Mechanisms Linking Depression to Cardiovascular Disease: What Do Epidemiological Studies Tell Us?

4

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Contents

Abstract

The burden of disease for depression goes beyond functioning and quality of life and extends to somatic health. Depression has shown to subsequently increase the risk of cardiovascular morbidity and mortality. These somatic consequences can be partly explained by mediating mechanisms such as unhealthy lifestyle (smoking, excessive alcohol use, physical inactivity, unhealthy diet) or unfavorable pathophysiological disturbances (metabolic, immuno-inflammatory, autonomic, and HPA-axis dysregulations). This chapter presents epidemiological evidence for the existence of these plausible underlying mechanisms that link

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B.T. Baune, P.J. Tully (eds.), *Cardiovascular Diseases and Depression*,
DOI 10.1007/978-3-319-32480-7_4

depression to cardiovascular disease. However, alternative explanations for an increased cardiovascular risk in depressed persons are also discussed, namely, the confounding hypothesis, iatrogenic effects, or noncausal "third factors."

4.1 Somatic Consequences of Depression

The impact of depression on health extends beyond mental health. Over the last 20 years, many studies illustrated the adverse impact of depression on somatic health as well. As described previously, the evidence is convincing that depression increases the subsequent risk of cardiovascular disease development. Cardiovascular disease refers to those conditions that affect the heart and blood vessels, including among others coronary heart disease, cerebrovascular disease, and peripheral artery disease. Meta-analyses integrating longitudinal evidence concluded that depression results in an at least 80 % increased risk of cardiovascular disease onset (Nicholson et al. 2006; van der Kooy et al. 2007). In line with a dose-response association, the cardiovascular morbidity risk is higher among persons with major depressive disorder than among those with subthreshold depressive symptoms, but the risk is also significantly increased in the latter group. This epidemiological evidence also extends to subclinical cardiovascular processes. Depressed persons are also at increased risk for peripheral atherosclerosis as indicated through, e.g., coronary or aortic calcification, impaired endothelial function, and increased arterial stiffness (Seldenrijk et al. 2010, 2011; Hamer et al. 2010).

This chapter will mainly focus on evidence that considers depression to be an etiological risk factor for cardiovascular disease. However, it is good to note that this is only a small part of the complex interaction between depression and cardiovascular disease. First, beyond increasing the risk of cardiovascular disease onset, depression also increases the risk of cardiovascular mortality when cardiovascular disease has already emerged (Doyle et al. 2015). So, there is extensive evidence that depression contributes not only to the onset but also to the progression of cardiovascular disease. Several of the underlying mechanisms discussed in this chapter are not specific for explaining why depression is an etiological risk factor but may also explain why depression is a prognostic risk factor among patients with clinically overt cardiovascular disease. Second, although I focus mainly on the mechanisms through which depression can increase subsequent cardiovascular risk, it is clear that a bidirectional link exists. Cardiovascular disease itself can – either through direct physical consequences or through indirect biological, bodily, or psychosocial changes – also increase the risk of developing depressive symptoms and disorders.

Furthermore, it is good to realize that the impact of depression on somatic health is not restricted to cardiovascular disease alone. There are various meta-analyses that have shown similar evidences when integrating results from longitudinal studies among initially somatic disease-free subjects. Depression also increases the onset risk of overall mortality (relative risk (RR) = 1.81), diabetes (RR = 1.60),

hypertension (RR = 1.42), stroke (RR = 1.34), obesity (RR = 1.58), Alzheimer's disease (RR = 1.66), and to a lesser extent even cancer (RR = 1.29) (Penninx et al. 2013). To even provide a larger picture, the increased cardiovascular risk associated with depression is not specific for depression either. For various other psychiatric conditions, similar observations have been described. In a large-scale population-based study incorporating data from over 50,000 subjects across the world, also panic disorder, specific phobia, post-traumatic stress disorder, and alcohol use disorders were found to predict subsequent heart disease onset (Scott et al. 2013). For nonspecific anxiety disorder, a recent meta-analysis summarizing a total of 37 papers including 1,565,699 persons also indicated a 50 % increased risk of cardiovascular disease onset (Batelaan et al. 2016).

The fact that depression is not only associated with the onset of cardiovascular disease but also that of various other somatic conditions combined with the fact that this association extends to other psychiatric conditions as well already illustrates that it is not likely that underlying mechanisms are very disease specific. In the paragraphs below, I will describe which underlying mechanisms may likely contribute to the increased cardiovascular risk in depressed individuals. For this purpose I will mainly focus on results provided by large-scale epidemiological studies.

4.2 The "Confounding Hypothesis" as Mechanism Linking Depression to Cardiovascular Health

Subjects with depression are usually older, more often female, and have a lower socioeconomic status, and their general health is worse than that of their non-depressed peers. This leads to the hypothesis that age, sex, sociodemographics, and baseline health conditions rather than depression per se might be responsible for the differential subsequent cardiovascular health patterns between depressed and non-depressed subjects. This "confounding hypothesis" (see Table 4.1) is likely to contribute to finding worse cardiovascular outcomes among the depressed. Generally, most longitudinal population studies that examined the risk of cardiovascular events in depressed persons have found that the risk associated with depression declined with 20–30 % after considering these sociodemographic and baseline health conditions (Nicholson et al. 2006; van der Kooy et al. 2007). However, after adjustment for these potential confounding variables in statistical analyses, the cardiovascular risk in depressed persons remained significantly increased compared to that of non-depressed persons illustrating that the link does not seem to be completely due to simply confounding. Of course, it can be that in some cases depression may be a prodrome of not yet discovered and diagnosed (and therefore not measurable) subclinical or medical conditions that affect subsequent cardiovascular disease onset. However, it is unlikely that this completely explains the increased cardiovascular risk as results are rather consistent across studies, not restricted to older samples only (in which other health conditions may be present), and have also been found for major depressive disorders with an early age of onset.

Table 4.1 Summary of proposed mechanisms linking depression to increased cardiovascular risk

Causal mediating mechanisms	
Unhealthy lifestyle	Smoking
	Excessive alcohol use
	Physical inactivity
	Unhealthy diet
Worse medical care	Inadequate medical attention
	Lower (e.g., somatic) treatment compliance
Pathophysiology	Metabolic dysregulations
	Immuno-inflammatory dysregulations
	Autonomic dysregulations
	HPA-axis dysregulations
Noncausal mechanisms	
Confounding	Depression picks up or is a prodrome of not yet discovered or measured (sub)clinical conditions
Iatrogenic effects	Pharmacological effect of, e.g., antidepressants increase cardiovascular risk
"Third underlying factors[a]"	Childhood stressors
	Personality
	Genetic pleiotropy

However, alternative explanations for an increased cardiovascular risk in depressed persons are also discussed, namely, the confounding hypothesis, iatrogenic effects, or noncausal "third factors"

[a]Factors that influence both cardiovascular risk and depression risk but rather independently from each other

4.3 Unhealthy Lifestyle as Mechanism Linking Depression to Cardiovascular Health

Increased behavioral risk profiles in depressed persons may explain their higher risk for adverse health consequences. Behavioral risk factors appear to cluster in the same individuals. Increased smoking and alcohol consumption are well documented in depression. Depressed persons not only smoke more often, they are found to be less likely to quit smoking and might inhale more deeply and smoke more of the cigarette than non-depressed smokers (Anda et al. 1990). In addition, the food intake of depressed persons has shown to be less adequate, healthy, and nutritious than that of non-depressed persons. It has been shown that depressed persons have a higher 24-h caloric intake than non-depressed persons (Sanhueza et al. 2013). On the other hand, certain vitamin deficiencies, such as vitamin D, B12, and folate deficiencies, are more prevalent in depressed older persons (Penninx et al. 2000; Milaneschi et al. 2014), which illustrates that certain depressed persons may not get adequate nutrition. Depressed persons also engage less in physical activities such as walking, gardening, and vigorous exercise activities such as sports. So, physical inactivity is common among depressed persons

(Stephens 1988), partly because their attitudes toward exercise and exercise self-efficacy may be more negative. These unhealthy lifestyles can contribute to the fact that depressed individuals are more at risk for adverse health outcomes, since these constitute the most important risk factors for the onset of cardiovascular disease. This is especially an important observation, since, e.g., the level of physical activity is potentially modifiable through an exercise regimen. There are several clinical trials that – although not consistent across all trials – illustrate that when depressed persons are randomized to an exercise intervention, their depressed mood significantly improves (Rosenbaum et al. 2014). Other lifestyle changing programs, such as nutritional interventions or smoking cessation, may also be relevant in depressed persons and may positively impact not just on mental health but also on cardiovascular health (Ward et al. 2015).

Finally, depressed mood has shown to impede recovery processes by discouraging persons from obtaining adequate medical attention and rehabilitation and following treatment regimens. It has been described that depressed persons are generally at least twice less compliant in taking medications or following up on certain lifestyle regimens provided by health-care professionals (DiMatteo et al. 2000). This lower compliance and poorer self-care with general health regimens could in part be due to lack of a supportive social network which has more often been observed in depressed than in non-depressed persons (Penninx et al. 1998). One study indeed confirmed that depressed cardiac patients received lower quality of care than their non-depressed peers and that this contributed to their higher mortality risk (Druss et al. 2001).

Meta-analyses on cardiovascular consequences of depression have reported pooled effect sizes for adjusted associations which considered potential mediating variables such as lifestyle indicators. This is possible as many – but not all – of the conducted longitudinal studies associating depression to incident cardiovascular morbidity have adjusted for lifestyle differences. These lifestyle-adjusted pooled effect sizes are only slightly lower than unadjusted ones, suggesting that the increased morbidity risks are not simply due to lifestyle differences (Nicholson et al. 2006; van der Kooy et al. 2007). However, considering the fact that, e.g., nutritional and physical activity patterns are not easy to assess in detail in large-scale observational studies, residual impact of these behavioral factors may still exist.

4.4 Biological Dysregulation Linking Depression to Cardiovascular Health

In addition to the above provided explanations, depression-related biological dysregulations that also constitute risk factors for somatic illnesses could further contribute to the observed depression and cardiovascular disease link. The next section describes evidence for biological dysregulations examined in this context. I focused on the most commonly examined biological dysregulations in this respect, namely, metabolic, immuno-inflammatory, autonomic, and HPA-axis dysregulations.

4.4.1 Metabolic Dysregulation

Often clinical metabolic dysregulations are assessed in the context of the metabolic syndrome: a clustering of general metabolic risk factors including abdominal obesity, increased blood glucose (hyperglycemia), elevated blood pressure, increased triglycerides, and decreased high-density lipoprotein (HDL) cholesterol. Metabolic dysregulations are well-established risk factors for the development of various somatic conditions, especially cardiovascular disease and diabetes (Mottillo et al. 2010). Pan et al. (2012) systematically reviewed 29 cross-sectional studies and found depression and the metabolic syndrome to be modestly associated (unadjusted odds = 1.42; adjusted odds = 1.34). Some reviewed prospective studies confirmed a bidirectional association with depression predicting the onset of metabolic syndrome, which in turn predicted depression onset over time. However, the metabolic syndrome is a heterogeneous concept: pathophysiological mechanisms of elevated blood pressure, dyslipidemia, and hyperglycemia are not necessarily similar. Consequently, various studies have tested consistency of associations with depression across different metabolic syndrome components. The most consistent evidence seems to exist between depression and obesity-related components (abdominal obesity, low HDL cholesterol, hypertriglyceridemia), whereas associations between depression with hyperglycemia and hypertension are less often confirmed (Pan et al. 2012). Also when evidence from longitudinal studies was pooled, consistent associations were only confirmed for the obesity-related components. The association between depression and metabolic dysregulations seems to follow a dose-response association as larger dysregulations were found with increasing level of depression severity (Van Reedt Dortland et al. 2010). Two longitudinal studies among depressed patients found that a combination of multiple metabolic dysregulations contributed to sustained chronicity of depression (Vogelzangs et al. 2011, 2014). Taken together, literature suggests that abdominal obesity and lipid disturbances are the driving force behind the relationship between depression and metabolic syndrome. Once both are present, abdominal obesity might give rise to multiple metabolic dysregulations, which in turn might be responsible for remaining in a depressed state.

Indeed, depression is a heterogeneous condition with multiple, diverging symptoms defining the concept. Metabolic dysregulations have found to be more specifically present in "atypical depression," a subtype present in 20–30 % of all depressed cases and marked by hypersomnia and fatigue, increased appetite and weight gain, mood reactivity, and interpersonal rejection sensitivity (Penninx et al. 2013). Two studies directly comparing atypical versus melancholic depressed persons both confirmed that metabolic syndrome were more present in atypical than in melancholic depression (Seppälä et al. 2012; Lamers et al. 2010). Also when examining longitudinal associations with abdominal obesity-related outcomes in a large-scale population sample, it was mainly atypical depression that was found to be predictive (Lasserre et al. 2014).

How could metabolic dysregulations in depression arise? White adipose tissue, especially in the abdominal area, is an active endocrine organ producing

inflammatory cytokines and hormones (e.g., leptin) and, therefore, a major contributor to pathogenic immune-metabolic responses both in the central nervous system and brain and in the rest of the body. For instance, leptin has shown to affect hippocampal and cortical structure through its actions on neurogenesis, axon growth, synaptogenesis, and dendritic morphology regulation (Paz-Filho et al. 2010). Another possible mechanism linking metabolic dysregulation and depression may be represented by cerebrovascular damage associated with metabolic syndrome, which according to the so-called "vascular depression" hypothesis predispose to depression especially in late life (Alexopoulos 2006). Finally, other depression-related biological dysregulations discussed below may constitute shared underlying pathways to metabolic alterations.

4.4.2 Immuno-Inflammatory Dysregulation

A consistent body of evidence indicates that depression is associated with dysregulated inflammation, an immune response that derives from activation of the innate immune system. The inflammatory mediator network is represented by a bewildering array of molecules, the most prominent of which are pro-inflammatory cytokines (e.g., interleukin (IL)-6 and TNF-α) produced within innate immune cells in response to immunologic challenge. Other cytokines, known as anti-inflammatory, oppose this response by attenuating the production of pro-inflammatory cytokine (e.g., IL-10) or by antagonizing their action at the receptor level (e.g., IL-1RA). The actions of pro-inflammatory cytokines on peripheral cellular targets such as hepatocytes lead to the synthesis of acute phase proteins (e.g., C-reactive protein (CRP)) responsible for the systemic inflammatory response. Chronic, low-grade systemic elevations of these molecules are considered abnormal and have shown to increase the onset of cardiovascular morbidity and mortality (Cesari et al. 2003; Kaptoge et al. 2010). There is a strong interconnection between metabolic abnormalities and inflammation illustrated by the facts that abdominal fat tissue produces cytokines, and these subsequently increase metabolic syndrome development (Visser et al. 1999).

Three recent meta-analyses reported significantly higher levels of the inflammatory markers TNF-α, sIL-2R, IL-6, and IL-1RA in drug-naïve depressed subjects compared to controls (Dowlati et al. 2010; Liu et al. 2012; Howren et al. 2009). Overall, effect sizes were modest (ranging from a Cohen's d of 0.15–0.35) with slightly stronger effect sizes for studies using clinical diagnoses of depression instead of symptom reports (Penninx et al. 2013). Although systemic inflammation has been found for both melancholic and atypical depressed subjects, it appears to be more strongly present in atypical depression (Lamers et al. 2013; Penninx et al. 2013). An essential role was found for body mass index (BMI) as a covariate: studies adjusting for BMI found much lower effect sizes, likely due to the fact that adipose tissue is an important source of cytokines. However, even after adjustment for BMI, elevated inflammation levels in the depressed were observed, indicating that immune and metabolic dysregulations are partly complementary.

Most meta-analyzed studies were cross-sectional which makes it hard to draw any causal inferences. However, several lines of research indicate that the link between inflammation and depression is likely bidirectional. It has been demonstrated that immunotherapy with IFN-α can precipitate depression (Bonaccorso et al. 2002). In turn, cytokines produced peripherally can access the brain – either directly crossing the blood-brain barrier through saturable active transport systems or indirectly via microglia activation – which can result in decreased neurogenesis also in emotion-regulating brain structures (Shelton and Miller 2010). Cytokines also catalyze the synthesis of kynurenine from tryptophan, which may result in reduced synthesis of serotonin and increased synthesis of tryptophan catabolites, which could all perturb neurotransmission and result in hippocampal neuron damage (Sublette and Postolache 2012). Finally, depression may facilitate weight gain – partly as a result of sedentary behavior and unhealthy dietary choice – which in turn promotes inflammation that ultimately may reinforce depression, creating a deleterious vicious cycle for physical and mental health.

4.4.3 Autonomic Dysregulation

Acute stress results into immediate activation of sympathetic nerves and reduction of parasympathetic nerves in order to prepare the body for a fight and flight response. A direct measurement method for autonomic tone is assessing noradrenaline spillover to plasma. Unfortunately, such invasive spillover studies are not implementable in large psychiatric cohorts, restricting our insights into generalizability of results and the role of potential confounding factors. That is why researchers have used noninvasive, but more indirect, indicators of autonomic tone obtained from electrical and impedance cardiography assessments. A noninvasive method for autonomic dysregulation assessment is heart rate variability (HRV), particularly in the respiratory frequency range, as an indicator of cardiac vagal control. HRV reflects an individual's capacity for parasympathetic inhibition of autonomic arousal and is an important predictor for cardiovascular disease and mortality (Dekker et al. 2000; Tsuji et al. 1996). Autonomic dysregulation is involved in cardiovascular somatic symptoms such as tachycardia, blood pressure liability, and tendencies toward hypertension and predicts the onset of metabolic dysregulations over time (Licht et al. 2013).

Depression is hypothesized to involve an autonomic nervous system that is in a relative state of more sympathetic and less parasympathetic activation. According to the polyvagal theory, this is partly due to the fact that impairments of low vagal tone are associated with reduced social engagement and a less flexible behavioral response to environmental changes (Porges 2001). Rottenberg (2007) summarized 13 studies including 312 depressed patients and 374 controls and found indeed a significantly reduced HRV in depression (Cohen's $d = 0.33$). Four years later, Kemp et al. (2010) repeated a meta-analysis in which only power-domain analyses were allowed to measure HRV, and all included subjects were free of cardiovascular disease. Meta-analyzing results of 14 studies (302 patients, 424 controls) yielded again a modest but significant pooled effect size indicating a lower HRV among the

depressed. Contrary to these results were studies by Licht et al. (2008) and Kemp et al. (2014) with a sample size that was by far larger than the total number of participants in the meta-analyses and could adjust for lifestyle. In these studies, more than 1,000 major depressive disorder patients without antidepressants did not consistently show differences in HRV as compared to control subjects, and in a 2-year follow-up, depression state (changes) was not associated with HRV (Licht et al. 2010). On the contrary, in both large-scale studies (Licht et al. 2008; Kemp et al. 2014), significantly lower HRV was found among antidepressant users, especially those using tricyclic antidepressants and serotonergic-noradrenergic reuptake inhibitors. This led to the authors' conclusion that it is not depressed state but use of antidepressants that changes autonomic tone. The TCA effect on HRV – likely through direct anticholinergic effects – was confirmed in a meta-analysis (Kemp et al. 2010). So, it remains rather unclear whether depression itself is associated with a reduced vagal tone. Of note is that studies included in these meta-analyses measured autonomic tone during resting condition. Depression could be more strongly associated with reduced parasympathetic tone when persons are exposed to stress conditions.

4.4.4 Hypothalamic-Pituitary-Adrenal (HPA) Axis Dysregulation

Hyperactivity of the HPA-axis in depression has been considered one of the most reliable findings in biological psychiatry. Chronic stress is perceived by the cortex of the brain and transmitted to the hypothalamus, where corticotropin-releasing hormone is released onto pituitary receptors, ultimately resulting in release of cortisol into the blood. To assess HPA-axis activity, salivary measures are increasingly used to reflect the active unbound form of cortisol. The cortisol awakening response assesses the natural response of the HPA-axis to awakening; evening cortisol levels reflect basal activity. In a meta-analysis by Knorr et al. (2010) summarizing 20 case-control studies including 1,354 depressed patients and 1,052 controls, salivary cortisol levels were on average 2.58 nmol/l increased in the morning and 0.27 nmol/l in the evening for depressed patients. In an even larger meta-analysis by Stetler and Miller (2011), evidence for higher cortisol levels across various bodily fluids (plasma, urine, saliva) was summarized. Again, this evidence illustrated that depressed individuals displayed increased cortisol levels ($d=0.60$), although the effect size was considerably less – and rather modest – when only high methodological quality studies were included ($d=0.33$). Vreeburg and colleagues (2009) showed that these findings were consistent among 701 current as well as among 579 remitted depressed cases, suggesting that HPA-axis hyperactivity represents a vulnerability rather than a state indicator. In line with this, HPA-axis hyperactivity has also been observed among non-affected offspring of depressed patients, suggesting that it may partly reflect a genetic vulnerability marker or endophenotype of depression (Vreeburg et al. 2010).

HPA-axis dysregulation appears to be more prevalent especially in persons with melancholic depression, characterized by a disturbance in affect marked by

anhedonia and nonreactive mood, by psychomotor disturbance, and by vegetative and cognitive symptoms of insomnia, loss of appetite and weight, diurnal mood variation, and impaired concentration. When summarizing several studies directly that compared cortisol levels across melancholic and atypical depression, we showed that in fact, cortisol levels among individuals with atypical depression may not be reliably higher than cortisol levels among healthy non-depressed persons (Lamers et al. 2013; Penninx et al. 2013). In line with this, a sub-analysis in Stetler and Miller's meta-analysis (2011) described that the effect size of the cortisol-depression association is higher when more melancholic depressed cases were included in studies and lower when more atypical depressed cases were included. Melancholic features were associated with 54 % larger effect sizes compared with depression without melancholic features.

Some studies have used a dexamethasone test to evaluate the sensitivity of the hypothalamus to feedback signals for the shutdown of CRH release, but results are more inconsistent. Nelson and Davis (1997) summarized that dexamethasone suppression studies found that the normal cortisol-suppression response is absent in about half of the patients with very severe symptoms (e.g., those hospitalized or those with psychotic symptoms). However, the non-suppression rate in outpatients with major depression was found to be much lower and not differential between 1,280 depressed outpatients and 308 controls (Vreeburg et al. 2009). So, the indicated larger non-suppression of the HPA-axis in depression is likely restricted to only the most severe (psychotic) cases.

Several mechanisms may underlie the relationship between HPA-axis dysregulation and depression. Depression research has focused mainly on the role of mineral corticoid and glucocorticoid receptors, acting as transcriptional regulators of cortisol effects on the initiation and termination of the stress response. Alterations of this regulating network, defined glucocorticoid resistance, may determine a chronic activation of the stress response resulting in atrophy of hippocampal cells, reduced neurogenesis, and synaptic plasticity and altered monoaminergic signaling, all of which may lead to a depressive state (De Kloet et al. 2005). Other factors such as early-life epigenetic programming of glucocorticoid genes and inflammatory processes may also be involved in the dysregulation of HPA-axis responsiveness in depressed subjects (Silverman and Sternberg 2012).

HPA-axis dysregulation has also been implicated in the onset and progression of cardiovascular disease, although evidence for this is not extensive. In two longitudinal observational studies, higher morning cortisol levels and a flatter slop in cortisol levels across the day were found to increase the risk of subsequent cardiovascular mortality in nonclinical populations (Vogelzangs et al. 2010; Kumari et al. 2011).

4.5 Iatrogenic Effects Linking Depression to Cardiovascular Risk

To what extent can antidepressant utilization contribute to an increased cardiovascular risk among depressed individuals? A few observational large-scale studies have reported increased cardiovascular risks among persons using antidepressants (Whang

et al. 2009; Hamer et al. 2011). It is an easy step to then point at the antidepressants as driving the increased cardiovascular risk. However, this type of finding cannot simply be interpreted as evidence for cardiovascular-induced risks through pathophysiological effects of antidepressants themselves mainly because such findings are heavily biased through "confounding by indication." In observational studies, subjects using antidepressants are likely to be different in many ways from subjects not using antidepressants: they are likely the most severe and chronic depression cases, or they may have other (mental or physical) reasons to be treated with antidepressants. Even if observational analyses adjust for presence and severity of depression, confounding by indication may still be present, and therefore one should be cautious with research interpretations of observational studies regarding effects of medications.

As described above, there is more and more consistent evidence that antidepressant medications, especially the tricyclic antidepressants and the serotonergic-noradrenergic reuptake inhibitors, may increase cardiac vagal tone (Licht et al. 2008, 2010; Kemp et al. 2014). However, whether this in the end may truly contribute to an increased subsequent cardiovascular disease risk remains unknown. Autonomic tone differences were generally completely diminished when antidepressant medication use was stopped (Licht et al. 2010), and it could simply be that detrimental effects of depressed mood status itself may be larger than that of antidepressants. In addition, experimental intervention results, however, do indicate that several antidepressants may in fact contribute to reduction of other specific pathophysiological disturbances such as inflammation and cortisol levels (Hannestad et al. 2011; Hinkelmann et al. 2012). In all, it is difficult to use epidemiological observational data to draw definitive conclusions of the presence of iatrogenic effects of antidepressants, and whether these truly contribute to cardiovascular disease risks. In order to formally test this, one would require a very large, long-term experimental trial, which is difficult, if not impossible, to conduct.

4.6 Other Noncausal Factors Linking Depression to Cardiovascular Risk

Alternative explanations for the link between depression and increased cardiovascular morbidity development could be "third underlying factors" that increase the risk of depression as well as the risk of cardiovascular disease but rather independently from each other (see Table 4.1). Several examples for such noncausal mechanisms exist. First, childhood maltreatment including emotional, physical, or sexual abuse has shown to be a very strong risk factor for the later onset of depression (Teicher and Samson 2013). However, childhood maltreatment has also found to be associated with both subclinical cardiovascular processes and an increased cardiovascular event risk, partly independent from depression (Bomhof-Roordink et al. 2015; Sumner et al. 2015). Consequently, if the same at-risk persons share increased risks for two conditions, associations would become apparent, but this does not have to reflect a causal, temporal association between the two conditions. Second, personality traits such as neuroticism, introversion, and type D personality have shown to be

linked to both the development of depression and cardiovascular events and could therefore constitute such a "third factor" that indirectly links both outcomes (Grande et al. 2012; Jokela et al. 2014).

Finally, an often ignored "third factor" is genetic vulnerability. If two conditions share similar genetic risk variants, persons with those high-risk genes could develop both conditions. The phenomenon of shared genetic effects is called genetic pleiotropy (de Geus 2006). This is an area that has not received a lot of research attention yet. However, it is not hard to imagine that the phenomenon of genetic pleiotropy may occur. Utilizing twin data, de Moor et al. (2008) and Bartels et al. (2012) illustrated that the link between reduced exercise behavior and mood symptoms is for a large extent due to shared genetic risks. Also for several of the biological mechanisms described above, for instance, inflammation or metabolic dysregulations, strong genetic influences have been described. These genetic influences may make persons vulnerable for biological dysregulations, which could then result in both depression as well as cardiovascular disease and in (longitudinal) relationships between both outcomes.

Conclusions

This review summarized longitudinal evidence indicating that depression increased the onset risk of cardiovascular disease onset. As summarized in Table 4.1, epidemiological evidence indicates that underlying mechanisms likely involve unhealthy lifestyles as well as a multitude of biological dysregulations that are more prevalent among depressed persons as compared to their non-depressed peers. To what extent each of these mediating mechanisms contribute to the observed increased cardiovascular risk among the depressed remains to be determined as hardly any studies have examined and quantified the mediating mechanisms in the link between depression and cardiovascular disease in a comprehensive manner. In addition, using an epidemiological observational study design for this has its limitations since the confounding hypothesis and the influence of noncausal "third factors" are hard to exclude. Nevertheless, considering the consistency of findings over multiple studies, there is convincing evidence that unhealthy lifestyles and various biological dysregulations interplay in reinforcing the vicious cycle through which depression and cardiovascular disease reinforce each other.

Acknowledgements Penninx was supported through a VICI grant (NWO grant 91811602).

Competing Interests The author has no conflict of interest to report.

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