-015-3618-0

REVIEW

Depression as a risk factor for acute coronary syndrome: a review

Genny S. Misteli · Petra Stute

Received: 27 October 2014 / Accepted: 9 January 2015 / Published online: 20 January 2015

Abstract
Purpose In the past few years more and more research focused on psychosocial risk factors of cardiovascular disease, including depression. This review focuses on depression as a long-term risk factor for acute coronary syndrome in initially heart disease-free people.
Methods The studies included ($n = 15$) comprised people without heart disease who were exposed to depression. The outcome was acute coronary syndrome (acute myocardial infarction, instable angina pectoris, sudden cardiac death). Only articles published in English between 2000 and 2013 were considered.
Results Most but not all studies found an association between depression and cardiac outcome. Possible explanations for the inconsistency of the findings are discussed.
Conclusions Most likely there is an association between depression and acute coronary syndrome. However, it remains unclear whether depression acts as an independent risk factor for developing an acute coronary syndrome, or if depression promotes the development of an acute coronary syndrome by indirect means.

Keywords Acute coronary syndrome · Acute myocardial infarction · Unstable angina pectoris · Sudden cardiac death · Depression · Review

Introduction

Acute coronary syndrome (ACS) is one of the most prevalent diseases [1, 2] and responsible for huge losses of life quality and life years, respectively [1–4]. Cardiovascular diseases (CVD) account for 30 % of deaths worldwide [1]. Traditional CVD risk factors include hypertension, diabetes, sedentary lifestyle, smoking, obesity and high blood cholesterol [5, 6]. However, in the past few years attention was drawn to psychosocial CVD risk factors such as depression [5, 7–9]. Lifetime prevalence for major depression is estimated to be 8–12 % [10] with women being more often affected than men [10, 11]. However, depression is thought to be underdiagnosed and thus, its prevalence may be much higher. Depression often presents as a chronic disease [10], and with each episode the risk of recurrence increases [12]. In cardiovascular diseased people, 15–22 % suffers from depressive disorders [13], with depression being associated with a two- to fourfold increased mortality risk in survivors from myocardial infarction (MI) [14]. However, much less is known about the impact of depression on coronary health in people without prevalent coronary heart disease (CHD). As depression is a treatable condition any association with CHD would have to prompt physicians to diagnose and treat depression more rigidly to reduce CHD morbidity and mortality, respectively. Here, we aim to review the current scientific literature for identifying the role that depression may play as a long-term ACS risk factor in people without prevalent CHD. We will also focus on current models of pathophysiology and possible gender differences.

Electronic supplementary material The online version of this article (doi:10.1007/s00404-015-3618-0) contains supplementary material, which is available to authorized users.

G. S. Misteli · P. Stute (✉)
Gynecological Endocrinology and Reproductive Medicine, Department of Obstetrics and Gynecology, Inselspital Bern, Effingerstrasse 102, 3010 Bern, Switzerland
e-mail: stutepe@web.de; petra.stute@insel.ch

Materials and methods

Inclusion criteria

To be included, the study population had to be exposed to depression but not to CHD. Depression had to be defined either by validated questionnaires or structured interviews according to ICD or DSM IV. The trials' outcome had to be ACS defined as MI, unstable angina pectoris or sudden cardiac death. Studies focusing on the impact of depression in people with prevalent CHD were excluded. To efficiently reduce the number of hits, we applied the filter "clinical trial", and only included studies in English published between 2000 and 2013.

Search strategy

In a first step, the term "myocardial ischemia" was combined with "psychology" using the Mesh database. Additionally, the Medline database was searched by combining "psychosocial" and the Mesh term "myocardial ischemia". The terms were always combined with the logical connective "AND". The Mesh term "myocardial ischemia" contains all outcomes of interest and beyond (ACS, MI, unstable angina pectoris, coronary disease, myocardial stunning and myocardial reperfusion injury). In a next step the risk factors ("depressive disorder", "depression", "affective symptoms" and "mood disorder") were separately searched in Medline in combination with "myocardial ischemia". To make sure none of the relevant studies were left out, related citations and important references to this subject were included if they matched the inclusion criteria (Fig. 1).

Results

Of 586 hits, 15 studies met the inclusion criteria [5, 8, 13–25] (Suppl. Table 1). Results were inconsistent. An association between depression and cardiac outcome was confirmed by most [8, 13–20] but not all studies [5, 21–25].

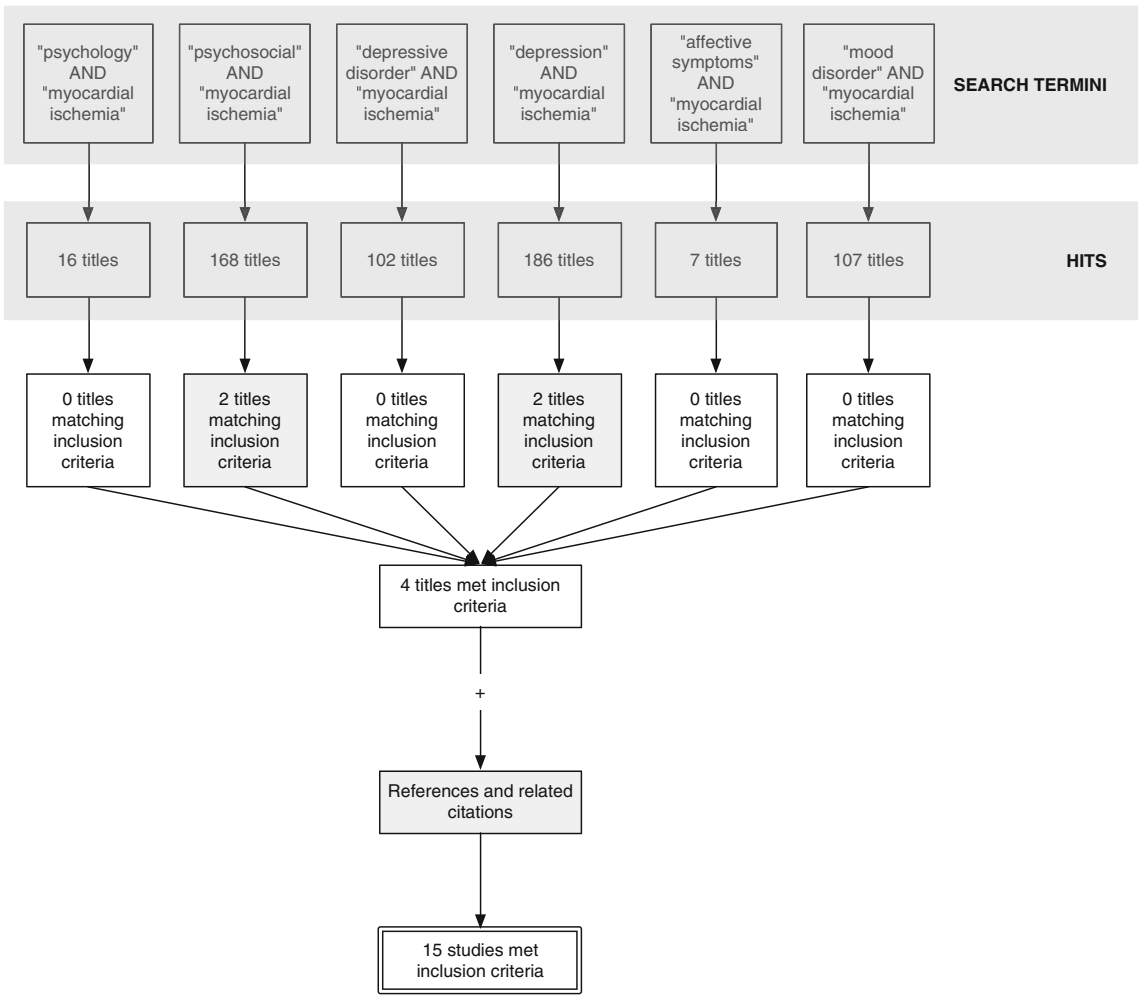

Fig. 1 Search strategy: flow chart of literature research

However, the selected studies differed tremendously with respect to sample size, study design, definition of depression and cardiac outcome, respectively, as well as the number and quality of factors adjusted for. The sample size ranged from 915 [23] to 93,676 [17]. 13 studies were cohort studies with mean follow-up time ranging from 3 [15] to 37 years [21]. The remaining 2 were case–control studies [8, 20]. Cardiac outcome definitions varied. Outcomes were CHD [15–17, 21]. Some investigators further differentiated between fatal and non-fatal CHD [13, 18, 24], ischemic heart disease mortality [5, 14, 19], cardiac mortality [14, 23] sudden cardiac death [18, 23], cardiovascular death [17], ACS [8], MI [18, 20, 21], non-fatal MI [23, 24], coronary artery disease [17], CVD [25], and hard coronary disease events (MI, coronary death) [22], respectively. Overall, in depressed people the relative risk (RR) for developing an ACS ranged from 0.64 [22] to 6.9 [14] with the RR being approximately 1.5 in most studies. Risk of ischemic heart disease mortality was not affected by the type of depressive symptoms, e.g., somatic or cognitive symptoms [19].

Discussion

Although the majority of studies found a positive association between depression and later ACS in initially cardiovascular non-diseased people the magnitude of results differed. Obviously, studies varied in many aspects making it difficult to compare results and balance reasons for or against an association. Those differences inbetween studies and their impact on results will be discussed.

Outcome definition

The association between depression and CHD depended on the exact outcome definition. For example, calculated RR was different when comparing the association of depression with non-fatal or fatal CHD [13]. Accordingly, depression was found to be an independent risk factor of CVD death but not of CHD [17]. Similarly, there was a positive association between depressive symptoms and sudden cardiac death, but not with non-sudden cardiac death or non-fatal MI [23]. In contrast, another study found an association between depressive symptoms with CHD but not with sudden cardiac death or non-fatal MI [18].

Depression assessment

Most investigators used the Center of Epidemiologic Studies Depression (CES-D) Scale [8, 13–17, 22]. However, the questionnaire was often modified or combined with other questionnaires [17] or structured interviews [14]. All [8, 13–17] but one [22] studies using the CES-D Scale found an association between depression and later CHD onset. If structured interviews were conducted by specialists to assess depression according to ICD or DSM IV criteria no association with CHD development was found [21, 25]. Furthermore, alternative scoring systems were applied such as the modified Minnesota Multiphasic Personality Inventory (MMPI-2) [24], General Well-Being Schedule subscale [5], Short Zung Depression Rating Scale (SZDRS) [23], Health and Life Experience questionnaire [19] and Mental Health Inventory-5 (MHI-5) questionnaire [18], respectively, that did [18, 19] or did [5, 23, 24] not find an association. Importantly, some investigators used absolute depression scores [5, 8, 13, 14, 16, 17, 19–21, 23–25], while others used defined increases in depression scores [15, 18, 22].

Specificity of depression assessment

It is questioned if the questionnaires applied specifically screen for depressive symptoms or if other conditions with negative emotional state (e.g., anxiety disorder, anger) also lead to an elevated score [17, 21, 24, 25]. Possibly, the questionnaires rather reflect general distress than depressive symptoms [21]. Thus, a positive screening test should be further evaluated by a psychiatric examination [17]. However, it is unknown if different emotional conditions have an impact on coronary health by separate patterns or rather have the same diathesis [24].

Recency, severity and chronicity of depression

Severity and chronicity of depression have been considered by some studies [14, 15, 18–20, 22, 23]. However, the questionnaires/structured interviews applied most likely do not assess these characteristics in the same way. For example, the prevalence of depression was lower when assessed by a psychologist using a structured interview as compared to studies using questionnaires to screen for depressive symptoms [21]. There is an indication for a "dose–response" relationship between depression and ACS in some [14, 15, 19] but not all [20] studies. CHD risk was found to rise with increasing mean cumulative depression scores that were even more predictive of ACS events than baseline depression scores [15]. Similarly, the risk of cardiac mortality was twice as high in major depression compared to minor depression [14] and if several episodes of depression occured [19]. When focusing on recency of depressive episodes, the strongest association between depression and ischemic heart disease mortality was found for current depression at baseline assessment [19]. However, individuals may remember depressive episodes more detailed while past episodes may be more susceptible to recall errors. Repeated depression assessment to capture

the effect of recurrent depressive episodes was found to more reliably predict vascular events [15].

Comorbidity among affective disorders

Comorbidity among affective disorders is common [10, 21, 24, 25]. To analyze the effect of depression other affective conditions were screened for by some investigators [21, 24, 25]. When assessing different mental disorders (e.g., general anxiety disorder, panic disorder, major depression, bipolar disease) and adjusting them for each other, both, mood disorders and anxiety disorders were strongly associated with CVD risk [25]. However, specific single mood disorders were not significantly associated with CVD risk after adjusting for other psychiatric conditions [24, 25]. If psychiatric conditions cumulated, a 20 % increase in CVD risk was found by each additional psychiatric disorder [25]. Due to the high comorbidity among mental disorders, these findings underline the importance of assessing various mental disorders preferably by a specialist to avoid misclassification and thus false-positive associations [21, 25].

Duration of follow-up

The study with the longest follow-up, 37 years, included young people aged 18–20 years at baseline to assess the impact of early-onset depression and anxiety on CHD risk in later life [21]. The advantage of including young people is that chances of an underlying undiagnosed progressive atherosclerosis or subclinical CHD that could facilitate depressive states are low, and the challenge of reverse causation (see "Reverse causation") is eliminated. However, long-term follow-up may also dilute the impact of depression, and even long-term follow-up starting at young ages may not be long enough since depression-related cardiovascular events may occur still later in life [21]. Depression has been found to be a time-dependent CHD risk factor by some [16] but not all [19]. While CHD risk was significantly increased within up to 5 years after depression diagnosis, risk was comparable to non-depressed participants during years 5–10 [16]. However, others found no attenuation of risk of ischemic heart disease mortality when stratifying for length of follow-up [19].

Depression as independent or covariate risk factor

Depression is associated with adverse health behavior. Depressed people are more often smokers [13, 15–19, 21, 22, 24–28], overweight [17–19], unemployed [16, 26], less educated [15–17, 24], less physically active [13, 15–19, 21, 26, 27], and less compliant with treatment recommendations [15, 28]. Furthermore, an association with alcohol consumption [13, 16, 21, 25, 27] and illicit drug abuse [25] has been reported. Single living people [13, 16] are more vulnerable to depression and higher perceived general stress [20]. When adjusting for smoking status, there was an increased cumulative risk of the independent risk factors smoking and depression on non-fatal CHD events [13]. Unfortunately most people present with multiple ACS risk factors. The combination of multiple risk factors is thought to be responsible for most ischemic heart disease events in the United States, while only little population attributable risk is due to single acting risk factors [5]. Importantly, depression qualified as predictor for sudden cardiac death in a similar extent as established CHD risk factors [23]. Certainly, several psychosocial risk factors are linked to each other and can be seen as covariate risk factors. Controlling for interactions of covariate risk factors is important. Otherwise, inconsistent findings may occur [19, 21]. When carefully controlling for well-established CHD risk factors as well as for other possible confounding and covariate risk factors, the risk of ischemic heart disease mortality due to depression was not attenuated indicating that depression acts as an independent risk factor [19, 21] (Fig. 2).

Gender differences

Depressive symptoms are more frequently observed in women than men [5, 10, 11, 13, 15, 19, 22, 29, 30]. In contrast, men suffer up to 4 times more often from MI than women [2, 8] and are usually younger when the first MI occurs [1, 8, 31]. The impact of gender on the association of depression with ACS was considered in 8 studies [5, 8, 13–15, 19, 20, 22]. The results are mixed, ranging from a higher ACS risk in depressed women [8, 13, 15], similar CHD risk in depressed men and women [5, 14, 20, 22] to a higher risk for ischemic heart disease mortality in depressed men [19].

Reverse causation

One of the biggest challenges is the so-called "reverse causation" addressing the question what comes first: depression or atherosclerosis [21, 26, 32]. On one hand, subclinical CVD may manifest as depression before presenting as clinical CHD and thus might lead to the wrong assumption, that depression causes clinical CHD. On the other hand depression might cause de novo atherosclerosis. In 6 studies the possibility of reverse causation was taken into account [13, 16–19, 21]. The investigators chose different methods to overcome this issue like excluding the first 2 [13] or 6 [19] years of follow-up, or censoring all cardiovascular death events occurring during the first 6 months of follow-up [17], respectively. However, results did not change with any procedures. Still, the possibility of unrecognized underlying CVD causing depressive symptoms has

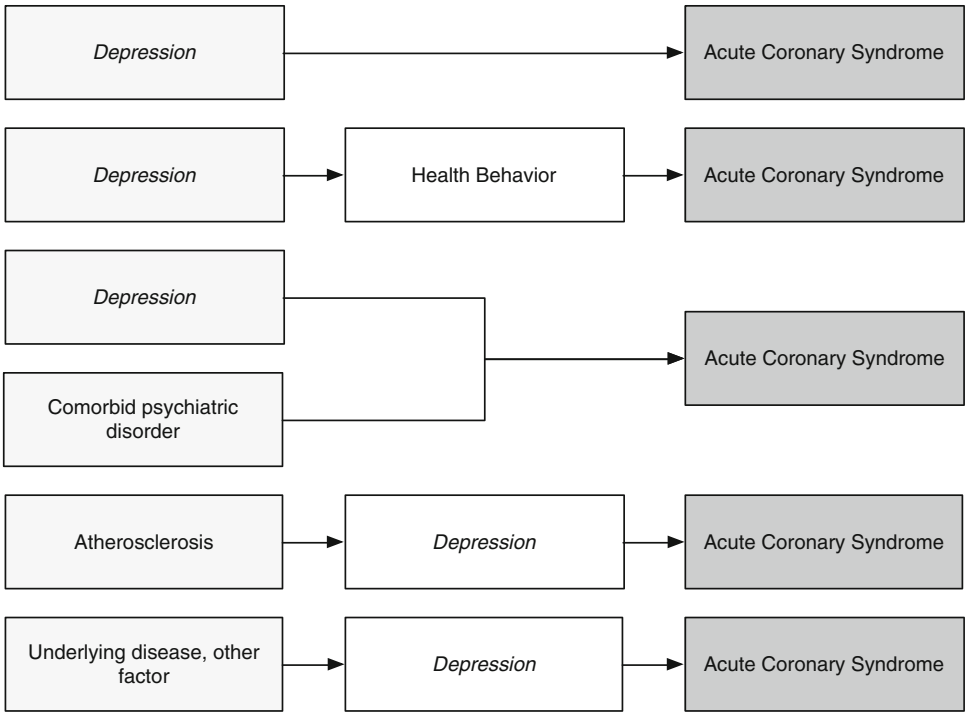

Fig. 2 Pathways of interaction: possible explanations for the association between depression and acute coronary syndrome

not been ruled out [17]. To do so, young and healthy people at study entry would need to be included [21].

The stronger association between recent episodes of depression and ischemic heart disease mortality may be due to recall bias (see "Recency, severity and chronicity of depression"). However, depression may also act as a trigger in the cascade finally leading to a cardiovascular event, or may "just" be another symptom of underlying subclinical CHD [19].

Possible pathophysiological mechanisms

In general, there are two possible mechanisms by which depression might influence the heart (Fig. 3). First, depression may act as a long-term risk factor by promoting atherosclerosis and thus CHD [7]. Second, depression may act as an acute trigger of ACS in people with advanced CHD by promoting cardiovascular activation, coronary constriction and alteration in the homeostasis of blood clotting mechanisms. To display long-term risk factor qualities for developing ACS one might expect one strong or several cumulating pathophysiological pathways. Indeed, several pathophysiological pathways have emerged during recent years like alteration of autonomic tone [13, 14, 16, 23, 26–28] with increased sympathetic activity [13, 15, 17, 18, 23, 27], decreased parasympathetic activity [23, 27, 29], lower heart rate variability [13, 14, 18, 19, 23, 26, 29], higher resting heart rate [18], and higher blood pressure variability [29]. In such states atherogenesis is promoted, and the individual's susceptibility to CHD increases [13] further contributing to ventricular fibrillation [13, 17] and arrhythmias [17, 18, 23, 28]. Depression is also associated with catecholamine release [13, 26] promoting platelet activation [13, 15, 26, 27], increasing platelet reactivity [13, 29], aggregation [13, 15, 17], numbers of circulating platelets [15] and facilitating impaired platelet function [14, 19]. Furthermore, blood clotting mechanisms are disturbed [16], and tachycardia as well as vasoconstriction [27] may occur. Vascular damage can result from increased activation of thrombocytes, which promotes the genesis of atherosclerosis [26, 27]. Hypercortisolemia as a stress response also increases blood pressure and may promote endothelial injury [27]. Additionally, depression may be linked to CHD by a hyperactive 5-HT2A-transporter enhancing the impact of serotonin on platelets' function [9, 27], by increasing circulating inflammatory markers, activating immune and inflammatory systems [14, 16, 19, 27, 28], and altering lipid metabolism [15]. Depression has also been thought to share some genetic similarity with CHD [33]. Finally, as mentioned before, behavioral risk factors associated with depression may play an important role [28].

Arguments for and against a direct correlation of depression and ACS

Obviously, it is almost impossible to compare such heterogenous studies and come to a strong conclusion. However,

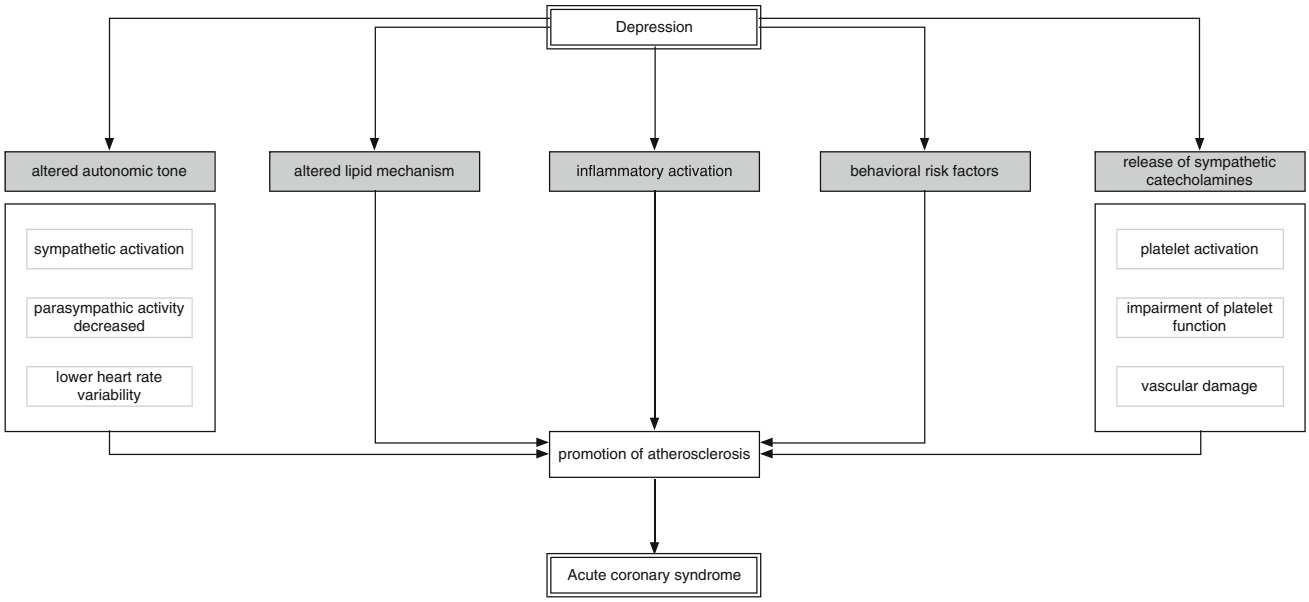

Fig. 3 Pathophysiology: possible pathophysiological mechanisms linking depression and acute coronary syndrome

if so many different study settings repeatedly point to a positive association between depression and ACS one might suggest a direct correlation to some extent. Indeed, there are several arguments to believe in a direct correlation [9]. First, most studies found a 1.5–2-fold increased risk for depressed people to suffer from an ACS [9, 26, 34]. Second, the increased risk was still present after controlling for conventional and non-conventional ACS risk factors [13–17, 19, 20, 22–24] making depression comparable to other established CHD risk factors [9]. Third, plausible pathophysiological mechanisms have been suggested to link depression to ACS [7, 9, 13–19, 23, 27, 28, 34]. Furthermore, depression has not only been associated with the pathogenesis of primary ACS but also presents as adverse factor in patients with established CHD [14]. Similarly, CHD seems to have unfavorable effects on depression [9]. The main reasons against a true relationship between depression and ACS are the risk of reverse causation and incomplete adjustment for conventional and confounding CHD risk factors.

Use of antidepressant medication

The possible influence of antidepressants on ACS in depressed individuals has been taken into account by some investigators [13–18, 23]. At least in one study adjustment for antidepressants did not change the results [14]. However, depressed individuals may be less compliant in taking their medication [17]. Importantly, the impact of antidepressants on the heart may depend on their type of action as, e.g., tricyclic antidepressants may have cardiotoxic [14] and proarrhythmic [18] effects whereas selective serotonin reuptake inhibitors have been shown to positively influence heart rate variability and, therefore, reduce morbidity and mortality from heart diseases [9].

Strength and limitations

The strength of this review is the extensive discussion of the challenges which emerge when investigating the correlation between depression and ACS. Being aware of these issues may help future studies to choose a design that considers those entanglements. Certainly this review also has its limitations. Although we performed a literature research we might have missed relevant studies that have been neither published in English nor in Medline, respectively. In addition, the review does not consider the impact of antidepressants on the relationship of depression and ACS. It is also important to keep in mind that comparing populations from different cultural backgrounds is only possible at limits as different lifestyles and distinct values will alter the prevalence of depression. Finally, there always is the possibility of publication bias [22, 26, 32, 34]. However, to negate all evidence in favor of an association between depression and ACS it would take 572 unpublished studies indicating the contrary [34].

Conclusion

This review compares a heterogeneous series of studies and explains various reasons for the inconsistency among their results. Most likely, there is an association between depression and ACS. However, it remains unclear whether

depression—via distinct pathophysiological pathways—acts as an independent risk factor or if depression promotes ACS by adverse health behavior, comorbidities or confounding factors. Future studies should control for established ACS risk factors as well as for comorbidities. To avoid reverse causation, ideally, the study population should be young and cardiovascular healthy at baseline, and the follow-up should be reasonably long enough. Furthermore, repetitive assessment of depression should be performed by specialists using structured interviews, to assess severity, chronicity and characteristics of depression. However, regardless of the exact pathomechanism, in clinical practice the possibility of a—direct or indirect—association between depression and ACS emphasizes the need for consequent diagnostics and treatment of depression to improve mental well-being as well as cardiovascular and general health.

Acknowledgments The authors are grateful for the support of Ramona Guelpa, secretary at the Department of Obstetrics and Gynecology, division of Gynecological Endocrinology and Reproductive Medicine, Inselspital Bern, Switzerland. The authors have received no funding for this article.

Conflict of interest The authors declare to have no conflict of interests.

References

1. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Soliman EZ, Sorlie PD, Sotoodehnia N, Turan TN, Virani SS, Wong ND, Woo D, Turner MB, American Heart Association Statistics C, Stroke Statistics S (2012) Heart disease and stroke statistics—2012 update: a report from the American Heart Association. Circulation 125(1):e2–e220. doi:10.1161/CIR.0b013e31823ac046
2. Zellweger U, Bopp M (2012) Zahlen und Daten über Herz-Kreislauf-Krankheiten in der Schweiz. Schweizerische Herzstiftung
3. 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 (2013) Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. Lancet 382(9904):1575–1586. doi:10.1016/S0140-6736(13)61611-6
4. WHO (2011) Global status report on noncommunicable diseases 2010—description of the global burden of NCDs, their risk factors and determinants. WHO Libr Cat Data
5. Chang M, Hahn RA, Teutsch SM, Hutwagner LC (2001) Multiple risk factors and population attributable risk for ischemic heart disease mortality in the United States, 1971–1992. J Clin Epidemiol 54(6):634–644
6. Reriani MK, Flammer AJ, Jama A, Lerman LO, Lerman A (2012) Novel functional risk factors for the prediction of cardiovascular events in vulnerable patients following acute coronary syndrome. Circulation J Off J Jpn Circ Soc 76(4):778–783
7. Steptoe A, Brydon L (2009) Emotional triggering of cardiac events. Neurosci Biobehav Rev 33(2):63–70. doi:10.1016/j.neubiorev.2008.04.010
8. Panagiotakos DB, Pitsavos C, Chrysohoou C, Stefanadis C, Toutouzas P (2002) Risk stratification of coronary heart disease in Greece: final results from the CARDIO2000 Epidemiological Study. Prev Med 35(6):548–556
9. Goldston K, Baillie AJ (2008) Depression and coronary heart disease: a review of the epidemiological evidence, explanatory mechanisms and management approaches. Clin Psychol Rev 28(2):288–306. doi:10.1016/j.cpr.2007.05.005
10. Andrade L, Caraveo-Anduaga JJ, Berglund P, Bijl RV, De Graaf R, Vollebergh W, Dragomirecka E, Kohn R, Keller M, Kessler RC, Kawakami N, Kilic C, Offord D, Ustun TB, Wittchen HU (2003) The epidemiology of major depressive episodes: results from the International Consortium of Psychiatric Epidemiology (ICPE) Surveys. Int J Methods Psychiatr Res 12(1):3–21
11. Baumeister H, Harter M (2007) Prevalence of mental disorders based on general population surveys. Soc Psychiatry Psychiatr Epidemiol 42(7):537–546. doi:10.1007/s00127-007-0204-1
12. Burcusa SL, Iacono WG (2007) Risk for recurrence in depression. Clin Psychol Rev 27(8):959–985. doi:10.1016/j.cpr.2007.02.005
13. Ferketich AK, Schwartzbaum JA, Frid DJ, Moeschberger ML (2000) Depression as an antecedent to heart disease among women and men in the NHANES I study. National Health and Nutrition Examination Survey. Arch Intern Med 160(9):1261–1268
14. Penninx BW, Beekman AT, Honig A, Deeg DJ, Schoevers RA, van Eijk JT, van Tilburg W (2001) Depression and cardiac mortality: results from a community-based longitudinal study. Arch Gen Psychiatry 58(3):221–227
15. Ariyo AA, Haan M, Tangen CM, Rutledge JC, Cushman M, Dobs A, Furberg CD (2000) Depressive symptoms and risks of coronary heart disease and mortality in elderly Americans. Cardiovascular Health Study Collaborative Research Group. Circulation 102(15):1773–1779
16. Majed B, Arveiler D, Bingham A, Ferrieres J, Ruidavets JB, Montaye M, Appleton K, Haas B, Kee F, Amouyel P, Ducimetiere P, Empana JP, Group PS (2012) Depressive symptoms, a time-dependent risk factor for coronary heart disease and stroke in middle-aged men: the PRIME Study. Stroke J Cereb Circ 43(7):1761–1767. doi:10.1161/STROKEAHA.111.645366
17. Wassertheil-Smoller S, Shumaker S, Ockene J, Talavera GA, Greenland P, Cochrane B, Robbins J, Aragaki A, Dunbar-Jacob J (2004) Depression and cardiovascular sequelae in postmenopausal women. The Women's Health Initiative (WHI). Arch Intern Med 164(3):289–298. doi:10.1001/archinte.164.3.289
18. Whang W, Kubzansky LD, Kawachi I, Rexrode KM, Kroenke CH, Glynn RJ, Garan H, Albert CM (2009) Depression and risk of sudden cardiac death and coronary heart disease in women: results from the Nurses' Health Study. J Am Coll Cardiol 53(11):950–958. doi:10.1016/j.jacc.2008.10.060
19. Surtees PG, Wainwright NW, Luben RN, Wareham NJ, Bingham SA, Khaw KT (2008) Depression and ischemic heart disease mortality: evidence from the EPIC-Norfolk United Kingdom prospective cohort study. Am J Psychiatry 165(4):515–523. doi:10.1176/appi.ajp.2007.07061018
20. Rosengren A, Hawken S, Ounpuu S, Sliwa K, Zubaid M, Almahmeed WA, Blackett KN, Sitthi-amorn C, Sato H, Yusuf S, investigators I (2004) Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-

control study. Lancet 364(9438):953–962. doi:10.1016/S0140-6736(04)17019-0
21. Janszky I, Ahnve S, Lundberg I, Hemmingsson T (2010) Early-onset depression, anxiety, and risk of subsequent coronary heart disease: 37-year follow-up of 49,321 young Swedish men. J Am Coll Cardiol 56(1):31–37. doi:10.1016/j.jacc.2010.03.033
22. Wulsin LR, Evans JC, Vasan RS, Murabito JM, Kelly-Hayes M, Benjamin EJ (2005) Depressive symptoms, coronary heart disease, and overall mortality in the Framingham Heart Study. Psychosom Med 67(5):697–702. doi:10.1097/01.psy.0000181274.56785.28
23. Luukinen H, Laippala P, Huikuri HV (2003) Depressive symptoms and the risk of sudden cardiac death among the elderly. Eur Heart J 24(22):2021–2026
24. Kubzansky LD, Cole SR, Kawachi I, Vokonas P, Sparrow D (2006) Shared and unique contributions of anger, anxiety, and depression to coronary heart disease: a prospective study in the normative aging study. Ann Behav Med: Publ Soc Behav Med 31(1):21–29. doi:10.1207/s15324796abm3101_5
25. Goodwin RD, Davidson KW, Keyes K (2009) Mental disorders and cardiovascular disease among adults in the United States. J Psychiatr Res 43(3):239–246. doi:10.1016/j.jpsychires.2008.05.006
26. Rugulies R (2002) Depression as a predictor for coronary heart disease. a review and meta-analysis. Am J Prev Med 23(1):51–61
27. Serrano CV Jr, Setani KT, Sakamoto E, Andrei AM, Fraguas R (2011) Association between depression and development of coronary artery disease: pathophysiologic and diagnostic implications. Vasc Health Risk Manag 7:159–164. doi:10.2147/VHRM.S10783
28. Joynt KE, Whellan DJ, O'Connor CM (2003) Depression and cardiovascular disease: mechanisms of interaction. Biol Psychiatry 54(3):248–261
29. Prescott E, Holst C, Gronbaek M, Schnohr P, Jensen G, Barefoot J (2003) Vital exhaustion as a risk factor for ischaemic heart disease and all-cause mortality in a community sample. A prospective study of 4084 men and 5479 women in the Copenhagen City Heart Study. Int J Epidemiol 32(6):990–997
30. Alonso J, Lepine JP, Committee ESMS (2007) Overview of key data from the European Study of the Epidemiology of Mental Disorders (ESEMeD). J Clin Psychiatry 68(Suppl 2):3–9
31. Anand SS, Islam S, Rosengren A, Franzosi MG, Steyn K, Yusufali AH, Keltai M, Diaz R, Rangarajan S, Yusuf S, Investigators I (2008) Risk factors for myocardial infarction in women and men: insights from the INTERHEART study. Eur Heart J 29(7):932–940. doi:10.1093/eurheartj/ehn018
32. Nicholson A, Kuper H, Hemingway H (2006) 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 27(23):2763–2774. doi:10.1093/eurheartj/ehl338
33. Kendler KS, Gardner CO, Fiske A, Gatz M (2009) Major depression and coronary artery disease in the Swedish twin registry: phenotypic, genetic, and environmental sources of comorbidity. Arch Gen Psychiatry 66(8):857–863. doi:10.1001/archgenpsychiatry.2009.94
34. Wulsin LR, Singal BM (2003) Do depressive symptoms increase the risk for the onset of coronary disease? A systematic quantitative review. Psychosom Med 65(2):201–210