Understanding the somatic consequences of depression:
Biological mechanisms and the role of depression symptom profile

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Abstract

Depression is the most common psychiatric disorder worldwide. 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 e.g. cardiovascular, stroke, diabetes and obesity morbidity. These somatic consequences could partly be due to metabolic, inflammatory, HPA-axis and autonomic dysregulations which have suggested to be more often present among depressed patients. Evidence linking depression to metabolic syndrome abnormalities indicates that depression is especially associated with its obesity-related components (e.g. abdominal obesity and dyslipidemia). In addition, systemic inflammation and hyperactivity of the HPA-axis have been consistently observed among depressed patients. Slightly less consistent observations are for autonomic dysregulation among depressed patients. The heterogeneity of the depression concept seems to play a differentiating role: metabolic syndrome and inflammation upregulations appear more specific to the atypical depression subtype, whereas hypercortisolemia appears more specific for melancholic depression. This review finishes with potential treatment implications for the downward spiral in which different depressive symptom profiles and biological dysregulations may impact on each other and interact with somatic health decline.

Keywords:
Depression, Metabolic Syndrome, Inflammation, Cortisol, Autonomic Tone, Cardiovascular, Obesity, Symptom profile, Treatment
Introduction

Depressive feelings are a normal component of distress or grief. When depressive feelings turn into a chronic, disabling disorder interfering with daily life, a clinical diagnosis of major depressive disorder (MDD or shortly termed depression) ensues. Depression refers to a range of mental problems characterized by loss of interest and enjoyment in ordinary experiences, low mood and associated emotional, cognitive, physical and behavioural symptoms. Depression is one of the most prevalent diseases globally: 6% of the population meets the MDD criteria at a specific time point. During lifetime, depression affects 1 out of every 6 adults with women being affected twice as often as men.[1] Currently, depression is the third leading contributor to the global disease burden, but will rise to a first-place ranking in 2030.[2] This is largely due to the facts that depression is common, has major impact on functioning and quality of life, and affects persons often in early life and for sustained periods thereby causing many disease years. Consequently, depression largely affects public health and involves high societal costs.

Somatic consequences of depression

The impact of depression on health extends beyond quality of life and functioning outcomes. Over the last 20 years, many studies illustrated the impact of depression on somatic disease development. Table 1 summarizes meta-analyses integrating evidence from longitudinal studies conducted among initially disease-free subjects. These meta-analyses consistently show that depression increases the risk of overall mortality (RR=1.81) and the development of cardiovascular-related outcomes such as heart disease (RR=1.81), diabetes (RR=1.60), hypertension (RR=1.42), stroke (RR=1.34) and obesity (RR=1.58). Meta-analyses also indicate that depression increases the risk of developing Alzheimer’s disease (RR=1.66) and to a lesser extent even cancer (RR=1.29). Most meta-analyses were based on longitudinal studies using depressive symptom checklists which pick up many subthreshold depression cases. However, the
increased somatic morbidity has also been found in patients fulfilling psychiatric diagnostic
criteria, who - in line with a dose-response association – have slightly higher incident morbidity
rates.[3-5]

Meta-analyses on somatic consequences of depression have reported pooled effect sizes
for adjusted associations which considered potential confounding variables such as lifestyle
indicators. Depressed persons live on average unhealthier: they are more likely to smoke, drink
excessive amounts of alcohol, eat unhealthy, and be physically inactive than non-depressed
peers.[6] However, lifestyle adjusted pooled effect sizes are only slightly lower than unadjusted
ones, indicating that the increased morbidity risks are not simply due to lifestyle differences.
Consequently, depression-related biological dysregulations that also constitute risk factors for
somatic illnesses could further contribute to the observed depression and somatic diseases link.
The next section describes evidence for the most common biological dysregulations examined in
this context.

**Biological dysregulation linking depression to somatic health**

**Metabolic dysregulation**

Often clinical metabolic dysregulations are assessed in the context of the metabolic syndrome: a
cluster of general metabolic risk factors including abdominal obesity, increased blood glucose
(hyperglycemia), elevated blood pressure, increased triglycerides, and decreased HDL
cholesterol. Pan et al.[7] systematically reviewed 29 cross-sectional studies and found depression
and the metabolic syndrome to be modestly associated (unadjusted OR=1.42; adjusted OR=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. Therefore,
various studies have tested consistency of associations with depression across different metabolic syndrome components. The most consistent evidence exists for depression and obesity-related components (abdominal obesity, low HDL cholesterol, hypertriglyceridemia).[8-37] Depression associations with hyperglycemia[10,12,13,22,24,26-32,35] and hypertension were less often confirmed.[13,17,32,38-41] Also when evidence from longitudinal studies was pooled, consistent associations were only confirmed for the obesity-related components.[7] This is in line with a recent meta-analysis[42] which showed that abdominally obese persons are at an 1.38 increased odds of having depression (Table 2). One longitudinal study among depressed patients found that a combination of multiple metabolic dysregulations contributed to chronicity of depression.[18] 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 dysregulation and depression be explained? 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 immunometabolic responses linked to metabolic diseases and depression. For instance, inflammatory factors stimulate the release of lipids in the bloodstream to provide energy for host defense and cause a reduction in HDL cholesterol.[43] Moreover, obesity-related chronic inflammation is involved in the development of insulin resistance through activation of the inhibitor of kB kinase-β/nuclear factor-kβ (IKKβ/NFκβ) complex.[44] Leptin is an anti-obesity hormone regulating nutritional intake and energy expenditure. In the central nervous system obesity-associated inflammation can disrupt leptin hypothalamic action through IKKβ/NFκβ regulation of SOCS-3 (suppressor of cytokine signaling-3), a key inhibitor of leptin signaling.[45] The resulting state of leptin central resistance, characterized by the failure of high levels of leptin to suppress food intake and decrease adiposity, is a hypothesized shared biological mechanism.
underlying obesity and depression. Leptin receptors are expressed in limbic substrates related to mood regulation, and in animal models leptin exerts antidepressant behavioral effects.[46] Leptin has also shown to affect hippocampal and cortical structure through its actions on neurogenesis, axon growth, synaptogenesis and dendritic morphology regulation.[47]

Another possible mechanism linking metabolic dysregulation and depression may be represented by cerebrovascular damage associated with metabolic syndrome, which have been hypothesized to predispose to depression especially in late-life.[48] Finally, other depression-related biological dysregulations described in this review may constitute shared underlying pathways to metabolic alterations. For instance, adipose tissue expresses a high density of glucocorticoid receptors, and their binding with cortisol activates lipoprotein lipase and inhibits lipid mobilization, leading to accumulation of triglycerides.[49] Similarly, sympathetic nervous system overactivation is connected to high blood pressure.[50]

**Immune dysregulation**

Immune dysregulation refers to a state of chronic overactivation of the immune system resulting in chronically elevated levels of cytokines, called inflammation. Pro-inflammatory cytokines are molecules produced by e.g. monocytes and macrophages that become secreted into the bloodstream in response to immunologic challenge. Systemic elevations of these cytokines in the absence of infection or tissue injury are considered abnormal and increase the onset of e.g. cardiovascular disease, diabetes and mortality.[51,52] 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.[53,54]

Three recent meta-analyses reported significantly higher levels of the pro-inflammatory cytokines TNF-α, sIL-2R, IL-6 and IL-1RA in depressed subjects compared to controls (see Table 2). Dowlati et al.[55] confirmed increased levels of IL-6 and TNF-α among drug-naive MDD patients. Liu et al.[56] recently extended this evidence to sIL-2R. For IL-1β, no consistent
significant association was found in both meta-analyses.[55,56] Howren et al.[57] confirmed the depression-inflammation association also in larger population samples many of which used depressive symptom reports and most often studied IL-6 and CRP, a nonspecific acute-phase protein synthesized in the liver in response to cytokine stimulation. They confirmed stronger associations with inflammatory markers for studies using clinical diagnoses of depression than those using symptom reports. 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.[58] It has been demonstrated that immunotherapy with IFN-α can precipitate depression.[59] Cytokines produced peripherally can access the brain directly crossing the blood-brain barrier through saturable active transport systems, or via indirect pathways including activation of microglia, diffusion into the brain through leukocytes in the choroid plexus and circumventricular region, and attraction in the brain of monocytes by chemo-attractant proteins released by microglia.[60] Activated microglia employ IL-6 and TNF-α as antineurogenic signals, which can interact directly with neural progenitor cells via TNF and IL-6 receptors causing a decrease in neurogenesis, also in emotion-regulating brain structures involved in depression.

Another mechanism relating pro-inflammatory cytokines to mood is their capacity to induce the indoleamine-2,3-dioxygenase enzyme, which catalyzes the synthesis of kynurenine from dietary tryptophan.[61] This may contribute to depressive symptoms by reducing the availability of the requisite precursor for the synthesis of serotonin and melatonin. Perhaps even more importantly, kynurenine gives rise to metabolites such as quinolinic acid, an endogenous N-
methyl-D-aspartate agonist, that could perturb neurotransmission along glutamatergic pathways and may lead to hippocampal neuron damage and apoptosis which could contribute to depression symptoms.[62]

Pro-inflammatory cytokines have been shown to induce stress-reactive neuroendocrine and central neurotransmitter changes reminiscent of those in depression.[58] Inflammatory processes can influence central serotonin availability also through increased uptake after phosphorylation of the high-affinity serotonin transporter via the activation of p38 mitogen-activated protein kinases.[60] Finally, as discussed above, fat mass and its associated metabolic regulations are strongly connected to inflammation. Nutrition overload causes adipocytes to become hypertrophic and to secrete chemo-attractant proteins, which lead to recruitment of macrophages that produce their own pro-inflammatory cytokines and chemokines, attracting additional macrophages and setting up a feed-forward inflammatory process.[44] Depression may also 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.

**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 non-invasive method for autonomic dysregulation is the assessment of 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 in emotional expression and regulation, and is an important predictor for cardiovascular disease and mortality.[63,64] 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.[65]

Rottenberg[66] summarized 13 studies including 312 depressed patients and 374 controls and found indeed a significantly reduced HRV in depression (Cohen’s d= 0.33, see Table 2). Four years later, Kemp et al.[67] 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 a significant pooled effect size indicating a lower HRV among the depressed. Contrary to these results, was a study by Licht et al.[68] 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 this study, 1018 MDD patients without antidepressants and 515 controls did not consistently show differences in HRV on all measures. Only on the respiratory sinus arrhythmia indicator of HRV the depressed persons scored slightly lower with a small effect size of 0.12. In their 2-year follow-up[69] it was confirmed that MDD state (changes) were not associated with HRV. On the contrary, significantly lower HRV was found among MDD patients using antidepressant medication, especially TCAs and SNRIs. 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 recently confirmed in a meta-analysis.[67] 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.

Sympathetic tone has been less often examined, and no meta-analysis is available. Some small-scale studies reported increased sympathetic activity in depressed subjects measured by spillover of (nor)epinephrine, skin conductance responses, QT interval variability, or the pre-ejection period (PEP),[70-74] although not consistently.[75] A recent large study compared PEP, a thoracic impedance cardiography measure indexing changes in β-adrenergic inotropic drive to
the left ventricle, among 1093 MDD patients and 621 controls.[76] Cross-sectional nor 2-year longitudinal results could confirm a higher sympathetic tone in the depressed. Again, antidepressant medication – especially TCAs and to a lesser extent SNRIs - was associated with increased sympathetic tone.

Overall, although some evidence points towards a hypersympathetic/hypovagal state among depressed persons, the evidence is not consistent and antidepressant treatment has shown to be a strong confounding factor. Autonomic dysregulation is involved in cardiovascular somatic symptoms such as tachycardia, blood pressure liability and tendencies toward hypertension. In a large cohort study[77] lower HRV was associated with more metabolic syndrome dysregulations, but not to HPA-axis activity. Finally, sympathetic activation may have a role in the stress-induced activation of the immune system as catecholamines can trigger the inflammatory signaling cascade.[78]

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.[79] 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. Knorr et al.[80] meta-analyzed twenty case–control studies including 1354 depressed patients and 1052 controls (Table 2). The average salivary cortisol level was 2.58 nmol/l increased in the morning and 0.27 nmol/l in the evening for depressed patients. A recent study among 701 current and 579 remitted depressed cases found that both groups had higher cortisol awakening response and evening levels as compared to 308 healthy controls,[81] suggesting that HPA-axis hyperactivity represents more a vulnerability 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.[82]

In an even larger meta-analysis by Stetler & Miller[83] evidence for higher cortisol levels across various bodily fluids was summarized. Again, this evidence illustrated that depressed individuals displayed increased cortisol levels (d=0.60), although the effect size was considerably less when only high methodological quality studies were included (d=0.33). Effect sizes were higher for cortisol levels determined in plasma or urine than for those in saliva. The authors also meta-analyzed other HPA-axis indicators and found elevated levels of adrenocorticotropic hormone among the depressed (d=0.28), but no elevation in CRH (d=0.02).

Some studies used a dexamethasone test to evaluate the sensitivity of the hypothalamus to feedback signals for the shutdown of CRH release. No meta-analysis has compared dexamethasone suppression across regular depressed cases and controls. Nelson et al.[84] described 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). The non-suppression rate in outpatients with major depression was found to be much lower. A recent large-scale study did not find a different cortisol response after dexamethasone (0.5 mg) suppression in 1280 MDD outpatients versus controls.[81] 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. Although hypercortisolism may be related to alterations at any level of the HPA-axis, research in depression focused on the role of mineralcorticoid (MR) and glucorticoid (GR) receptors, acting as transcriptional regulators of cortisol effects on the initiation and termination of the stress response.[85] Both type of receptors are abundantly expressed in neurons of limbic regions but have different affinity to cortisol (~10-fold higher for MR that is heavily occupied by
basal glucocorticoids levels, while GR is only heavily occupied during stress) and different transcriptional activity. MR is implicated in the appraisal process that triggers the stress response, while GR is part of a negative feedback aimed at normalizing HPA-axis output. 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 signalling, all of which may lead to a depressive state.[85] Other factors may be involved in the dysregulation of HPA-axis responsiveness, including early-life epigenetic programming of GR genes and inflammatory processes.[86] A wide range of studies showed that pro-inflammatory cytokines may promote the release of CRH, ACTH and cortisol by acting directly on hypothalamic and pituitary cells and disrupting GR function leading to glucocorticoid resistance.[86,87]

Heterogeneity of depression: the role of symptom profiles

All meta-analyses described in Table 2 indicated a considerable amount of heterogeneity in biological dysregulations among depressed persons. Such variability could be attributable to sampling (e.g. clinical sample vs. community), sample composition (e.g. age and ethnic composition) or methodological differences in depression and biological measures. However, variability could also be due to heterogeneity of depression. There is general consensus that clinical heterogeneity hinders efforts to identify biologic, genetic and environmental underpinnings of depression. In fact, the lack of genetic markers associated with MDD in the largest collaborative genetic study was interpreted to be largely attributable to its widespread heterogeneity.[88] It is crucial that depressive subtypes constituting more homogeneous phenotypes are taken into account in research and that in-depth studies of biological correlates of depressive subtypes are conducted in order to bring the psychiatric field forward.

The current DSM-classification includes three specifiers of symptom characteristics during depressive episodes: catatonic, melancholic and atypical features. Most outpatient and
community studies focus on melancholic and atypical subtypes because of the low frequency of catatonia. Atypical depression is marked by hypersonnia and fatigue, increased appetite and weight gain, mood reactivity and interpersonal rejection sensitivity. Unlike its name suggests, it is present in approximately 15% to 30% of depressed cases.[89,90] Melancholic depression is characterized by a disturbance in affect marked by anhedonia and non-reactive mood, by psychomotor disturbance and by vegetative and cognitive symptoms of insomnia, loss of appetite and weight, diurnal mood variation and impaired concentration. Approximately 25-30% of depressed individuals display melancholic features.[89] Criteria for subtypes were originally established based on clinical observations, but it should be noted that not all core criteria of these subtype definitions have been justified through research. In fact, some of the core characteristics of the atypical subtype have received increased scrutiny by research showing that the cardinal symptom of mood reactivity is not associated with the other subtype symptoms,[91,92] and the interpersonal rejection sensitivity may be more a personality trait than a symptom.[93]

Nevertheless, recent data-driven techniques examining a wide range of depressive symptoms have confirmed that depressed populations can generally be divided into a melancholic (sometimes termed ‘typical’) and an atypical subtype which are not very different in overall severity but differentiate mainly in terms of appetite, weight and sleep symptoms (more in atypical, less in melancholic depression)[89,90,94-96] and to a lesser extent in terms of feelings of worthlessness, guilt and suicidal ideation (more in melancholic depression).[89] Distinction in these subtypes is rather stable over time, as pointed out in a recent longitudinal study among chronic patients[90]: of persons with atypical depression at baseline, 79% still had the atypical subtype after two years, which was 70% in those with melancholic depression.

Increasing evidence suggests that melancholic and atypical depressive subtypes contribute to variability in associations with biological measures. Table 3 lists studies examining this issue. Comparing melancholic depressed versus non-melancholic depressed persons, Seppälä et al.[38] found metabolic syndrome to be increased in those with atypical depression but not in
melancholic depression. In line with this, when directly comparing 319 melancholic versus 201 atypical depressed patients, Lamers et al.[89] found metabolic syndrome and in particular its obesity-related disturbances to be more present in atypical depression.

In addition, some studies confirmed higher inflammation levels among atypical depression (see Table 3). Kaestner et al.[97] observed higher levels of IL-1β and IL-1RA in non-melancholic patients than in melancholics and controls. Also Yoon et al.[98] found higher IL-2 and lower IL-4 in atypical depression than in melancholic depression. On the contrary, other studies found higher IL-1β in persons with melancholic features than in those without, or found no inflammation differences between melancholic and atypical depression groups.[99-101] The largest study to date recently compared 111 chronic melancholic depressed cases versus 122 chronic atypical depressed cases and confirmed higher levels of IL-6, TNF-α and CRP in atypical depression as compared to both melancholic depression and healthy controls.[102] Overall, evidence seems emerging that metabolic and inflammation dysregulations are more advanced in atypical than in melancholic depressed subjects.

The picture is quite different for hypercortisolemia. Table 3 illustrates that several studies directly comparing cortisol levels across melancholic and atypical depression point out that hypercortisolemia is more often observed in melancholic depression.[97,101-103] Cortisol levels among individuals with atypical depression may not be reliably higher than cortisol levels among healthy non-depressed persons. Some studies[100,102] even suggest a relative hypocortisolism in atypical depression. Findings in Table 3 are in line with a sub-analysis in Stetler & Miller’s meta-analysis[83] in which 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.

Although some studies suggested differences in autonomic tone dysregulation depending on specific depression symptoms,[66,104,105] no studies directly compared autonomic tone
dysregulation between melancholic versus atypical depression. In all, research into the specificity of the association of metabolic dysregulations to specific depression subtypes has just begun. Its findings seem to suggest that metabolic and inflammation dysregulations may be more involved in atypical depression, whereas hypercortisolism appears more specific for melancholic depression. Consequently, not considering the heterogeneity of depression in pathophysiological research may contribute to blurred effect sizes. That metabolic syndrome and inflammation dysregulations cluster in atypical depression cases is understandable from the tight associations between appetite, fat mass, dyslipidemia and inflammation. Weight gain is a cardinal symptom of atypical depression, and a higher BMI has been observed among atypical versus melancholic depressed patients.[89] These mechanisms may not be as strongly related to HPA-axis hyperactivity. Although the HPA-axis in normal situations tempers inflammatory reactions, prolonged hyperactivity could result in blunted anti-inflammatory responses to glucocorticoids resulting in increased inflammation.[106,107] However, the relationship between HPA-activation and its effect on inflammation is extremely complex: whether glucocorticoids increase or decrease inflammation may depend on factors such as dose, duration and timing of glucocorticoids exposure and brain area involved.[108] Animal models show that GR activation during chronic stress increases LPS-induced NFκB activation and TNF-α and IL-1β expression in the hippocampus and frontal cortex, but has opposite effects in the hypothalamus.[109] Furthermore, communication between these systems could also be hampered after prolonged dysregulation of one of the stress systems. This may explain that the HPA-axis and the inflammation/metabolic stress systems operate more independent of each other, and their activities can be differentially linked to different depression subtypes. In line with this, in a cohort of 2900 subjects, we confirmed strong intercorrelations between inflammation and metabolic syndrome indicators but no significant association between these systems with HPA-axis functioning.[77]
Therapeutic implications for biological dysregulation in depression

Do antidepressant treatments reduce biological dysregulations in depression? And if there indeed exists a different pathophysiology across depressive subtypes, does this suggest differential effective treatment strategies across subtypes? These are adequate questions that so far have only been partly addressed. We will briefly summarize what is currently known in this research area.

Regarding inflammatory and metabolic dysregulations, an observational cohort study among over 1000 MDD patients found that – independent of potential differences in severity - TCA users had more metabolic and inflammatory dysregulations than medication-naïve depressed persons.[15,110] In contrast, SSRI users had slightly lower inflammatory levels than non-medicated depressed patients.[110] Also others found inflammatory and metabolic dysregulations to be more prominent in persons using SNRI, TCA or TeCA,[24,111] whereas beneficial inflammatory profiles were present in SSRI users.[78] In line with this, two meta-analyses showed that SSRI treatment – but not other types of antidepressants - reduced inflammatory levels.[112,113] In vitro studies[114] demonstrate that administration of SSRI produces anti-inflammatory effects in blood of both people with depression and healthy volunteers through their effects on increasing intracellular cyclic adenosyl monophosphate, serotonin metabolism or direct action on neurogenesis.[115] On the contrary, TCAs could result in slightly more metabolic dysregulation since its antihistaminergic and adrenergic effects may induce weight gain and subsequent dyslipidemia and hypertension.[116,117] Also, both longitudinal observational studies[69,74,76] and a meta-analysis[67] observed increased sympathetic activation and reduced parasympathetic activation among TCA users. The anticholinergic effects of TCAs - and potentially also SNRIs - increase circulating norepinephrine levels, also in the sinoatrial node and left ventricle,[118] thereby directly affecting contractility and heart rate. In contrast, SSRIs do not exert such an effect but instead reduce the firing rate in the noradrenergic locus coeruleus,[119] involved in generating cardiac sympathetic activity.[120] Consequently, the different effects of antidepressant medication classes on cardiac sympathetic
effects appear to have a plausible biological basis, and deserve attention in clinical practice as these effects have shown impact on clinically relevant outcomes such as hypertension.[117]

Whether standard antidepressant treatments improve HPA-axis hyperactivity has not been often addressed. Since this hyperactivity has been observed among remitted depressed patients[81] and non-affected offspring of depressed patients,[82] it may be more a vulnerability than a state characteristic. Nevertheless, some evidence suggests that at least a subgroup of depressed patients shows improved HPA-axis regulation, e.g. as indicated by a decreased DEX-CRH test response, after a 2-week antidepressant treatment period which was subsequently associated with beneficial treatment response.[121]

Not only can antidepressants impact on biological dysregulation, dysregulation can also impact on the efficacy of antidepressants. A few recent studies provide evidence for this. A study in 24 MDD inpatients showed that higher IL-6 levels predict non-response to a 6-week treatment with amitriptyline, while TNF-α levels were high in both responders and non-responders but only decreased during treatment in responders.[122] In another study among 100 depressed patients, higher TNF-α levels predicted non-response to a 12-week treatment with escitalopram.[123] Poor treatment response could be the result of inflammatory and metabolic dysregulation having direct negative effects on the monoamine system, such as increasing the activity of monoamine transporters [124] and reducing monoamine precursors[125] and monoamine biosynthesis,[126] which counterbalance effects of antidepressant medication.

What about other than antidepressant medication interventions? Some recent evidence suggests that add-on anti-inflammatory agents may be useful in clinical depression management. In a placebo-controlled trial of 60 treatment-resistant MDD patients, Raison et al.[127] found a TNF-α antagonist to reduce depressive symptoms in persons with high baseline inflammatory markers. Furthermore, behavioral interventions such as exercise were able to normalize immune and metabolic dysregulation[128] and improve mood to some degree,[129] and might therefore be an indicated treatment especially for the depressed subgroup with inflammatory and metabolic
dysregulation. This idea is supported by a recent study showing that exercise treatment appeared to be more effective in reducing depressive symptoms among patients with high baseline levels of TNF-α.[130] However, at this moment, these considerations for treatment implications are still largely speculative and should be confirmed in longitudinal and experimental studies. A recent study did not find larger efficacy of SSRIs or TCAs in melancholic versus atypical depression.[131] Since this review illustrated more inflammatory and metabolic dysregulations in atypical depression, it should be explored whether e.g. add-on anti-inflammatory agents or alternative treatment regimen such as exercise are more beneficial to this depression subgroup.

**Conclusions**

This review summarized longitudinal evidence indicating that depression increased the onset risk of a multitude of somatic disorders including e.g. cardiovascular, stroke, diabetes and obesity morbidity. These somatic consequences may partly be due to biological dysregulation present among depressed patients. Less consistent observations are for autonomic dysregulation among depressed patients. However, inflammation and metabolic dysregulation involving mainly abdominal obesity and dyslipidemia are more often present among depressed persons, especially among those with atypical depression features. Hyperactivity of the HPA-axis has also been observed, but most consistently among depressed patients with melancholic features. These observations suggest that not considering the heterogeneity of depression in pathophysiological research may contribute to blurred effect sizes. Future research needs to examine to which extent existing and new antidepressant interventions can reduce biological dysregulation thereby improving the vicious cycle in which depression and somatic ill-health interact.
List of abbreviations

ACTH  Adrenocorticotropin hormone
BMI    Body mass index
CRH    Corticotropin releasing hormone
CRP    C-reactive protein
DSM    Diagnostic statistical manual of mental disorders
DEX-CRH Dexamethason-Corticotropin releasing hormone
HDL    High-density lipoprotein
HPA-axis Hypothalamic-pituitary-adrenal axis
HRV    Heart rate variability
IKKβ/NFκβ Inhibitor of κB kinase-β/nuclear factor-κB
IL     Interleukin
MDD    Major depressive disorder
OR     Odds ratio
PEP    Pre-ejection period
RR     Relative risk
SOCS-3 Suppressor of cytokine signaling-3
SNRI   Serotonergic-noradrenergic reuptake inhibitor
SSRI   Selective serotonin reuptake inhibitor
TCA    Tricyclic antidepressant
TeCA   Tetracyclic antidepressant
TNF-α  Tumor necrosis factor-α
**Competing interests**

None of the authors have any conflict of interest to report

**Authors’ contributions**

BP initiated the paper; BP, YM, FL, NV helped drafting the paper; BP, YM, FL, NV have seen and approved the final version.

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Table 1: Overview of meta-analyses examining the association between depression status and incidence of mortality or morbidity events over time in disease-free subjects

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<tr>
<th>Incident event</th>
<th>Reference</th>
<th>Nr studies included</th>
<th>Nr subjects included</th>
<th>Pooled risk (95% CI) of depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall mortality</td>
<td>Cuijpers et al.[5]</td>
<td>25</td>
<td>106,628</td>
<td>1.81 (1.58-2.07)</td>
</tr>
<tr>
<td>Heart disease</td>
<td>Nicholson et al.[3]</td>
<td>21</td>
<td>124,509</td>
<td>1.81 (1.53–2.15)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Meng et al.[132]</td>
<td>9</td>
<td>22,367</td>
<td>1.42 (1.09–1.86)</td>
</tr>
<tr>
<td>Stroke</td>
<td>Dong et al.[133]</td>
<td>17</td>
<td>206,641</td>
<td>1.34 (1.17-1.54)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Mezuk et al.[4]</td>
<td>13</td>
<td>212,019</td>
<td>1.60 (1.37–1.88)</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>Gao et al.[134]</td>
<td>4</td>
<td>5,656</td>
<td>1.66 (1.29–2.14)</td>
</tr>
<tr>
<td>Obesity (BMI≥30)</td>
<td>Luppino et al.[135]</td>
<td>9</td>
<td>6,436</td>
<td>1.58 (1.33-1.81)</td>
</tr>
<tr>
<td>Cancer</td>
<td>Chida et al.[136]</td>
<td>25</td>
<td>n.a.</td>
<td>1.29 (1.14-1.46)</td>
</tr>
</tbody>
</table>

BMI=body mass index, n.a.= not available
Table 2: Overview of meta-analyses examining the cross-sectional association between metabolic dysregulations and depression status

<table>
<thead>
<tr>
<th>Metabolic dysregulation</th>
<th>Reference</th>
<th>Nr studies included</th>
<th>Nr subjects included</th>
<th>Pooled effect size (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic syndrome</td>
<td>Pan et al. 2012(^\text{1}) [7]</td>
<td>29</td>
<td>155,333</td>
<td>OR=1.42 (1.28-1.57)</td>
</tr>
<tr>
<td>Abdominal obesity</td>
<td>Xu et al. 2011(^\text{1}) [42]</td>
<td>15</td>
<td>34,832</td>
<td>OR=1.38 (1.22-1.57)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Immune dysregulation</th>
<th>Reference</th>
<th>Nr studies included</th>
<th>Nr subjects included</th>
<th>Pooled effect size (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-Reactive Protein</td>
<td>Howren et al. 2009(^\text{1}) [57]</td>
<td>49</td>
<td>51,234</td>
<td>d = 0.15 (0.10-0.21)</td>
</tr>
<tr>
<td>Interleukin-6</td>
<td>Dowlati et al. 2010(^\text{2}) [55]</td>
<td>16</td>
<td>892</td>
<td>MD=1.8 pg/mL (1.2-2.3)</td>
</tr>
<tr>
<td>Interleukin-1β</td>
<td>Dowlati et al. 2010(^\text{2}) [55]</td>
<td>13</td>
<td>788</td>
<td>MD=4.0 pg/mL (2.2-5.7)</td>
</tr>
<tr>
<td>Interleukin-1RA</td>
<td>Liu et al. 2012(^\text{2}) [56]</td>
<td>9</td>
<td>1,214</td>
<td>d = 0.25 (0.04-0.46)</td>
</tr>
<tr>
<td>Interleukin-6</td>
<td>Liu et al. 2012(^\text{2}) [56]</td>
<td>18</td>
<td>923</td>
<td>MD=4.0 pg/mL (0.44-0.92)</td>
</tr>
<tr>
<td>TNF-α</td>
<td>Liu et al. 2012(^\text{2}) [56]</td>
<td>15</td>
<td>995</td>
<td>MD=0.55 pg/mL (0.13-0.99)</td>
</tr>
<tr>
<td>Interleukin-1RA</td>
<td>Liu et al. 2012(^\text{2}) [56]</td>
<td>10</td>
<td>580</td>
<td>MD=0.53 pg/mL (-1.36-0.31)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Autonomic dysregulation</th>
<th>Reference</th>
<th>Nr studies included</th>
<th>Nr subjects included</th>
<th>Pooled effect size (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate variability</td>
<td>Rottenberg, 2007(^\text{2}) [66]</td>
<td>13</td>
<td>686</td>
<td>d = 0.33 (0.18-0.49)</td>
</tr>
<tr>
<td>Heart rate variability</td>
<td>Kemp et al. 2010(^\text{2}) [67]</td>
<td>14</td>
<td>726</td>
<td>Hedges’ g =-0.21 (-0.40- -0.02)(^\text{4})</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HPA-axis dysregulation</th>
<th>Reference</th>
<th>Nr studies included</th>
<th>Nr subjects included</th>
<th>Pooled effect size (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher cortisol (^\text{3})</td>
<td>Stetler &amp; Miller 2011(^\text{1}) [83]</td>
<td>354</td>
<td>18,374</td>
<td>d = 0.60 (0.54–0.66)</td>
</tr>
<tr>
<td>Higher ACTH</td>
<td></td>
<td>96</td>
<td>3,812</td>
<td>d = 0.28 (0.16-0.41)</td>
</tr>
<tr>
<td>Higher CRH</td>
<td></td>
<td>16</td>
<td>888</td>
<td>d = 0.53 (-1.71-0.65)</td>
</tr>
<tr>
<td>Saliva morning cortisol</td>
<td>Knorr et al. 2010(^\text{1})[80]</td>
<td>20</td>
<td>2,318</td>
<td>MD=2.6 nmol/l (1.0–4.2)</td>
</tr>
<tr>
<td>Saliva evening cortisol</td>
<td></td>
<td>10</td>
<td>1,617</td>
<td>MD=0.3 nmol/l (0.03–0.5)</td>
</tr>
</tbody>
</table>

TNF-α=Tumor Necrosis Factor-α; ACTH=adrenocorticotropic hormone, CRH=corticotropic-releasing hormone.
OR=Odds Ratio; MD= Mean Difference between depressed and non-depressed; d=Cohen’s d
1 included depressed cases based on self-report checklists or psychiatric diagnostic criteria
2 only included depressed cases conform to psychiatric diagnostic criteria
3 cumulative assessment of cortisol across body fluids and across various time points.
4 did not include data from one study including 1018 depression patients and 515 controls that found a much smaller effect size (d=0.12).
Table 3: Overview of studies comparing metabolic dysregulations across melancholic and atypical depression

<table>
<thead>
<tr>
<th>Reference</th>
<th>Nr of melancholic depression</th>
<th>Nr of atypical depression</th>
<th>Nr of controls</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic dysregulation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamers et al. 2010 [89]</td>
<td>379</td>
<td>201</td>
<td>-</td>
<td>AD more MetS than MD</td>
</tr>
<tr>
<td>Seppala et al. 2012 [38]</td>
<td>293</td>
<td>139(^1)</td>
<td>2388</td>
<td>AD more MetS than C, no association with MD</td>
</tr>
<tr>
<td>Immune dysregulation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anisman et al. 1999 [100]</td>
<td>17</td>
<td>31</td>
<td>27</td>
<td>No difference in IL-1b+IL-2</td>
</tr>
<tr>
<td>Kaestner et al. 2005 [97]</td>
<td>21</td>
<td>16(^1)</td>
<td>37</td>
<td>AD higher IL-1b+IL-1RA than C+MD</td>
</tr>
<tr>
<td>Huang et al. 2007 [99]</td>
<td>25</td>
<td>17(^1)</td>
<td>40</td>
<td>MD higher IL-1b than AD no difference in IL-10 and TNF-(\alpha)</td>
</tr>
<tr>
<td>Yoon et al. 2012 [98]</td>
<td>70</td>
<td>35</td>
<td>-</td>
<td>AD higher IL-2 and lower IL-4 than MD no differences in IL-6+TNF-(\alpha)</td>
</tr>
<tr>
<td>Lamers et al. 2012 [102]</td>
<td>111</td>
<td>122</td>
<td>543</td>
<td>AD higher IL-6+CRP+TNF-(\alpha) than MD+C</td>
</tr>
<tr>
<td>Karlovcic et al. 2012 [101]</td>
<td>32</td>
<td>23</td>
<td>18</td>
<td>MD+AD higher IL-6+CRP than C no difference in TNF-(\alpha)</td>
</tr>
<tr>
<td>HPA-axis dysregulation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nelson et al. 1997 [84]</td>
<td>662</td>
<td>617(^1)</td>
<td>-</td>
<td>MD more DST non-suppression than AD</td>
</tr>
<tr>
<td>Anisman et al. 1999 [100]</td>
<td>17</td>
<td>31</td>
<td>27</td>
<td>AD lower cortisol than C</td>
</tr>
<tr>
<td>Wong et al. 2000 [103]</td>
<td>10</td>
<td>-</td>
<td>14</td>
<td>MD higher cortisol than C</td>
</tr>
<tr>
<td>Kaestner et al. 2005 [97]</td>
<td>21</td>
<td>16(^1)</td>
<td>37</td>
<td>MD higher cortisol than AD + C</td>
</tr>
<tr>
<td>Lamers et al. 2012 [102]</td>
<td>66</td>
<td>82</td>
<td>393</td>
<td>MD higher cortisol than AD + C</td>
</tr>
<tr>
<td>Karlovcic et al. 2012 [101]</td>
<td>32</td>
<td>23</td>
<td>18</td>
<td>MD higher cortisol than AD+C</td>
</tr>
</tbody>
</table>

\(^1\) Atypical depression was assessed as the absence of melancholic depression (non-melancholic depression). MD= Melancholic Depression; AD=Atypical Depression; C=Healthy Controls, DST=dexamethasone suppression test
References


56. Liu Y, Ho RC-M, Mak A: Interleukin (IL)-6, tumour necrosis factor alpha (TNF-alpha) and soluble interleukin-2 receptors (sIL-2R) are elevated in patients with major depressive disorder: a meta-analysis and meta-regression. *J Affect Disord* 2012, 139: 230-239.


