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Review article

Depression and cardiovascular disease: Epidemiological evidence on their linking mechanisms

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ABSTRACT

Depression's burden of disease goes beyond functioning and quality of life and extends to somatic health. Results from longitudinal cohort studies converge in illustrating that major depressive disorder (MDD) subsequently increases the risk of cardiovascular morbidity and mortality with about 80%. The impact of MDD on cardiovascular health may be partly explained by mediating mechanisms such as unhealthy lifestyle (smoking, excessive alcohol use, physical inactivity, unhealthy diet, therapy non-compliance) and unfavorable pathophysiological disturbances (autonomic, HPA-axis, metabolic and immuno-inflammatory dysregulations). A summary of the literature findings as well as relevant results from the large-scale Netherlands Study of Depression and Anxiety (N = 2981) are presented. Persons with MDD have significantly worse lifestyles as well as more pathophysiological disturbances as compared to healthy controls. Some of these differences seem to be specific for (typical versus 'atypical', or antidepressant treated versus drug-naive) subgroups of MDD patients. Alternative explanations are also present, namely undetected confounding, iatrogenic effects or 'third factors' such as genetics.

Contents

1. Epidemiological evidence for cardiovascular 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. Evidence is convincing that depression increases the risk of subsequent cardiovascular

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disease onset. Cardiovascular disease refers to those conditions that affect the heart and blood vessels, including amongst others coronary heart disease, cerebrovascular disease, and peripheral artery disease. Meta-analyses integrating longitudinal evidence from 21 studies involving over 120,000 subjects concluded that depression results in a 80–90% increased risk of cardiovascular disease onset (Nicholson et al., 2006). In line with a dose-response gradient, the cardiovascular morbidity risk is higher for a clinical diagnosis of major depressive disorder than for self-reported depressive symptoms, but the risk is also significantly increased for the latter. Epidemiological evidence also extends to subclinical cardiovascular processes: depressed persons are at increased risk for peripheral atherosclerosis as indicated through e.g. coronary or aortic calcification, impaired endothelial function and increased arterial stiffness (Hamer et al., 2010; Seldenrijk et al., 2010, 2011). In addition, 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 and prognosis of cardiovascular disease. Finally, it is clear that a mutual, 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. In fact, the association between depression and cardiovascular disease can be best considered a downward spiral in which depression and cardiovascular disease mutually reinforce each other.

In this paper, in line with this Special Issue theme 'Stress, Behavior and the Heart', the focus will be mainly on contributing mechanisms that may explain how depression contributes to cardiovascular disease onset in initially healthy subjects. It is important to realize that the impact of depression on somatic health is not restricted to cardiovascular disease alone. Various meta-analyses summarizing longitudinal studies among initially somatic-disease free subjects, converge in their findings that depression increases the risk of subsequent overall mortality (Relative Risk (RR) = 1.81, Cuijpers et al., 2014), diabetes (RR = 1.60, Mezuk et al., 2008), hypertension (RR = 1.42, Meng et al., 2012), stroke (RR = 1.34, Dong et al., 2012), obesity (RR = 1.58, Luppino et al., 2010), dementia (RR = 1.96, Cherbuin et al., 2015) and to a lesser extent potentially even cancer (RR = 1.29, Chida et al., 2008). Not only in the general population but also in specific somatic disease groups, depression increases the mortality risk with 60–80%, confirming that depression increases both onset as well as prognosis of disease (Cuijpers et al., 2014; Walker et al., 2015).

When further extending the picture, it is clear that an increased cardiovascular risk is also 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, 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 non-specific anxiety disorder a recent meta-analysis, summarizing a total of 37 papers including 1,565,699 persons, indicated a 50% increased risk of cardiovascular disease onset (Batelaan et al., 2016). The fact that depression is associated to other somatic conditions beyond cardiovascular disease, and that somatic risks extend to other psychiatric conditions as well, already illustrates that it is not likely that underlying mechanisms linking depression to cardiovascular disease are purely organ- or disease-specific, but are rather general. An overview of the discussed mechanisms in subsequent sections of this paper are listed in Table 1, and contain both potential causal mediating mechanisms as well alternative mechanisms.

Table 1
Summary of potential mechanisms linking depression to increased cardiovascular risk.

Causal mediating mechanisms	
Unhealthy lifestyle	Smoking Excessive alcohol use Physical inactivity Unhealthy diet Lower treatment compliance and worse medical care
Pathophysiology	Metabolic dysregulations Immuno-inflammatory dysregulations Autonomic dysregulations HPA-axis dysregulations
Alternative mechanisms	
Residual cConfounding	Depression picks up or is a prodrome of not yet discovered or not measured (sub)clinical conditions
Iatrogenic effects	Pharmacological impact of antidepressants increase cardiovascular risk
'Third underlying factors'[a]	Childhood stressors Personality Genetic pleiotropy

[a] Factors that influence in parallel both cardiovascular risk as well as depression risk, but potentially independently from each other.

2. The 'residual confounding hypothesis' as mechanism linking depression to cardiovascular health

Subjects with depression are usually older, more often female, have a lower socioeconomic status and their general health is worse than that of their non-depressed peers. Consequently, sociodemographics and baseline health conditions rather than depression per se might be in part responsible for the poorer subsequent cardiovascular health in depressed subjects. Generally, most longitudinal population studies that examined the risk of cardiovascular events in depressed persons, have found that the risk associated with depression declined only with 20% or less after considering standard sociodemographic (age, gender, education level) and baseline health conditions (Nicholson et al., 2006; Van der Kooy et al., 2007). Importantly, after adjusting for these potential confounding variables, the cardiovascular risk in depressed persons remains significantly increased compared to that of non-depressed persons. This illustrates that the link does not seem to be completely driven by simply confounding. However, it should be mentioned that some remaining confounding is hard to completely rule out, as several indicators may only partly cover the entire underlying concept. For instance, socioeconomic status may not be completely covered through an adjustment for educational level and simple dichotomous disease presence indicators do not take disease severity into account. Therefore, it can be that in some cases depression may be a prodrome of not yet discovered and diagnosed (and therefore not measurable) sociodemographic, subclinical or medical conditions that affect subsequent cardiovascular disease onset. Consequently, even in rather extensively adjusted epidemiological models, residual confounding may still exist. This 'residual confounding hypothesis' may therefore still contribute to finding worse cardiovascular outcomes among the depressed. 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 are most present), and have also been confirmed in depressed subjects with an early age of onset.

3. Unhealthy life style as mechanism linking depression to cardiovascular health

Increased behavioral risk profiles in depressed persons may contribute to their higher risk for adverse cardiovascular health consequences. Indeed, 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. For instance, it has been shown that depressed persons have a higher 24-h caloric intake than non-depressed persons (Sanhueza et al., 2013), whereas certain vitamin deficiencies, such as vitamin D, B12 and folate deficiencies are more prevalent in depressed persons (Milaneschi et al., 2014; Penninx et al., 2000). 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 (Penninx et al., 1998; Stephens, 1988), partly because their attitudes toward exercise and exercise self-efficacy may be more negative.

Depressed mood has also shown to impede health by discouraging persons from obtaining adequate medical attention and rehabilitation and following treatment regimens. In a meta-analysis it was found that depressed persons on average are twice less compliant in taking medications or following up on certain life style regimens provided by health care professionals (DiMatteo et al., 2000). One study 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).

The above described general unhealthy lifestyles can contribute to the fact that depressed individuals are more at risk for adverse health outcomes, since these constitute important risk factors for the onset of cardiovascular disease. Table 2 summarizes results from the Netherlands Study of Depression and Anxiety (NESDA, www.nesda.nl), a national large-scale study in which depressed patients, recruited from the general population, primary care and secondary care settings, as well as healthy controls were assessed in detail and followed over time (Penninx et al., 2008). In NESDA, behavioral risk profiles were compared across 524 healthy controls (no lifetime psychiatric disorders), 774 persons with a remitted (non-current) Major Depressive Disorder (MDD), and 1075 persons with a current (6-month recency) MDD. DSM-IV based diagnoses were assessed using the Composite International Diagnostic Interview (CIDI, version 2.1). All measured unhealthy life style indicators were significantly more common in both current and remitted MDD patients as compared to controls (Table 2).

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 taken life style differences into account in their statistical analyses. The 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 is not easy to assess in detail in large-scale observational studies, residual impact of these behavioral factors may still exist.

4. Biological dysregulation linking depression to cardiovascular health

Depression-related biological dysregulations that also constitute risk factors for somatic illnesses could further contribute to the observed depression and cardiovascular diseases link. The next section describes evidence for biological dysregulations, with a focus on autonomic, HPA-axis, metabolic and immuno-inflammatory dysregulations. These reflect processes that are considered to be stress-related and have been most often examined in association with depression in large-scale epidemiological studies.

4.1. 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. 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 activity are associated with reduced social engagement and a less flexible behavioral response to environmental changes (Porges, 2001). A direct measurement method for autonomic activity is assessing noradrenaline spillover to plasma. Unfortunately, such invasive spillover studies are not implementable in large studies, restricting our insights into generalizability of results and the role of potential confounding factors. That is why researchers have used non-invasive, more indirect indicators of autonomic activity obtained from electrical and impedance cardiography assessments. The assessment of heart rate variability (HRV), particularly in the respiratory frequency range, is an indicator of cardiac vagal control. HRV reflects an individual's capacity for parasympathetic inhibition of autonomic arousal and is a predictor for cardiovascular disease and mortality (Dekker et al., 2000; Tsuji et al., 1996). Autonomic dysregulation has shown to be 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). Rottenberg summarized 13 studies including 312 depressed patients and 374 controls and found indeed a significantly reduced HRV in depression (Cohen's d = 0.33) (Rottenberg et al., 2007). Four years later, Kemp et al. repeated a meta-analysis in which only power-domain analyses of HRV and subjects free of cardiovascular disease were allowed (Kemp et al., 2010). 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. In contrast with these findings, are results from our NESDA study in which more than 1000 major depressive disorder patients did not consistently show differences in HRV as compared to control subjects, and in a 2-year follow-up depression state (changes) were not associated with changes in HRV (Licht et al., 2008, 2010a,b). Two other recent large-scale studies by Licht et al. (2015) and Kemp et al. (2014) did also not confirm an association between depression and lower HRV. So in all, there are inconsistent findings for the association between depression and lower HRV. How to explain this controversial literature? The above mentioned studies have clearly evaluated potential confounding roles of sociodemographics or co-existing (preclinical) cardiovascular disease, so this is not a likely explaining factor for the inconsistent results. Controversy may be partly explained by the fact that prior studies differed in type and severity (community-dwelling versus inpatients) of included depressed patients. Also, depression is a heterogeneous condition, and it may be that depending on the exact symptom profile (e.g. melancholic versus anxious distress versus atypical features) a divergent picture in relationship to autonomic dysregu-

Table 2
Lifestyle differences between healthy controls, subjects with remitted Major Depressive Disorder (MDD) and subjects with current Major Depressive Disorder: Results from the Netherlands Study of Depression and Anxiety (NESDA).

	Healthy controls N = 524	Subjects with remitted MDD N = 774	Subjects with current MDD N = 1075	(p)
Current smoking	21.9%	29.3%	27.8%	<0.001
Moderate (<20 cigarettes/day)	4.1%	10.2%	17.4%	
Heavy (≥20 cigarettes/day)				
Alcohol dependence[a]	1.4%	5.2%	9.1%	<0.001
Physical inactivity[b]	12.8%	15.2%	21.1%	<0.001
Regular sports activity[c]	57.5%	51.4%	37.0%	<0.001
Medication non-adherence[d]	28.8%	35.8%	40.4%	<0.001

[a] Based on DSM-IV criteria for current (6-month recency) Alcohol Dependence defined with CIDI psychiatric interview.
[b] Measured using the International Physical Activity Questionnaire and expressed as one's resting metabolic rate multiplied by minutes of physical activity per week.
[c] Regular sports activity is defined as participation in sports at least weekly.
[d] Medication non-adherence was defined by the tendency to forget a dose, change the dose, stop for a while, skip one dose, or take a smaller dosage than prescribed.

lation emerges. Another option is that the developmental trajectory to depression may play a discriminating role, with differentiating roles for age of onset, duration and genetic vulnerability. Of note is also that all studies discussed above measured cardiac autonomic control during resting conditions. Autonomic activity dysregulations may become more obvious when persons are exposed to stress conditions. Indeed, when undergoing stressful emotional testing, we did observe that depressed persons showed less parasympathetic and sympathetic activity (Hu et al., 2016). Consequently, the extent to which depressed persons are stressed at time of assessment – due to both their emotional state or their environmental (testing) circumstances- may also play a discriminating role in prior observations. All of the above discussed topics need to be further studied in order to shed light on the rather controversial literature.

One clearly important aspect when examining depression and autonomic activity is to consider the role of antidepressant treatment. Studies that do not separate treated and non-treated patients are difficult to interpret as a consistent finding in the literature is the effect of antidepressants on autonomic dysregulation. In his meta-analysis, Kemp et al. (2010) found a strong decreasing effect of TCAs on HRV, likely through direct anticholinergic and adrenergic properties. The HRV reducing effect of TCAs was also confirmed in our NESDA study (Licht et al., 2008) as well as in various other large-scale naturalistic studies (Licht et al., 2015; Noordam et al., 2016; Kemp et al., 2014; van Zyl et al., 2008), seems to follow a dosis-response association (Licht et al., 2008) and shows a consistent parallel HRV change pattern in new starters and stoppers of TCAs (Licht et al., 2010a,b; Noordam et al., 2016). Some studies also described HRV reducing effects of antidepressants in the SNRIs and SSRIs classes, but these seem of a lesser magnitude and not consistent across studies. In NESDA TCAs and SNRIs – but not SSRIs or depression itself – were also seen on non-invasive cardiography measures that reflect an increased sympathetic cardiac control, namely higher heart rate and lower pre-ejection period. (Licht et al., 2013), see Table 3 indicating that these medications act through changing both parasympathetic as well as the sympathetic activity.

Overall, the picture emerges that, despite a disputable role of depression itself, antidepressants – especially TCAs and to a lesser extent SNRIs and SSRIs – have a detrimental impact on autonomic activity which may contribute to an unfavourable cardiovascular profile.

4.2. 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 (CRH) is released onto pituitary receptors, ultimately resulting in release of cortisol into the blood. Alterations of the mineralcorticoid and glucocorticoid receptors, acting as transcriptional regulators of cortisol effects on the initiation and termination of the stress response, may determine a chronic activation of the stress response resulting in atrophy of hippocampal cells, reduced neurogenesis and synaptic plasticity and altered monoaminergic signalling, 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 may also be involved in the dysregulation of HPA-axis responsiveness (Silverman and Sternberg, 2012).

To assess HPA-axis activity, salivary measures have often been used to reflect the active unbound form of cortisol. The cortisol awakening response assesses the natural activation of the HPA-axis to awakening, evening cortisol levels reflect basal activity. In a meta-analysis by Knorr et al. summarizing twenty case–control studies including 1354 depressed patients and 1052 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 (Knorr et al., 2010). In an even larger meta-analysis by Stetler and Miller, evidence for higher cortisol levels across various bodily fluids (plasma, urine, saliva) was summarized (Stetler and Miller, 2011). 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). Similar observations have been found in other psychiatric conditions, such as schizophrenia and bipolar disorder (Girshkin et al., 2014), so HPA-axis dysregulation is not restricted to major depressive disorder.

In the NESDA study, we found a significantly – although modestly – increased cortisol awakening response that was consistently present among 701 current as well as among 579 remitted depressed cases, suggesting that HPA-axis hyperactivity represents a vulnerability rather than a state indicator (Vreeburg et al., 2009). In line with this, HPA-axis hyperactivity was also 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). Some studies used a dexam-

Table 3
Summary of pathophysiological differences between subjects with current Major Depressive Disorder (cMDD), subjects with remitted Major Depressive Disorder (rMDD) and healthy controls (HC): Results from the Netherlands Study of Depression and Anxiety (NESDA, n = 2981).

Pathophysiological mechanism	Result[a]	Specifics of results	References
Autonomic Nervous System:	cMDD = rMDD = HC	Antidepressant use strongly associated	Licht et al., 2008, 2010a,b, 2013
Heart Rate Variability ↓	cMDD = rMDD = HC cMDD = rMDD = HC	with HRV, HR, PEP in dose-response	
Heart rate ↑		gradient	
Pre-ejection period ↓			
HPA-axis:	cMDD + rMDD > HC cMDD > HC	No dosis-response associations	Vreeburg et al., 2009
Cortisol awakening response ↑	cMDD = rMDD = HC		
Evening cortisol level ↑			
Dexamethason suppression ↓			
Metabolic abnormalities:	cMDD > HC	Dosis-response gradient for abdominal	van Reedt Dortland et al., 2010; van
Abdominal obesity ↑	cMDD > HC	obesity and lipids	Reedt Dortland et al., 2013
Triglycerides ↑	cMDD > HC		
HDL cholesterol ↓	cMDD = rMDD = HC		
Fasting glucose ↑	cMDD = rMDD = HC		
Blood pressure ↑			
Inflammation:	cMDD > HC	Dose-response association	Vogelzangs et al., 2012
CRP ↑	cMDD > HC	Men stronger associations than women	
Interleukin-6 ↑	cMDD = rMDD = HC		
TNF-α ↑			

[a] cMDD = rMDD = HC means that the current MDD, remitted MDD and HC groups did not differ significantly in pathophysiological indicator; cMDD > HC means that the pathophysiological indicator was significantly more present in the current MDD group than in the HC group; cMDD + rMDD > HC means that the pathophysiological indicator was significantly more present in current MDD and remitted MDD groups than in the HC group.

ethasone test to evaluate the sensitivity of the hypothalamus to feedback signals for the shutdown of CRH release, but results are inconsistent. Nelson and Davis 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) (Nelson and Davis, 1997). However, in NESDA we found the non-suppression rate in 1280 depressed outpatients to be much lower, and not differential from 308 controls (Vreeburg et al., 2009). So, the indicated larger non-suppression of the HPA-axis in depression may likely be restricted to only the most severe (psychotic) cases. HPA-axis dysregulation has been implicated in the onset and progression of cardiovascular disease Indeed, higher saliva cortisol levels have found to be more prevalent in patients with cardiovascular disease as well as in persons with the preclinical metabolic syndrome (Cohen et al., 2015; Bradley and Rumsfeld 2015). It should be noted though that findings are inconsistent as several large-scale studies have not been able to confirm these associations or found opposite findings (Licht et al., 2010a,b; Kuehl et al., 2015). In addition, whether HPA-axis dysregulation is truly contributing to the development of CVD over time is even harder to prove, as this requires well-powered longitudinal studies. In two longitudinal observational studies higher morning cortisol levels and a flatter slope in cortisol levels across the day were associated with increased risk of subsequent cardiovascular mortality. (Kumari et al., 2011; Vogelzangs et al., 2010) Also, higher cortisol response to an acute stressor has been associated with the onset of hypertension (Hamer and Steptoe 2012). Nevertheless, longitudinal evidence is limited and to what extent and through what mechanisms HPA-axis dysregulation contributes to CVD development over time needs to be more examined in future longitudinal studies.

4.3. Metabolic dysregulation

Clinical metabolic dysregulations are often 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. The metabolic syndrome indicates a preclinical state, characteristics by a clustering of well-established risk factors, for the development of cardiovascular disease and diabetes (Mottillo et al., 2010). Pan et al. systematically reviewed 29 cross-sectional studies and found depression and the metabolic syndrome to be modestly associated (adjusted Odds = 1.34) (Pan et al., 2012). Also in the NESDA study, we confirmed an association between depression and metabolic syndrome, and showed evidence for a dose-response association between the two. ((van Reedt Dortland et al., 2010), see Table 3) Some reviewed prospective studies confirmed a bidirectional association with depression predicting the onset of metabolic syndrome, which in turn predicted depression onset over time. 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).

However, the metabolic syndrome is a heterogeneous concept: pathophysiological mechanisms of elevated blood pressure, dyslipidemia and hyperglycemia are not necessarily similar. Most consistent evidence exists between depression and obesity-related components (abdominal obesity, low HDL cholesterol, hypertriglyceridemia), whereas associations with hyperglycemia and hypertension are less often confirmed (Pan et al., 2012). 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.

How could a link between metabolic dysregulations and 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 as well as 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, which according to the so called 'vascular depression' hypothesis predispose to depression especially in late-life (Alexopoulos, 2006). Finally, other depression-related biological dysregulations may constitute shared underlying pathways to metabolic alterations. For instance, 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).

4.4. 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 mediators 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. 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).

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; Howren et al., 2009; Liu et al., 2012). Overall, effect sizes are 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). Also in the NESDA study, we confirmed that depression – especially in men – is associated with elevated CRP and Il-6 levels according to a dose-response association ((Vogelzangs et al., 2012), see Table 3).

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). 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 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 perturb neurotransmission and result in hippocampal neuron damage (Sublette and Postolache, 2012). Finally, depression may facilitate weight gain – partly as a result of inactivity and unhealthy dietary choice – which in turn promotes inflammation that may reinforce depression, creating a deleterious vicious cycle between physical and mental health.

4.5. Is pathophysiological dysregulation uniformly present among all depressed patients?

Depression is a heterogeneous disorder with multiple, diverging symptoms defining the concept. There is growing recognition that the heterogeneity of major depressive disorder is hampering efforts to identify pathophysiology of depression. More homogenous subgroups could give us a better understanding and larger effect sizes of pathophysiological differences. In NESDA we have examined the existence of depression subtypes based on clinical symptom profiles. Using latent class analyses in which information on the central 9 DSM-depression symptoms was entered, two distinct depression subtypes were identified which were stable over time (Lamers et al., 2010, 2012a). The identified classes partly resembled the melancholic (also considered the more 'typical' features of depression) and the atypical specifiers of the psychiatric DSM-classification and were largely discriminated on the basis of opposite scoring on neurovegetative symptoms. A total of 46% of cases belonged to a melancholic ('typical') depression group in which especially appetite and weight decline as well as insomnia, early morning awakening were relatively more prevalent. Over time, patients in this group maintained slightly higher suicidality and anxiety scores (Lamers et al., 2016). Another 25% belonged to an 'atypical' depression group in which appetite and weight increase and leaden paralysis were more prevalent. (see Fig. 1) Similar depression subtypes have been found in latent class analyses using other cohort studies (Sullivan et al., 1998, 2002; Lamers et al., 2012a,b), and are consistent when either psychiatric interview data (e.g. CIDI) or self-report symptoms reports (e.g. Inventory of Depressive Symptoms) are being used to assess symptom presence.

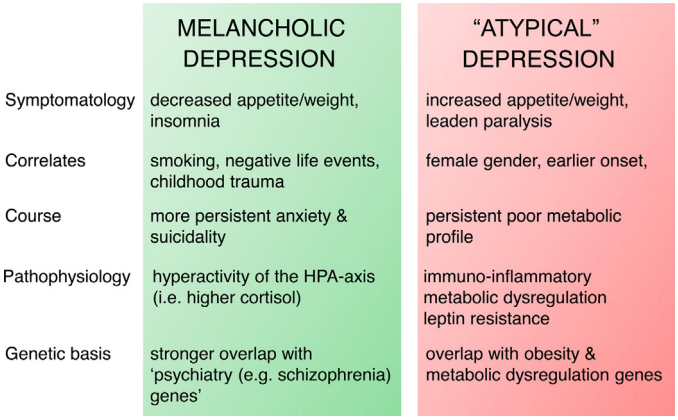

Fig. 1. Evidence for existence of depression subtypes with a differential clinical and pathophysiological profile. Based on findings reported in: Lamers et al., 2010, 2012a, 2013, 2016; Penninx et al., 2013; Milaneschi et al., 2016a,b.

Interestingly, despite their differences in specific symptom patterns, the melancholic and atypical depression groups did not differ in prevalence of core symptoms of depression, in overall severity or duration of depression, or in disability or psychiatric comorbidity patterns. Also did the groups not differ in the extent or type of antidepressant treatment they received. Melancholic cases were more often smokers and had more reports of childhood trauma and recent negative life events, whereas atypical cases were slightly more often female and had an earlier age of onset. In addition to these descriptors, pathophysiological patterns differed as well. The melancholic type showed more strongly hyperactivity of the HPA-axis, while the atypical type showed elevated levels of inflammatory markers as well as more metabolic abnormalities including increased BMI and abdominal obesity which maintained over time (Lamers et al., 2013, 2016) In line with these findings, we subsequently confirmed a differential genetic basis of these two subtypes. Using genome-wide profile risk scores generated from meta-analysis results of large international consortia, we found that MDD subtypes had differential polygenic signatures: melancholic depression was more strongly associated with a genomic schizophrenia risk score (indicating a general psychiatric vulnerability), whereas only atypical depression was associated with genome-wide body mass index and triglycerides genetic risk (Milaneschi et al., 2016a).

NESDA is not the only study indicating that melancholic and atypical depression subtypes may have a partly differential pathophysiological basis. Various cross-sectional studies indicate that metabolic and immune-metabolic dysregulations are relatively more present in 'atypical depression' (Penninx et al., 2013). 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). Cross-sectional studies also converge in the findings that HPA-axis dysregulation is more prevalent in persons with

melancholic depression (Penninx et al., 2013). In line with this, Stetler & Miller's meta-analysis 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 (Stetler and Miller, 2011). Melancholic features were associated with 54% larger effect sizes compared with depression without melancholic features. In all, NESDA results as well as other recent literature, indicate that differential clinical symptomatology may point towards differential underlying pathophysiology, which may open up further avenues for personalized medicine approaches (Penninx et al., 2013). Whether these different MDD subtypes are similarly associated with subsequent cardiovascular morbidity needs to be further determined.

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 (Hamer et al., 2011; Whang et al., 2009). However, it is important to realize that these observational findings cannot simply be interpreted as causal evidence for cardiovascular-inducing effects through pharmaceutical effects of antidepressants. These findings have likely a strong bias due to 'confounding-by-indication'. In observational studies, subjects using antidepressants are likely to be different in many ways from drug naive subjects: they are generally more severe, chronic, or have specific other reasons to be treated with antidepressants. Even if observational analyses adjust for severity of depression, confounding-by-indication may still be present. In order to truly test whether antidepressant medication contribute to cardiovascular risk, one would require a very large, long-term placebo-controlled randomized trial, which is costly and ethically difficult to conduct. Among several large-scale trials conducted specifically among cardiovascular patients, the treatment arm group, which also received antidepressants, was not better or worse off in terms of cardiovascular outcomes as the control arm group (Glassman et al., 2002; Taylor et al., 2005; van Melle et al., 2007).

Although impact on cardiovascular morbidity cannot be indicated, there are several studies that showed that antidepressants might affect (subtle) pathophysiological dysregulations, which could require specific clinical attention. As described above, there is consistent evidence that antidepressant medications, especially TCAs and SNRIs may increase cardiac vagal control (Kemp et al., 2014; Licht et al., 2008, 2015). We further confirmed this in a 2-year longitudinal design in which we showed that stoppers and starters of antidepressants were the only groups of subjects with significant (and opposite) change in autonomic activity (Licht et al., 2010a,b, 2012). These differences contributed to elevated systolic and diastolic blood pressure resulting in more clinically overt hypertension among medication users (Licht et al., 2009). Autonomic activity differences were generally completely diminished when antidepressant medication use was stopped (Licht et al., 2010a,b). Contrary to these detrimental effects of antidepressants, are findings from experimental intervention studies that indicated that several antidepressants may in fact contribute to reduction of other specific pathophysiological disturbances such as cortisol (Hinkelmann et al., 2012) or inflammation levels (Hannestad et al., 2011). Hannestad et al. (2011) meta-analyzed 22 studies and found that pharmacological antidepressant treatment reduced levels of IL-1β and possibly those of IL-6. Stratified analysis by class of antidepressant indicated that mainly SSRIs, but not other antidepressants, reduced cytokine levels. In a recent meta-review of Eyre et al. (2016) it was emphasized that it is difficult to draw conclusions on differences in anti-inflammatory response across antidepressant classes as these are based on non-comparative studies with much methodological heterogeneity. But in general, these reviews indicate that some antidepressants may partly block the effects of inflammatory cytokines on the brain. In all, even though some (subtle) pathophysiological impact of antidepressants have been indicated, 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. This still requires more extensive (intervention) research.

6. Alternative mechanisms 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 1). Several examples for such 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 these two conditions. Second, personality traits such as neuroticism, introversion and type D personality have shown to be linked to both the development of depression as well as 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, and has been more extensively described before (de Geus, 2006; Mulle and Vaccarino, 2013). 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. and Bartels et al. illustrated that the link between reduced exercise behaviour and mood symptoms is for a large extent due to shared genetic risks (Bartels et al., 2012; de Moor et al., 2008). 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, but do not reflect a direct relationship between depression and cardiovascular disease.

7. Conclusions

This paper summarized longitudinal evidence indicating that depression increased the risk of cardiovascular disease onset. As summarized in Table 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, evidence for the association between depression and cardiovascular outcomes stems mainly from epidemiological observational study designs. Such a design has its limitations since the residual confounding hypothesis, iatrogenic effects of antidepressants as well as the influence of 'third factors' are hard to objectify and exclude as alternative mechanisms. 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 impact on each other.

Competing interests

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