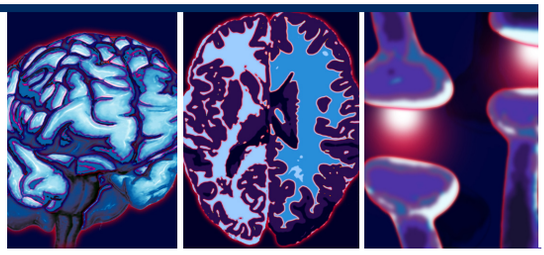
REVIEW



Role of metabolic dysfunction in treatment resistance of major depressive disorder

Marisa S Toups[1] & Madhukar H Trivedi[†1]

Practice points

- Major depressive disorder (MDD) and metabolic syndrome (MetS) are both disorders that cause serious morbidity.
  - We model both disorders as arising when environmental factors act on intrinsic patient risk factors.
- Epidemiological overlap of MDD and MetS: patients with either disorder have approximately doubled incidence of the other.
- MetS and MDD cause overlapping inflammatory, endocrine and neurobiological pathology.
  - MDD and MetS share a systemic profile of inflammatory cytokines and cortisol resistance.
  - Inflammation leads to insulin resistance, cardiovascular disease and diabetes.
  - MetS and MDD are associated with atrophy and dysfunction of several common brain regions.
  - MetS and MDD are both associated with decreased brain-derived neurotrophic factor.
  - Insulin resistance and chronic inflammation impair hypothalamic regulation of metabolism and hippocampal function.
  - MDD and MetS are both associated with changes in tryptophan metabolism that may contribute to medication failure in MDD.
- Clinical research findings that support the treatment of MetS in MDD patients: the direct treatment of metabolic dysfunction or inflammation is very likely to improve depressive symptoms.
- Clinical relevance of the pathophysiological links: we believe that in some patient with treatment-resistant depression, MetS in an unrecognized cause.
- Clinical recommendations: an algorithm for diagnosis and treatment of MetS with patients with depression.
- Future research should focus on validating the importance of MetS in MDD treatment: we suggest studies validating metabolic parameters as predictors of treatment outcome.

[1]Department of Psychiatry, UT Southwestern Medical Center, Dallas TX 75235, USA
[†]Author for correspondence: madhukar.trivedi@utsouthwestern.edu

part of future medicine fsg

SUMMARY Major depressive disorder (MDD) and metabolic syndrome (MetS) are both widespread and cause enormous morbidity. The presence of one syndrome approximately doubles the risk of the other. Standard antidepressant treatments lead to remission in less than a third of the patients; a majority of patients experience treatment resistance at some point during their illness. Research focusing on clinical and biological markers has yet to provide evidence for the cause(s) of treatment resistance. MDD and MetS share endocrine and immune abnormalities that account for their overlap and suggest potential mechanisms for treatment resistance for a subgroup of patients with MDD. Cortisol resistance and positive energy balance work together to create inflammation. Chronic inflammation leads to insulin resistance. In the brain, inflammation and insulin resistance cause changes in metabolic control, decreases in serotonin synthesis, decreased hedonic drive and lower hippocampal neurogenesis, all of which are consistent with the neurobiology of MDD. We hypothesize that treatment-resistant MDD may result when MetS reinforces the pathophysiology of MDD, making it harder to reverse.

Major depressive disorder (MDD) is the fourth leading cause of disability and is expected to become the second leading cause of disability worldwide by 2020 [1]. MDD affects an estimated 2.5% of the population at any given time [1], with a lifetime prevalence of approximately 20% [2]. Although many different treatments – pharmacologic, behavioral and neurostimulatory – have been developed, MDD remains difficult to manage. Indeed, resistance to treatment is a major problem in contemporary psychiatric practice. Only approximately a third of patients will remit fully with any given trial of medication [3], and the rate of remission drops as the number of medication trials increase [4]. Although definitions of treatment resistance vary [5] in the number and type of failed treatment trials required, approximately 30% of patients with MDD remain resistant to treatment even following several well-documented treatment trials [6]. Much of the confusion over the 'right' definition is related to the lack of knowledge – other than some demographic and clinical characteristics [7] – about the differences between those patients who have good outcomes and those who do not. What is known is that patients with treatment-resistant depression (TRD) have higher lifetime illness burden and mortality, as well as a lower quality of life than patients without treatment resistance [8,9]. Understanding the biological mechanisms of TRD would be useful not only in developing a concrete definition, but would also make a large impact on patient outcomes by providing new avenues of research and treatment.

Similarly, metabolic syndrome (MetS) and Type 2 diabetes mellitus (DM2) are common in developed countries, particularly the USA. MetS is defined as a combination of abnormally elevated triglycerides, blood pressure, fasting glucose, increased waist circumference and decreased high-density lipoprotein, with or without a direct or indirect measure of insulin resistance (IR) [10]. MetS has high clinical utility because all of its components, with the exception of IR, can quickly and easily be assessed by clinicians in most practice areas, and because its presence is highly predictive of serious morbidity via stroke, heart attack or other vascular disease [11]. The definition of MetS has evolved over time, and several national and international organizations have developed definitions [12] that differ in clinical feasibility of diagnostic criteria and whether MetS is viewed as simply epidemiological (i.e., predictive of risk) or as a discrete syndrome. The assessed rate of MetS in the USA varies between 23 and 40% depending on the definition used [13]. The term 'metabolic dysfunction' may refer to any or all of the aspects of MetS, without reference to specific abnormal values – although less precise, it is used here as a rough synonym for MetS. On the other hand, DM2 is a natural sequela of MetS, resulting when IR progresses such that fasting blood sugar is outside the normal range, affecting 18% of North Americans [14]. In this article, we have chosen to use the term MetS as inclusive of DM2 since all of the pathophysiological features we discuss later are shared between them. We attempted to find experimental results in human studies that applied specifically to MetS populations; however, in those instances when we were unable to do so, we have used studies of DM2 patients but have specifically noted this fact in the text.

At first glance, a biological link between depression and metabolic dysfunction may seem implausible, since they appear to have differing causes as well as symptoms. To make the link as clear as possible, we start with a model of MDD as a disorder that occurs when intrinsic genetic and

epigenetic susceptibilities of an individual are acted upon by the individual's environment; we also have a similar model of MetS. In this article, we will deal almost exclusively with extrinsic factors and present evidence that these cause similar pathology in patients. We will also discuss how we believe that the common pathology may lead to treatment resistance. We hypothesize that in cases in which both syndromes are present, they exert additive physiological effects that lead to a lower probability of positive outcomes for treatment for either syndrome. To support our hypothesis that MetS is likely an underappreciated cause of TRD, we will focus on mechanisms – both peripheral and central – by which MetS may reinforce depression symptoms and pathology, as well as interfere with the action of antidepressant treatment.

Simplifying somewhat, we will take the primary exogenous factor in MetS to be chronic positive energy balance (PEB), a state in which more calories are consumed than expended. For MDD, the primary environmental influence appears to be chronic or severe stress. We will begin by reviewing epidemiological studies that demonstrate high comorbidity of MetS and MDD. Next, we will discuss significant similarities in how the endocrine and immune systems respond to the two environmental factors, stress and PEB, and how this leads to similar profiles of cytokine and hormone abnormalities in those with MDD and MetS. Following the examination of systemic dysfunction, we will look at common structural and functional changes that occur in the brains of those with MDD and MetS. We will also discuss some of the pathophysiological mechanisms underlying these abnormalities in an effort to demonstrate that the presence of one of these disorders creates positive feedback that may make the other more difficult to reverse.

Epidemiological overlap of MDD & MetS

Major depressive disorder and MetS share many qualities: both are chronic, cause high morbidity and require sustained, coordinated treatment that manages rather than cures. However, beyond the superficial similarities, there is a significant epidemiological overlap between them. Both cross-sectional and longitudinal studies have found that having depression approximately doubles the rate of MetS [15–18] and *vice versa* [19,20], although some authors have found an elevated, but not doubled, risk of MDD in DM2 [21,22]. Several studies found that subjects reporting high levels of stress with or without MDD had similarly elevated MetS rates [18,23]. Rates of TRD in patients with MetS have not accurately been determined – few placebo-controlled studies of treatments exist, and those that do have small sample sizes [24,25].

Shared systemic profile of inflammatory cytokines & cortisol resistance in MetS & MDD

Inflammation has emerged as a major, if not the primary, pathophysiological link between MDD and MetS [26]. An inflammatory model of MetS that begins with changes in metabolic activity of adipose tissue as it increases in volume has become increasingly validated with ongoing research. In response to chronic PEB, adipocytes produce factors that recruit macrophages and decrease the number and/or function of anti-inflammatory Tregs [27,28]. Adipocytes also begin to produce the proinflammatory cytokines IL-1β and TNF-α. These attract macrophages and incline them to switch from an anti-inflammatory M2 state to a proinflammatory M1 state, in which they produce the same cytokines, as well as IL-6 [27]. It appears that these inflammatory processes are enhanced by leptin, an 'adipokine', which is an immunologically and metabolically active factor produced by adipocytes. Leptin serves as a signal of energy balance, and is high when energy balance is positive [29]. In ongoing PEB, high leptin directly activates macrophages and induces their expression of inflammatory cytokines [30]. This cascade in turn recruits more macrophages, which stimulate further cytokine production in a feed-forward manner, setting up a chronic inflammatory state. Clinically, this is reflected in elevations of circulating TNF-α, IL-1β and IL-6 in the blood of MetS patients [31–34].

This same cascade of macrophage-associated inflammation occurs in MDD. It has been hypothesized that MDD itself is an inflammatory illness [35]; certainly, inflammation caused by autoimmune disease or administration of cytokines (such as IFN-γ for the treatment of hepatitis C) induces depression in a sizable minority (30–50%) of patients [36,37]. Even depressed patients without known autoimmune or infectious processes have elevated levels of M1 inflammatory cytokines, with IL-6 and TNF-α having the most consistent evidence [38]. Although cortisol is acutely anti-inflammatory, MDD- or chronic stress-associated cortisol resistance, as manifested by glucocorticoid receptor (GR) insensitivity, leads to activation of proinflammatory pathways that are normally suppressed

by cortisol [39,40]. Once activated, macrophages can also support chronic stress induced hypercortisolemia; exposure to IL-1β can activate expression of adrenocorticotropic hormone from macrophages themselves [41], as well as via the hypothalamus [42]. Thus the effects of stress are synergistic with PEB-associated inflammation; the two feed forward to create a chronic state of inflammation and high systemic cortisol and/or cortisol resistance. The changes in inflammatory factors that are in common with MetS and MDD are listed in **Table 1**.

While it is clear that chronic elevations of cortisol can cause IR – this is the basis of high rates of diabetes in patients with Cushing's disease [43] – the role of cortisol and GR insensitivity in most cases of MetS is less straightforward. Basal levels of cortisol may be normal in MetS; however, if corticosteroid suppression testing is performed, GR insensitivity is often found [44,45] – the variability in cortisol levels is likely accounted for by increased cortisol clearance in obesity [46].

Inflammation leads to IR

If this chronic inflammatory and cortisol resistant state persists, it leads to IR, which occurs by several mechanisms. First, cortisol decreases insulin-mediated expression of the GLUT4 glucose transporter – the primary systemic transporter of glucose into cells – by decreasing insulin receptor activity [47]. Similarly, cortisol promotes release of free fatty acids from lipoproteins [48], leading to an increase in circulating lipids. Free fatty acids also cause decreased sensitivity of the insulin receptor, particularly on muscle cells [49]. Chronic elevations of inflammatory cytokines, particularly TNF-α, cause similar, additional suppression of insulin receptor signaling [50]. An additional mechanism of IR is a PEB-associated decrease in the expression of adiponectin, another adipokine. Unlike leptin, adiponectin levels are inversely related to body weight, and it appears to promote insulin sensitivity [51,52] and oppose the MetS-associated inflammatory cascade [53]. Adiponectin-knockout mice are not diabetic at baseline but develop IR more easily when fed diets that induce PEB [54]. Cytokines, particularly TNF-α, can also act to decrease expression of adiponectin [55], such that lower levels are found in MDD patients independent of weight [56,57]. The overlap in these mechanisms suggests that weight-independent IR may be found in patients with MDD. In fact, outside of the population of patients with comorbid MetS and MDD, a significant minority of patients with MDD alone show IR when given oral glucose tolerance testing [58]. **Figure 1** summarizes the peripheral inflammatory changes associated with MetS and MDD.

Table 1. Shared inflammatory changes in major depressive disorder and metabolic syndrome.

Factor	Change in MetS	Change in MDD
Adiponectin	–	–
IL-6	+	+
CRP	+	+
TNF-α	+	+
IL-1-β	+	+
Leptin	+	+
Insulin	+ (resistance)	+ (resistance)
Cortisol	± (resistance)	+ (resistance)

CRP: C-reactive protein; MDD: Major depressive disorder; MetS: Metabolic syndrome.

Chronic inflammation leads to morbidity from cardiovascular disease & DM2

Over time, if the environmental influences of stress and PEB continue, inflammation leads to vascular disease – the major cause of morbidity associated with MetS. Patients with MDD also have higher rates of morbidity/mortality from cardiovascular disease [59]. The general inflammatory marker C-reactive protein is also consistently increased in MDD [60] and MetS [61,62]. This increase in C-reactive protein is associated with elevation in a wide variety of factors that contribute to the development of arteriosclerosis [63]. Cardiovascular disease risk is elevated threefold in patients with MetS [14], making this the primary cause of serious morbidity and mortality in MetS. When there is systemic IR, the pancreas compensates by increasing insulin output, but over time diabetes develops because blood glucose can no longer be kept within the normal range. Feed-forward IL-1β signaling occurs within the pancreas and sets up chronic, local islet inflammation, which leads to islet cell death, and eventually patients require supplementary insulin [64].

MetS & MDD are associated with atrophy & dysfunction of several common brain regions

Although we have so far focused on systemic pathology, MDD at least is thought of as a brain disease, and has been characterized by both structural and functional changes in the brain. While MetS may have its roots in adipose tissue,

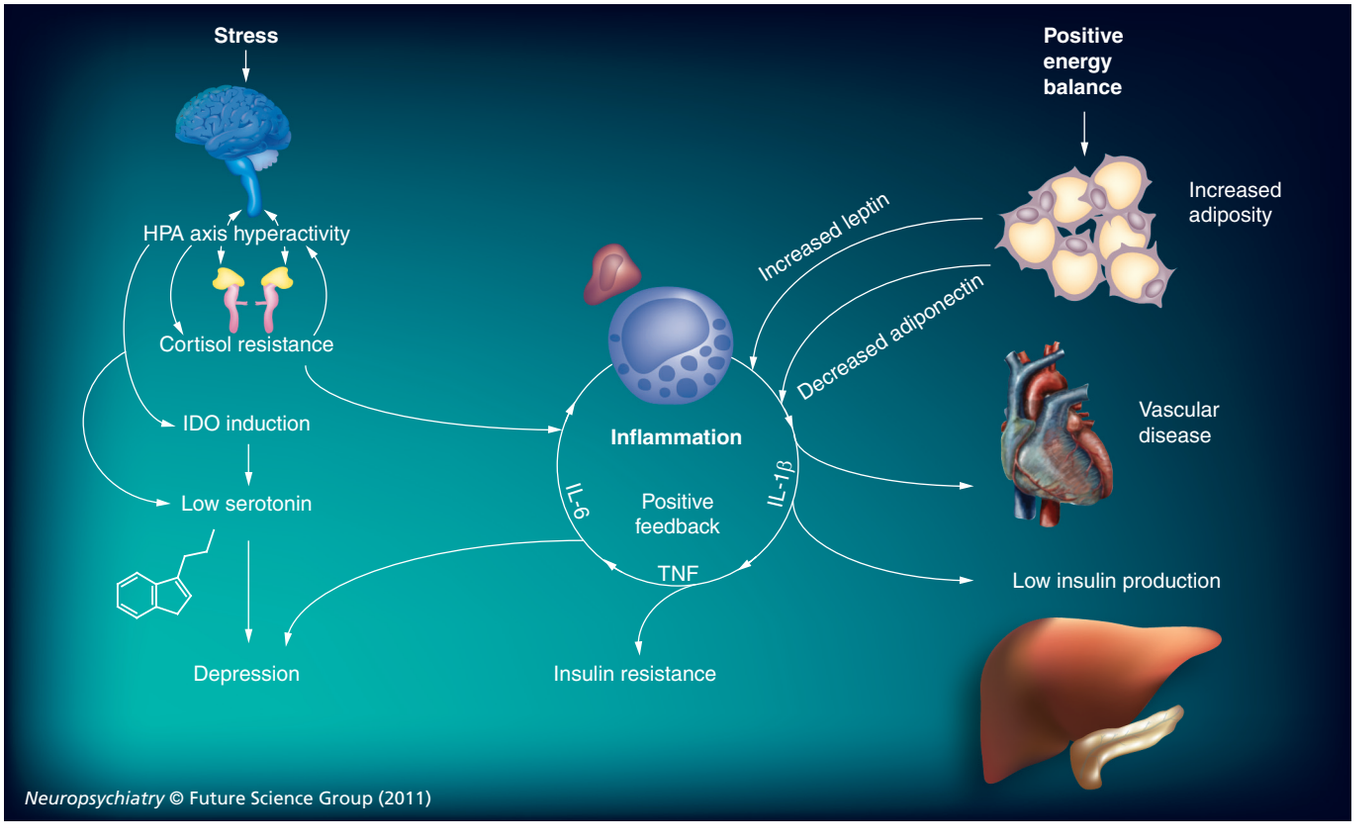


Figure 1. Network showing the links between metabolic syndrome and depression via inflammation.
HPA: Hypothalamic–pituitary–adrenal; IDO: Indoleamine-2,3-dioxygenase.

it also causes brain changes that overlap anatomically to a large extent with those associated with depression. Perhaps the most consistently identified structural abnormality in MDD is hippocampal atrophy [65]. Some studies also have found thinning of the prefrontal cortices [66]. It has been debated whether this atrophy represents an underlying vulnerability to MDD [67] or an effect of the illness [68], but these areas are clearly part of the biological substrate on MDD. A similar pattern of hippocampal and prefrontal atrophy is seen in MetS and DM2 [69,70]. BMI itself is positively correlated with decreased hippocampal volume and frontal cortex thickness [71].

The consequence of brain atrophy is reduced cognitive function in patients with MDD and MetS. MDD is associated with decreased attention and verbal working memory [72]. MetS is found to correlate with similar deficits [73,74]. Both syndromes have been associated with an increased risk of dementia [75,76]. At least some authors have found that comorbid MDD and MetS is associated with more impairment than either alone [77]. IR has been isolated from the other components of MetS as the most associated with cognitive decline [74,78] and is correlated with decreases in blood flow in frontal cortical areas [79]. Hippocampal atrophy and impaired hippocampal learning are both associated with normal aging [80], and some authors have proposed that inflammation plays a significant role in the accelerated cognitive decline associated with MDD and MetS [81]. **Figure 2** shows the putative relationships leading to hippocampal dysfunction.

Changes in growth factor expression (see later) and accumulation of microvascular damage over the lifespan may contribute to these structural abnormalities, but clearly some common factors in MDD and MetS that we have already discussed play a role by acting in the brain much as they do systemically. For example, inflammatory cytokines appear to increase the activity of the serotonin transporter [82], possibly impairing serotonin neurotransmission and decreasing the efficacy of selective serotonin-reuptake inhibitors (SSRIs). However, perhaps the most important of these is central IR, which develops in association with peripheral resistance. Insulin

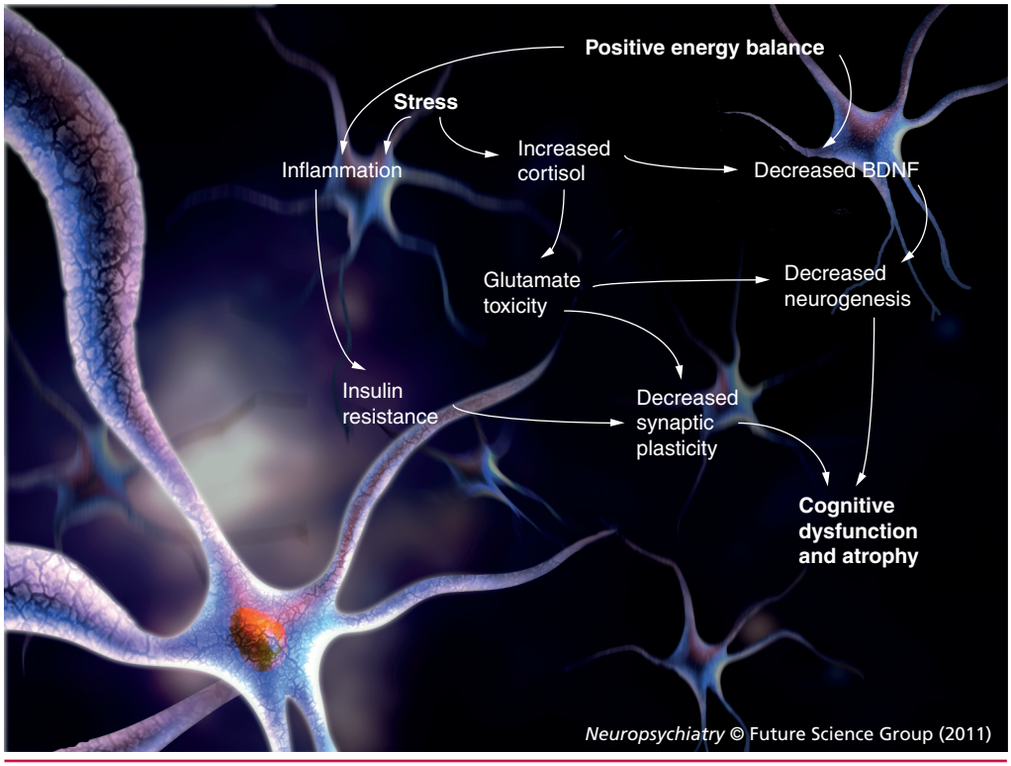


Figure 2. Model of the effects of stress and positive energy balance on the hippocampus.
BDNF: Brain-derived neurotrophic factor.

is important in the hippocampus because insulin receptors mediate changes in glutamate neurotransmission – a form of long-term depression that plays a role in memory and cognitive function – and promote growth of synaptic architecture and dendritic spines [83]. In fact, intranasal insulin administration improves cognitive function in normal controls [84] and those with mild dementia [85] and may also improve mood [86]. Cortisol is also known to cause hippocampal dysfunction by several mechanisms. It induces increases in NMDA receptor glutamate neurotransmission, which are thought to be neurotoxic over long time periods, making growing hippocampal cells more vulnerable to apoptosis. It also causes decreased dendritic arborization and synaptic plasticity [87]. As in the periphery, cortisol also synergistically downregulates insulin receptor signaling [88], contributing to the effect of CNS IR.

MetS & MDD both decrease expression of brain-derived neurotrophic factor

An additional mechanism is tied to brain-derived neurotrophic factor (BDNF) – a growth factor that is already well known as a primary mediator in the hippocampal dysfunction related to depression. It appears to be necessary to maintain hippocampal neurogenesis and it promotes synaptic growth and arborization in neurons [89,90]. Although the relationship between central and peripheral BDNF is not fully understood, serum BDNF is low in MDD [91] and is thought to reflect a decrease in central, particularly hippocampal, BDNF expression. The exact mechanisms that cause low BDNF in MDD are not fully understood, although various stress paradigms in animals result in decreased hippocampal BDNF [92], and cortisol appears to suppress neuronal *BDNF* gene expression [93]. However, antidepressants appear to require BDNF expression in the hippocampus for efficacy [94], so low BDNF may predispose to treatment failure – mice with lowered BDNF expression do not respond to SSRI treatment neurochemically or behaviorally [95]. However, these mice display an aggressive rather than depressed phenotype [96], and humans with genetically decreased BDNF expression do not clearly manifest TRD, although this relationship has been abundantly examined [97]. These results potentially suggest that genetic differences in BDNF expression may not affect the brain in the same way as environmentally

induced changes, but ultimately highlight that the clinically relevant effects of BDNF in MDD are still unclear.

The body of literature linking decreased BDNF to MetS is less well known to psychiatrists, but consistently links decreased BDNF to dysfunction in metabolic control. PEB induced through a high-fat diet causes a decrease in hippocampal BDNF expression in mice, as well as decreased neurogenesis [98]. As with MDD, human subjects with MetS have lower levels of peripheral BDNF [99,100], which improves with correction of PEB through dieting [101]. It appears that in humans, genetically determined decreases in BDNF, whether due to functional deletion [102–104] or allelic variation [105,106], are associated with obesity and hyperphagia. Centrally, BDNF plays a role in the hypothalamic control of appetite and eating behavior by modulating the appetite-lowering response to high-fat-containing meals [107]. It also appears to potentiate dopamine responses to food rewards [108]. In addition to its central role in mood and metabolic regulation, BDNF also appears to promote development of muscles and peripheral nerves in response to exercise [109] and may thus connect physical activity to improvements in mood as well as metabolic improvement. It appears that both MDD and MetS are associated with decreased BDNF expression, and that, at least in the case of MetS, decreases in BDNF can be a primary cause. A drop in BDNF related to MetS could thus reasonably lead to TRD by blocking antidepressant-induced neurogenesis in the hippocampus.

IR & chronic inflammation impair hypothalamic regulation of metabolism

Insulin receptors are expressed in the hypothalamus as part of its role in regulating metabolism and appetite [110]. It also sits at the 'top' of the hypothalamic–pituitary–adrenal axis and provides central regulation of the stress response. This combination places it critically in the network linking MDD and MetS, relationships that are depicted in **Figure 3**. Normally, the hypothalamus maintains bodyweight by modulating metabolic rate and appetite according to current energy needs. Insulin and leptin both act on the arcuate nucleus to signal current energy status [111]. However, under conditions of chronic PEB, the same macrophage-associated inflammatory cascade that causes IR in the periphery occurs locally in the hypothalamus and leads to insulin and leptin resistance [112]. Decreased insulin and leptin receptor signal transmission results in maintenance of appetite and bodyweight despite ongoing PEB. This appears to account for the difficulty many obese people have in losing meaningful weight – chronic central changes have reset the body's metabolic regulatory mechanism to favor obesity [111]. Although less-rigorously validated, patients with MDD may experience a similar kindling phenomenon in which each depressive episode increases the probability of future depression [113].

One possible mechanism through which these inflammatory changes in the hypothalamus could affect mood is via orexin. Orexin was first discovered as the key component lacking in animal and human narcolepsy; it plays a central role in maintaining arousal [114]. However, narcoleptics also display metabolic abnormalities – increased weight despite lower food intake [115] – that suggested orexin influences energy metabolism. Orexin is made in neuronal cell bodies in the lateral hypothalamus [116] whose axons project widely over the brain [117], including the raphe nuclei and locus ceruleus. Orexin activity responds to the nutritional state over short time frames, such as when blood sugar and/or leptin is low [114]. Orexin increases arousal and food-seeking activity by raising serotonergic and noradrenergic tone. Serotonin and norepinephrine in turn can inhibit orexin release [118]. Orexin neurons also project to the ventral tegmental area of the midbrain where they increase dopamine reward signaling [119]. Orexin appears to mediate parts of the acute stress response that is impaired in orexin-knockout mice [120]. The exact relationships between orexin, metabolism and mood remain to be elucidated, but animal studies have demonstrated that orexin can block chronic stress-induced depression-like behavioral changes in mice [121] and that this mechanism is dependent on leptin. This suggests that obesity-related leptin resistance may leave patients less resilient to stress. In addition, since orexin increases signaling of monoamine transmitters, lack of its activity may lead to anhedonia or make antidepressants less effective. While research in this area is still in fairly early stages, understanding the orexin system has the potential to greatly improve our understanding of the central connection between metabolism and mood.

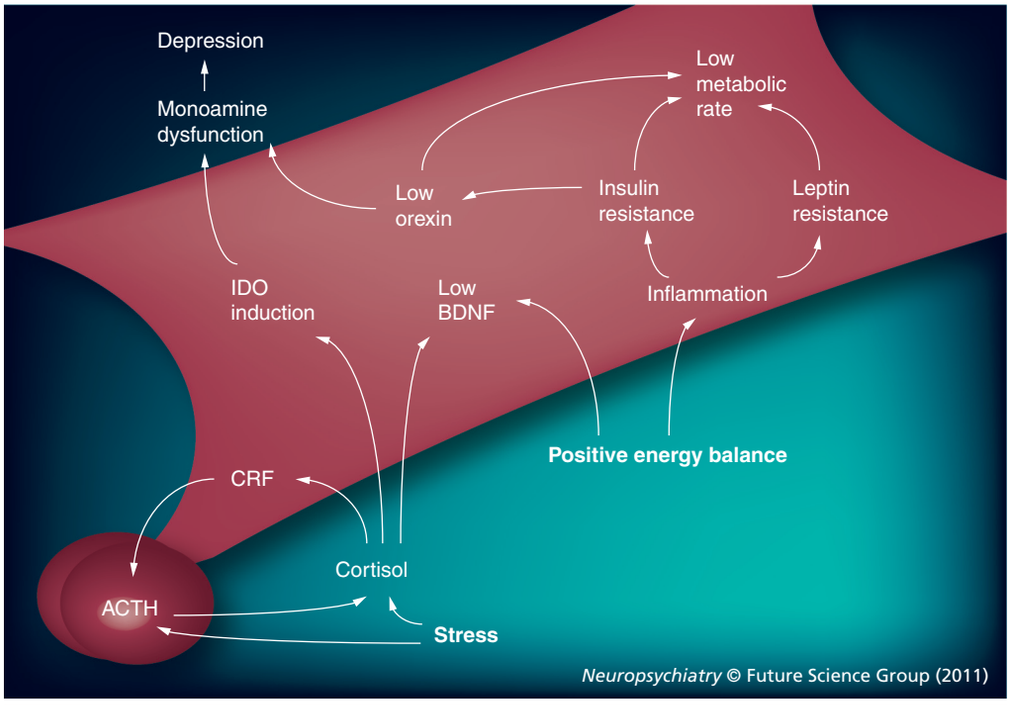


Figure 3. Model of the effects of stress and positive energy balance on the hypothalamus.
ACTH: Adrenocorticotrophic hormone; BDNF: Brain-derived neurotrophic factor; CRF: Cortocotrophin-releasing factor; IDO: Indoleamine-2,3-dioxygenase.

Changes in tryptophan metabolism may cause medication failure in MDD

The inflammatory cytokines share an additional mechanism with stress-induced hypothalamic–pituitary–adrenal axis hyperactivity that is an appealing possible explanation for TRD in those with MetS. Cortisol, TNF-α and interferon all induce one or both of the enzymes indoleamine-2,3-dioxygenase (IDO) and tryptophan-2,3-dioxygenase [36,122]. These enzymes shift the metabolism of tryptophan away from synthesis of serotonin and toward kynurenine. Increased peripheral metabolism of tryptophan by IDO and tryptophan-2,3-dioxygenase creates a state of relative tryptophan depletion, and alters the ratio of tryptophan to kynurenine and its metabolites in the brain [123].

Acute experimental induction of tryptophan depletion appears insufficient for the induction of MDD in healthy people, but can reverse symptomatic improvements from SSRI treatment in those with depression [124,125]. Although patients with MDD may have lower circulating tryptophan than controls [126,127], no large, well-controlled studies have examined whether supplementation improves treatment outcome [128]. In addition, while IFN-γ appears to be the primary mediator of IDO induction [129], patients with MDD do not appear to have higher IFN-γ levels than controls [38]. This may mean that cortisol and other regulators are more important in activating IDO in most depressed patient with low tryptophan. However, this pathway does have good evidence of relevance for those who are treated with cytokines. First, the behavioral importance of IDO induction due to interferon is supported by the finding that mice that do not express IDO are resistant to the depression-like, but not the sickness-like, behaviors caused by an inflammatory stimulus [130]. Second, in cancer patients treated with IFN-γ, a drop in circulating tryptophan correlates with depression symptom severity [131].

There is also good evidence that IDO induction occurs in MetS. Plasma tryptophan is low in obese subjects [132] and is thought to be related to adipose tissue inflammation-induced IDO activation [133]. While few studies have directly measured IFN-γ levels in MetS, and in those that have, the results have been mixed [62,134], it appears more certain that the low tryptophan in MetS is mediated by IDO [135]. Inflammation- and IDO-mediated tryptophan depletion may also feed forward to maintain PEB because

serotonin also mediates satiety – those with low tryptophan may be more likely to over-eat [133]. Tryptophan depletion associated with MetS could potentially induce or worsen depression, and to the extent that experimental depletion acts as a model, this depletion could have negative impacts on treatment.

Clinical research findings that support the treatment of MetS in MDD patients

The common pathology described earlier leads to the question of whether the treatment of MetS can be used to address the treatment of MDD. IR is a possible subclinical feature of MDD, as described earlier. Several studies have examined whether IR in patient with MDD but not MetS responds to antidepressant treatment [136–139] using oral glucose tolerance testing (OGTT). The fact that all of these studies found improvements in IR with antidepressants strongly supports conceptualizing metabolic dysfunction as a feature of MDD. In one study, the outcome was specifically linked with improvement on OGTT [139], suggesting that IR may function as a moderator of treatment. However, further research is needed to clarify whether the clinical relationship between MDD and MetS is bidirectional or if it is more meaningful in one direction only. Nonetheless, taken together, these studies imply that in patients with TRD, it is reasonable to consider testing for IR even in the absence of full criteria for MetS, as well as studying treatment responses in patients in whom it is found.

Addressing the issue from the opposite direction, some studies examining the effects of metabolic medications on depression have already been performed based on the evidence of pathophysiological overlap. The thiazolidinediones (pioglitazone and rosiglitazone), which improve insulin sensitivity, have shown antidepressant effect in rodents [140] and are beginning to be studied in human subjects. In one published case, a patient with severe TRD and subclinical IR improved dramatically with pioglitazone [141]. Similarly, in a small pilot study, eight out of 12 patients who received augmentation treatment with rosiglitazone showed improvements in mood [142].

It may also be possible for medication to act at on inflammation that links MDD to MetS – several trials of antidepressant treatments have found elevated cytokines are associated with failure to respond [143–145]. In this vein, the group of TNF-α inhibitors recently approved to treat rheumatoid arthritis and other autoimmune diseases have also generated some interesting data regarding their possible use in patients with TRD. Groups of patients with psoriasis [146] and ankylosing spondilysis [147] showed improvements in symptoms of MDD when treated with TNF-α antagonists, effects that were measured separately from illness burden and fatigue. These drugs may also improve metabolic markers in MetS [148], suggesting that for severe and/or comorbid cases, they may be worth further research despite their side effects.

Clinical relevance of the pathophysiological links

There is significant clinical and pathophysiological overlap between metabolic derangement and depressed mood. More specifically, systemic inflammation and IR in MetS predispose to depression through central IR. Decreased insulin signaling in the brain is synergistic with stress-related inhibition in GR function and creates abnormalities in serotonin signaling, reward circuitry and hippocampal cognitive function. Metabolic dysfunction in patients with MDD certainly leads to entrenchment of pathophysiology. It may also interfere directly and indirectly with the actions of antidepressants through inhibition of growth factors and interference with monoamine neurotransmission. Although the specific clinical effects of these interactions have not yet been adequately studied, because of the high comorbidity and similar underlying pathophysiology, we believe that MetS is likely to be a significant source of treatment resistance in depression. We suggest that clinicians should be aware of MetS in their patients and consider medical management of MetS.

Clinical recommendations

Based on the biological connections between MetS and MDD, we recommend that clinicians aggressively cross-screen patients with either MDD or MetS. These recommendations are presented as an algorithm in **Box 1**. Because of growing concern about specific metabolic effects of certain psychiatric medications, it has already become more common for psychiatrists to monitor metabolic status in their patients. However, the connection between MetS and MDD suggests that all patients with depression could benefit from screening regardless of treatment type. The major components of MetS can be measured easily in the office at every visit – BMI, waist circumference and blood pressure – and laboratory

testing of lipids is easy to perform on a periodic basis. Referrals to primary care providers should be made for cases in which the psychiatrist is not comfortable managing metabolic abnormalities. Even in the absence of direct clinical evidence that metabolic treatment will improve mood, it certainly will reduce the long-term risk of morbidity and be of benefit to patients.

While many factors have been associated with occurrence of TRD, few of them are modifiable at the time a patient sees a psychiatrist. Genetics and childhood experiences are fixed, and patients have often been depressed for years or have had multiple episodes. MetS, on the other hand, has numerous approved medications already on the market for its treatment, in addition to evidence-based lifestyle modifications. The long and expensive process of drug development would not be needed if aggressive management of comorbid MDD and metabolic dysfunction is found to be effective – treatment algorithms could be moved almost immediately into clinical practice, where they could profoundly effect treatment outcome for many patients.

Since exercise has been independently shown to dramatically reduce progression from MetS to DM2 [149] and to improve the majority of cases of DM2 [150] and many cases of MDD [151–154], exercise should also be considered as a viable treatment either alone or in conjunction with antidepressant medications for patients with comorbid illness. Structured exercise and behavioral modification programs may prove to be worth the extra upfront expense in these patients by increasing adherence, and thus benefit.

Future perspective: we should focus on validating the importance of MetS in MDD treatment

Although clinical decision-making can be guided to some extent by currently known information, there remains no clearly established link between treatment resistance *per se* and MetS. Although there are several possible mechanisms, it remains to be determined which are the most relevant clinically. We propose that patients with comorbid MetS (and perhaps those with subclinical MetS features) are a distinct subtype of depressed patient who may benefit from specialized treatment that is superior to usual care of MDD plus usual care of metabolism. Studies examining treatment outcomes in this subgroup specifically would be of great value in determining unique treatment characteristics and defining rates of TRD. Currently, while mood symptoms may be measured as a secondary outcome in large studies of metabolic disease, few groups within psychiatric research focus on the study of patients with medical illness-associated depression. These patients may be found to respond more to particular medications or to other types of treatments. Studies comparing symptom profiles, response/remission rates and biomarkers of depressed patients with comorbid metabolic disturbance with those without these features may further define this group of patients and lead to enhanced personalized treatment.

However, some MDD patients will not meet criteria for MetS, as it is currently defined, but will have elevations in cytokines and IR. Although, as mentioned earlier, MDD-associated IR has been shown to improve with antidepressant treatment, no study has yet attempted to determine if IR is a predictor of TRD, nor has any study compared response rates between patients with MDD who differ in the presence or severity of IR. If IR reduction is beneficial to outcome, it is possible that these patients would demonstrate additional improvements in depressive symptoms if treated with metabolic or anti-inflammatory agents. Testing patients with TRD with OGTT for IR, or drawing blood for cytokine levels, is not burdensome and would select a target population. An open-label study

Box 1. Treatment algorithm for diagnosing and treating metabolic syndrome in patients with major depressive disorder.

- Collection of a thorough medical, psychiatric and medication history
- Measurement of blood pressure, weight and waist circumference
- Laboratory assessment of blood glucose and lipids
- Diagnosis of metabolic syndrome, if present
- Prescription of appropriate medication(s), appropriate referral to primary care providers and specialists to manage metabolic abnormalities, and suggestion of lifestyle changes (diet and exercise)
- Assessment of antidepressant response over 4–12 weeks
- Continued monitoring of metabolic criteria and mood symptoms

in which patients with MDD and IR are treated with antidepressants and then randomized to a metabolic agent versus placebo to directly compare remission rates would provide results of high clinical utility and be straightforward and low risk to conduct.

Financial & competing interests disclosure

MH Trivedi reports that he has received research support from the Agency for Healthcare Research and Quality (AHRQ), Corcept Therapeutics, Inc., Cyberonics, Inc., Merck, National Alliance for Research in Schizophrenia and Depression, National Institute of Mental Health, National Institute on Drug Abuse, Novartis, Pharmacia & Upjohn, Predix Pharmaceuticals (Epix), Solvay Pharmaceuticals, Inc. and Targacept. He has received consulting and speaker fees from Abbott Laboratories, Inc., Abdi Ibrahim, Akzo (Organon Pharmaceuticals, Inc.), AstraZeneca, Bristol-Myers Squibb Company, Cephalon, Inc., Evotec, Fabre Kramer Pharmaceuticals, Inc., Forest Pharmaceuticals, GlaxoSmithKline, Janssen Pharmaceutica Products, LP, Johnson & Johnson PRD, Eli Lilly & Company, Meade Johnson, Medtronic, Neuronetics, Otsuka Pharmaceuticals, Parke-Davis Pharmaceuticals, Inc., Pfizer Inc., Sepracor, SHIRE Development, VantagePoint and Wyeth-Ayerst Laboratories. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Bibliography

Papers of special note have been highlighted as:

- ▪ of interest
- ▪▪ of considerable interest

1 Ustun TB, Ayuso-Mateos JL, Chatterji S, Mathers C, Murray CJ. Global burden of depressive disorders in the year 2000. *Br. J. Psychiatr.* 184, 386–392 (2004).

2 Gelenberg AJ. The prevalence and impact of depression. *J. Clin. Psychiatr.* 71(3), E06 (2010).

3 Trivedi MH, Rush AJ, Wisniewski SR *et al.* Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am. J. Psychiatr.* 163(1), 28–40 (2006).

▪ **Outcomes of the STAR*D study, demonstrating real-world response and remission rates to antidepressant treatment.**

4 Rush AJ, Trivedi MH, Wisniewski SR *et al.* Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am. J. Psychiatr.* 163(11), 1905–1917 (2006).

▪ **Looks at outcomes for subjects in the STAR*D study who required multiple treatment trials.**

5 Souery D, Papakostas GI, Trivedi MH. Treatment-resistant depression. *J. Clin. Psychiatr.* 67(Suppl. 6), 16–22 (2006).

6 Fava M, Davidson KG. Definition and epidemiology of treatment-resistant depression. *Psychiatr. Clin. N. Am.* 19(2), 179–200 (1996).

7 Corey-Lisle PK, Nash R, Stang P, Swindle R. Response, partial response, and nonresponse in primary care treatment of depression. *Arch. Intern. Med.* 164(11), 1197–1204 (2004).

▪▪ **Examination of the characteristics of patients with successful and unsuccessful treatment for major depressive disorder (MDD).**

8 Fekadu A, Wooderson SC, Markopoulo K, Donaldson C, Papadopoulos A, Cleare AJ. What happens to patients with treatment-resistant depression? A systematic review of medium to long term outcome studies. *J. Affect. Disord.* 116(1–2), 4–11 (2009).

9 Trivedi MH, Corey-Lisle PK, Guo Z, Lennox RD, Pikalov A, Kim E. Remission, response without remission, and nonresponse in major depressive disorder: impact on functioning. *Int. Clin. Psychopharmacol.* 24(3), 133–138 (2009).

10 Fulop T, Tessier D, Carpentier A. The metabolic syndrome. *Pathol. Biol. (Paris)* 54(7), 375–386 (2006).

▪▪ **Comprehensive and accessible review of metabolic syndrome.**

11 Bonora E. The metabolic syndrome and cardiovascular disease. *Ann. Med.* 38(1), 64–80 (2006).

12 Alberti KG, Eckel RH, Grundy SM *et al.* Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 120(16), 1640–1645 (2009).

13 Bray GA, Bellanger T. Epidemiology, trends, and morbidities of obesity and the metabolic syndrome. *Endocrine* 29(1), 109–117 (2006).

14 Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. *Nature* 414(6865), 782–787 (2001).

15 Goldbacher EM, Bromberger J, Matthews KA. Lifetime history of major depression predicts the development of the metabolic syndrome in middle-aged women. *Psychosom. Med.* 71(3), 266–272 (2009).

16 Holt RI, Phillips DI, Jameson KA, Cooper C, Dennison EM, Peveler RC. The relationship between depression and diabetes mellitus: findings from the Hertfordshire Cohort Study. *Diabet. Med.* 26(6), 641–648 (2009).

17 Kinder LS, Carnethon MR, Palaniappan LP, King AC, Fortmann SP. Depression and the metabolic syndrome in young adults: findings from the Third National Health and Nutrition Examination Survey. *Psychosom. Med.* 66(3), 316–322 (2004).

18 Raikkonen K, Matthews KA, Kuller LH. Depressive symptoms and stressful life events predict metabolic syndrome among middle-aged women: a comparison of World Health Organization, Adult Treatment Panel III, and International Diabetes Foundation definitions. *Diabet. Care* 30(4), 872–877 (2007).

19 Koponen H, Jokelainen J, Keinanen-Kiukaanniemi S, Kumpusalo E, Vanhala M. Metabolic syndrome predisposes to depressive symptoms: a population-based 7-year follow-up study. *J. Clin. Psychiatr.* 69(2), 178–182 (2008).

20 Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. *Diabet. Care* 24(6), 1069–1078 (2001).

21 Mezuk B, Eaton WW, Albrecht S, Golden SH. Depression and Type 2 diabetes over the lifespan: a meta-analysis. *Diabet. Care* 31(12), 2383–2390 (2008).

22 Nouwen A, Winkley K, Twisk J *et al.* Type 2 diabetes mellitus as a risk factor for the onset of depression: a systematic review and meta-analysis. *Diabetologia* 53(12), 2480–2486 (2010).

23 Pyykkonen AJ, Raikkonen K, Tuomi T, Eriksson JG, Groop L, Isomaa B. Stressful life events and the metabolic syndrome: the Prevalence, Prediction and Prevention of Diabetes (PPP)–Botnia Study. *Diabet. Care* 33(2), 378–384 (2010).

24 Lustman PJ, Freedland KE, Griffith LS, Clouse RE. Fluoxetine for depression in diabetes: a randomized double-blind placebo-controlled trial. *Diabet. Care* 23(5), 618–623 (2000).

25 Lustman PJ, Griffith LS, Clouse RE *et al.* Effects of nortriptyline on depression and glycemic control in diabetes: results of a double-blind, placebo-controlled trial. *Psychosom. Med.* 59(3), 241–250 (1997).

26 Shelton RC, Miller AH. Eating ourselves to death (and despair): the contribution of adiposity and inflammation to depression. *Prog. Neurobiol.* 91(4), 275–299 (2010).

■■ **Examination of the role that inflammation plays in connecting adiposity to mood disturbance.**

27 Anderson EK, Gutierrez DA, Hasty AH. Adipose tissue recruitment of leukocytes. *Curr. Opin. Lipidol.* 21(3), 172–177 (2010).

28 Matarese G, Procaccini C, De Rosa V, Horvath TL, La Cava A. Regulatory T cells in obesity: the leptin connection. *Trends Mol. Med.* 16(6), 247–256 (2010).

29 Kelesidis T, Kelesidis I, Chou S, Mantzoros CS. Narrative review: the role of leptin in human physiology: emerging clinical applications. *Ann. Intern. Med.* 152(2), 93–100 (2010).

30 Santos-Alvarez J, Goberna R, Sanchez-Margalet V. Human leptin stimulates proliferation and activation of human circulating monocytes. *Cell. Immunol.* 194(1), 6–11 (1999).

31 Matsushita K, Yatsuya H, Tamakoshi K *et al.* Comparison of circulating adiponectin and proinflammatory markers regarding their association with metabolic syndrome in Japanese men. *Arterioscler. Thromb. Vasc. Biol.* 26(4), 871–876 (2006).

32 Ohmura E, Hosaka D, Yazawa M *et al.* Association of free fatty acids (FFA) and tumor necrosis factor-α (TNF-α) and insulin-resistant metabolic disorder. *Horm. Metab. Res.* 39(3), 212–217 (2007).

33 Salmenniemi U, Ruotsalainen E, Pihlajamaki J *et al.* Multiple abnormalities in glucose and energy metabolism and coordinated changes in levels of adiponectin, cytokines, and adhesion molecules in subjects with metabolic syndrome. *Circulation* 110(25), 3842–3848 (2004).

34 Moon YS, Kim DH, Song DK. Serum tumor necrosis factor-α levels and components of the metabolic syndrome in obese adolescents. *Metabolism* 53(7), 863–867 (2004).

35 Smith RS. The macrophage theory of depression. *Med. Hypotheses* 35(4), 298–306 (1991).

36 Dantzer R, O'Connor JC, Lawson MA, Kelley KW. Inflammation-associated depression: from serotonin to kynurenine. *Psychoneuroendocrinology* 36(3), 426–436 (2011).

37 Musselman DL, Lawson DH, Gumnick JF *et al.* Paroxetine for the prevention of depression induced by high-dose interferon α. *N. Engl. J. Med.* 344(13), 961–966 (2001).

38 Dowlati Y, Herrmann N, Swardfager W *et al.* A meta-analysis of cytokines in major depression. *Biol. Psychiatr.* 67(5), 446–457 (2010).

■ **Meta-analysis confirming elevations of peripheral cytokines in MDD.**

39 Miller GE, Chen E, Sze J *et al.* A functional genomic fingerprint of chronic stress in humans: blunted glucocorticoid and increased NF-κB signaling. *Biol. Psychiatr.* 64(4), 266–272 (2008).

40 Miller GE, Rohleder N, Cole SW. Chronic interpersonal stress predicts activation of pro- and anti-inflammatory signaling pathways 6 months later. *Psychosom. Med.* 71(1), 57–62 (2009).

41 Nathan CF. Secretory products of macrophages. *J. Clin. Invest.* 79(2), 319–326 (1987).

42 Schmidt ED, Aguilera G, Binnekade R, Tilders FJ. Single administration of interleukin-1 increased corticotropin releasing hormone and corticotropin releasing hormone-receptor mRNA in the hypothalamic paraventricular nucleus which paralleled long-lasting (weeks) sensitization to emotional stressors. *Neuroscience* 116(1), 275–283 (2003).

43 Anagnostis P, Athyros VG, Tziomalos K, Karagiannis A, Mikhailidis DP. Clinical review: the pathogenetic role of cortisol in the metabolic syndrome: a hypothesis. *J. Clin. Endocrinol. Metab.* 94(8), 2692–2701 (2009).

44 Jessop DS, Dallman MF, Fleming D, Lightman SL. Resistance to glucocorticoid feedback in obesity. *J. Clin. Endocrinol. Metab.* 86(9), 4109–4114 (2001).

45 Wirtz PH, Ehlert U, Emini L, Suter T. Higher body mass index (BMI) is associated with reduced glucocorticoid inhibition of inflammatory cytokine production following acute psychosocial stress in men. *Psychoneuroendocrinology* 33(8), 1102–1110 (2008).

46 Mussig K, Remer T, Maser-Gluth C. Brief review: glucocorticoid excretion in obesity. *J. Steroid Biochem. Mol. Biol.* 121(3–5), 589–593 (2010).

47 Weinstein SP, Paquin T, Pritsker A, Haber RS. Glucocorticoid-induced insulin resistance: dexamethasone inhibits the activation of glucose transport in rat skeletal muscle by both insulin- and non-insulin-related stimuli. *Diabetes* 44(4), 441–445 (1995).

48 Ottosson M, Vikman-Adolfsson K, Enerback S, Olivecrona G, Bjorntorp P. The effects of cortisol on the regulation of lipoprotein lipase activity in human adipose tissue. *J. Clin. Endocrinol. Metab.* 79(3), 820–825 (1994).

49 Roden M, Price TB, Perseghin G *et al.* Mechanism of free fatty acid-induced insulin resistance in humans. *J. Clin. Invest.* 97(12), 2859–2865 (1996).

50 Solomon SS, Odunusi O, Carrigan D *et al.* TNF-α inhibits insulin action in liver and adipose tissue: a model of metabolic syndrome. *Horm. Metab. Res.* 42(2), 115–121 (2010).

51 Kondo H, Shimomura I, Matsukawa Y *et al.* Association of adiponectin mutation with Type 2 diabetes: a candidate gene for the insulin resistance syndrome. *Diabetes* 51(7), 2325–2328 (2002).

52 Stefan N, Vozarova B, Funahashi T *et al.* Plasma adiponectin concentration is associated with skeletal muscle insulin receptor tyrosine phosphorylation, and low plasma concentration precedes a decrease in whole-body insulin sensitivity in humans. *Diabetes* 51(6), 1884–1888 (2002).

53 Ouchi N, Walsh K. Adiponectin as an anti-inflammatory factor. *Clin. Chim. Acta* 380(1–2), 24–30 (2007).

54 Maeda N, Shimomura I, Kishida K *et al.* Diet-induced insulin resistance in mice lacking adiponectin/ACRP30. *Nat. Med.* 8(7), 731–737 (2002).

55 Maeda N, Takahashi M, Funahashi T *et al.* PPARγ ligands increase expression and plasma concentrations of adiponectin, an adipose-derived protein. *Diabetes* 50(9), 2094–2099 (2001).

56 Cizza G, Nguyen VT, Eskandari F *et al.* Low 24-hour adiponectin and high nocturnal leptin concentrations in a case–control study of community-dwelling premenopausal

women with major depressive disorder: the Premenopausal, Osteopenia/Osteoporosis, Women, Alendronate, Depression (POWER) study. *J. Clin. Psychiatr.* 71(8), 1079–1087 (2010).

57 Lehto SM, Huotari A, Niskanen L *et al.* Serum adiponectin and resistin levels in major depressive disorder. *Acta Psychiatr. Scand.* 121(3), 209–215 (2010).

58 Winokur A, Maislin G, Phillips JL, Amsterdam JD. Insulin resistance after oral glucose tolerance testing in patients with major depression. *Am. J. Psychiatr.* 145(3), 325–330 (1988).

59 Barth J, Schumacher M, Herrmann-Lingen C. Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. *Psychosom. Med.* 66(6), 802–813 (2004).

60 Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosom. Med.* 71(2), 171–186 (2009).

61 Valle Gottlieb MG, Da Cruz IB, Duarte MM *et al.* Associations among metabolic syndrome, ischemia, inflammatory, oxidatives, and lipids biomarkers. *J. Clin. Endocrinol. Metab.* 95(2), 586–591 (2010).

62 Ingelsson E, Hulthe J, Lind L. Inflammatory markers in relation to insulin resistance and the metabolic syndrome. *Eur. J. Clin. Invest.* 38(7), 502–509 (2008).

63 Devaraj S, Valleggi S, Siegel D, Jialal I. Role of C-reactive protein in contributing to increased cardiovascular risk in metabolic syndrome. *Curr. Atheroscler. Rep.* 12(2), 110–118 (2010).

64 Dinarello CA, Donath MY, Mandrup-Poulsen T. Role of IL-1β in Type 2 diabetes. *Curr. Opin. Endocrinol. Diabet. Obes.* 17(4), 314–321 (2010).

65 Sheline YI, Mittler BL, Mintun MA. The hippocampus and depression. *Eur. Psychiatr.* 17(Suppl. 3), 300–305 (2002).

■ **Clear summary of hippocampal abnormalities seen in MDD.**

66 Drevets WC, Price JL, Simpson JR Jr *et al.* Subgenual prefrontal cortex abnormalities in mood disorders. *Nature* 386(6627), 824–827 (1997).

67 Amico F, Meisenzahl E, Koutsouleris N, Reiser M, Moller HJ, Frodl T. Structural MRI correlates for vulnerability and resilience to major depressive disorder. *J. Psychiatr. Neurosci.* 36(1), 15–22 (2011).

68 Sheline YI, Sanghavi M, Mintun MA, Gado MH. Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. *J. Neurosci.* 19(12), 5034–5043 (1999).

69 Bruehl H, Wolf OT, Sweat V, Tirsi A, Richardson S, Convit A. Modifiers of cognitive function and brain structure in middle-aged and elderly individuals with Type 2 diabetes mellitus. *Brain Res.* 1280, 186–194 (2009).

70 Mcintyre RS, Kenna HA, Nguyen HT *et al.* Brain volume abnormalities and neurocognitive deficits in diabetes mellitus: points of pathophysiological commonality with mood disorders? *Adv. Ther.* 27(2), 63–80 (2010).

71 Raji CA, Ho AJ, Parikshak NN *et al.* Brain structure and obesity. *Hum. Brain Mapp.* 31(3), 353–364 (2010).

72 Mcdermott LM, Ebmeier KP. A meta-analysis of depression severity and cognitive function. *J. Affect. Disord.* 119(1–3), 1–8 (2009).

73 Taylor VH, Macqueen GM. Cognitive dysfunction associated with metabolic syndrome. *Obes. Rev.* 8(5), 409–418 (2007).

74 Hassenstab JJ, Sweat V, Bruehl H, Convit A. Metabolic syndrome is associated with learning and recall impairment in middle age. *Dement. Geriatr. Cogn. Disord.* 29(4), 356–362 (2010).

75 Profenno LA, Porsteinsson AP, Faraone SV. Meta-analysis of Alzheimer's disease risk with obesity, diabetes, and related disorders. *Biol. Psychiatr.* 67(6), 505–512 (2010).

76 Devanand DP, Sano M, Tang MX *et al.* Depressed mood and the incidence of Alzheimer's disease in the elderly living in the community. *Arch. Gen. Psychiatr.* 53(2), 175–182 (1996).

77 Janocha A, Bolanowski M, Pilecki W *et al.* Cognitive disorders in Type 2 diabetic patients with recognized depression. *Neuro. Endocrinol. Lett.* 31(3), 399–405 (2010).

78 Bruehl H, Sweat V, Hassenstab J, Polyakov V, Convit A. Cognitive impairment in nondiabetic middle-aged and older adults is associated with insulin resistance. *J. Clin. Exp. Neuropsychol.* 32(5), 487–493 (2010).

79 Baker LD, Cross DJ, Minoshima S, Belongia D, Watson GS, Craft S. Insulin resistance and Alzheimer-like reductions in regional cerebral glucose metabolism for cognitively normal adults with prediabetes or early Type 2 diabetes. *Arch. Neurol.* 68(1), 51–57 (2011).

80 Small SA, Tsai WY, Delapaz R, Mayeux R, Stern Y. Imaging hippocampal function across the human life span: is memory decline normal or not? *Ann. Neurol.* 51(3), 290–295 (2002).

81 Lynch MA. Age-related impairment in long-term potentiation in hippocampus: a role for the cytokine, interleukin-1 β? *Prog. Neurobiol.* 56(5), 571–589 (1998).

82 Mossner R, Heils A, Stober G, Okladnova O, Daniel S, Lesch KP. Enhancement of serotonin transporter function by tumor necrosis factor α but not by interleukin-6. *Neurochem. Int.* 33(3), 251–254 (1998).

83 Nelson TJ, Sun MK, Hongpaisan J, Alkon DL. Insulin, PKC signaling pathways and synaptic remodeling during memory storage and neuronal repair. *Eur. J. Pharmacol.* 585(1), 76–87 (2008).

84 Benedict C, Hallschmid M, Hatke A *et al.* Intranasal insulin improves memory in humans. *Psychoneuroendocrinology* 29(10), 1326–1334 (2004).

85 Reger MA, Watson GS, Green PS *et al.* Intranasal insulin improves cognition and modulates β-amyloid in early AD. *Neurology* 70(6), 440–448 (2008).

86 Hallschmid M, Benedict C, Schultes B, Born J, Kern W. Obese men respond to cognitive but not to catabolic brain insulin signaling. *Int. J. Obes. (Lond.)* 32(2), 275–282 (2008).

87 Warner-Schmidt JL, Duman RS. Hippocampal neurogenesis: opposing effects of stress and antidepressant treatment. *Hippocampus* 16(3), 239–249 (2006).

88 Piroli GG, Grillo CA, Reznikov LR *et al.* Corticosterone impairs insulin-stimulated translocation of GLUT4 in the rat hippocampus. *Neuroendocrinology* 85(2), 71–80 (2007).

89 Kuczewski N, Porcher C, Gaiarsa JL. Activity-dependent dendritic secretion of brain-derived neurotrophic factor modulates synaptic plasticity. *Eur. J. Neurosci.* 32(8), 1239–1244 (2010).

90 Schmidt HD, Duman RS. The role of neurotrophic factors in adult hippocampal neurogenesis, antidepressant treatments and animal models of depressive-like behavior. *Behav. Pharmacol.* 18(5–6), 391–418 (2007).

91 Sen S, Duman R, Sanacora G. Serum brain-derived neurotrophic factor, depression, and antidepressant medications: meta-analyses and implications. *Biol. Psychiatr.* 64(6), 527–532 (2008).

92 Badowska-Szalewska E, Spodnik E, Klejbor I, Morys J. Effects of chronic forced swim stress on hippocampal brain-derived neutrophic factor (BDNF) and its receptor (TrkB) immunoreactive cells in juvenile and aged rats. *Acta Neurobiol. Exp. (Wars.)* 70(4), 370–381 (2010).

93 Cosi C, Spoerri PE, Comelli MC, Guidolin D, Skaper SD. Glucocorticoids depress activity-dependent expression of BDNF mRNA in hippocampal neurones. *Neuroreport* 4(5), 527–530 (1993).

94 Adachi M, Barrot M, Autry AE, Theobald D, Monteggia LM. Selective loss of brain-derived neurotrophic factor in the dentate gyrus attenuates antidepressant efficacy. *Biol. Psychiatr.* 63(7), 642–649 (2008).

95 Deltheil T, Guiard BP, Cerdan J *et al.* Behavioral and serotonergic consequences of decreasing or increasing hippocampus brain-derived neurotrophic factor protein levels in mice. *Neuropharmacology* 55(6), 1006–1014 (2008).

96 Lyons WE, Mamounas LA, Ricaurte GA *et al.* Brain-derived neurotrophic factor-deficient mice develop aggressiveness and hyperphagia in conjunction with brain serotonergic abnormalities. *Proc. Natl Acad. Sci. USA* 96(26), 15239–15244 (1999).

97 Tsai SJ, Hong CJ, Liou YJ. Effects of BDNF polymorphisms on antidepressant action. *Psychiatr. Investig.* 7(4), 236–242 (2010).

98 Park HR, Park M, Choi J, Park KY, Chung HY, Lee J. A high-fat diet impairs neurogenesis: involvement of lipid peroxidation and brain-derived neurotrophic factor. *Neurosci. Lett.* 482(3), 235–239 (2010).

99 El-Gharbawy AH, Adler-Wailes DC, Mirch MC *et al.* Serum brain-derived neurotrophic factor concentrations in lean and overweight children and adolescents. *J. Clin. Endocrinol. Metab.* 91(9), 3548–3552 (2006).

100 Lommatzsch M, Zingler D, Schuhbaeck K *et al.* The impact of age, weight and gender on BDNF levels in human platelets and plasma. *Neurobiol. Aging* 26(1), 115–123 (2005).

101 Araya AV, Orellana X, Espinoza J. Evaluation of the effect of caloric restriction on serum BDNF in overweight and obese subjects: preliminary evidences. *Endocrine* 33(3), 300–304 (2008).

102 Gray J, Yeo GS, Cox JJ *et al.* Hyperphagia, severe obesity, impaired cognitive function, and hyperactivity associated with functional loss of one copy of the brain-derived neurotrophic factor (*BDNF*) gene. *Diabetes* 55(12), 3366–3371 (2006).

103 Han JC, Liu QR, Jones M *et al.* Brain-derived neurotrophic factor and obesity in the WAGR syndrome. *N. Engl. J. Med.* 359(9), 918–927 (2008).

104 Han JC, Muehlbauer MJ, Cui HN, Newgard CB, Haqq AM. Lower brain-derived neurotrophic factor in patients with Prader–Willi syndrome compared to obese and lean control subjects. *J. Clin. Endocrinol. Metab.* 95(7), 3532–3536 (2010).

105 Gunstad J, Schofield P, Paul RH *et al.* *BDNF* Val66Met polymorphism is associated with body mass index in healthy adults. *Neuropsychobiology* 53(3), 153–156 (2006).

106 Shugart YY, Chen L, Day IN *et al.* Two British women studies replicated the association between the Val66Met polymorphism in the brain-derived neurotrophic factor (BDNF) and BMI. *Eur. J. Hum. Genet.* 17(8), 1050–1055 (2009).

107 Xu B, Goulding EH, Zang K *et al.* Brain-derived neurotrophic factor regulates energy balance downstream of melanocortin-4 receptor. *Nat. Neurosci.* 6(7), 736–742 (2003).

108 Cordeira JW, Frank L, Sena-Esteves M, Pothos EN, Rios M. Brain-derived neurotrophic factor regulates hedonic feeding by acting on the mesolimbic dopamine system. *J. Neurosci.* 30(7), 2533–2541 (2010).

109 Pedersen BK, Pedersen M, Krabbe KS, Bruunsgaard H, Matthews VB, Febbraio MA. Role of exercise-induced brain-derived neurotrophic factor production in the regulation of energy homeostasis in mammals. *Exp. Physiol.* 94(12), 1153–1160 (2009).

110 Hill JM, Lesniak MA, Pert CB, Roth J. Autoradiographic localization of insulin receptors in rat brain: prominence in olfactory and limbic areas. *Neuroscience* 17(4), 1127–1138 (1986).

111 Belgardt BF, Bruning JC. CNS leptin and insulin action in the control of energy homeostasis. *Ann. NY Acad. Sci.* 1212, 97–113 (2010).

112 Thaler JP, Schwartz MW. Minireview: inflammation and obesity pathogenesis: the hypothalamus heats up. *Endocrinology* 151(9), 4109–4115 (2010).

113 Post RM. Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. *Am. J. Psychiatr.* 149(8), 999–1010 (1992).

114 Tsujino N, Sakurai T. Orexin/hypocretin: a neuropeptide at the interface of sleep, energy homeostasis, and reward system. *Pharmacol. Rev.* 61(2), 162–176 (2009).

▪ **Comprehensive review of the various brain functions of orexin.**

115 Poli F, Plazzi G, Di Dalmazi G *et al.* Body mass index-independent metabolic alterations in narcolepsy with cataplexy. *Sleep* 32(11), 1491–1497 (2009).

116 Elias CF, Saper CB, Maratos-Flier E *et al.* Chemically defined projections linking the mediobasal hypothalamus and the lateral hypothalamic area. *J. Comp. Neurol.* 402(4), 442–459 (1998).

117 Date Y, Ueta Y, Yamashita H *et al.* Orexins, orexigenic hypothalamic peptides, interact with autonomic, neuroendocrine and neuroregulatory systems. *Proc. Natl Acad. Sci. USA* 96(2), 748–753 (1999).

118 Yamanaka A, Muraki Y, Tsujino N, Goto K, Sakurai T. Regulation of orexin neurons by the monoaminergic and cholinergic systems. *Biochem. Biophys. Res. Commun.* 303(1), 120–129 (2003).

119 Narita M, Nagumo Y, Hashimoto S *et al.* Direct involvement of orexinergic systems in the activation of the mesolimbic dopamine pathway and related behaviors induced by morphine. *J. Neurosci.* 26(2), 398–405 (2006).

120 Kuwaki T. Orexin links emotional stress to autonomic functions. *Auton. Neurosci.* 161(1–2), 20–27 (2011).

121 Lutter M, Krishnan V, Russo SJ, Jung S, McClung CA, Nestler EJ. Orexin signaling mediates the antidepressant-like effect of calorie restriction. *J. Neurosci.* 28(12), 3071–3075 (2008).

122 Oxenkrug GF. Metabolic syndrome, age-associated neuroendocrine disorders, and dysregulation of tryptophan–kynurenine metabolism. *Ann. NY Acad. Sci.* 1199, 1–14 (2010).

123 Raison CL, Dantzer R, Kelley KW *et al.* CSF concentrations of brain tryptophan and kynurenines during immune stimulation with IFN-α: relationship to CNS immune responses and depression. *Mol. Psychiatr.* 15(4), 393–403 (2010).

124 Delgado PL, Charney DS, Price LH, Aghajanian GK, Landis H, Heninger GR. Serotonin function and the mechanism of antidepressant action. Reversal of antidepressant-induced remission by rapid depletion of plasma tryptophan. *Arch. Gen. Psychiatr.* 47(5), 411–418 (1990).

125 Moore P, Landolt HP, Seifritz E *et al.* Clinical and physiological consequences of rapid tryptophan depletion. *Neuropsychopharmacology* 23(6), 601–622 (2000).

126 Cowen PJ, Parry-Billings M, Newsholme EA. Decreased plasma tryptophan levels in major depression. *J. Affect. Disord.* 16(1), 27–31 (1989).

127 Demyer MK, Shea PA, Hendrie HC, Yoshimura NN. Plasma tryptophan and five other amino acids in depressed and normal subjects. *Arch. Gen. Psychiatr.* 38(6), 642–646 (1981).

128 Parker G, Brotchie H. Mood effects of the amino acids tryptophan and tyrosine: 'food for thought' III. *Acta Psychiatr. Scand.* doi: 10.1111/j.1600-0447.2011.01706.x (2011) (Epub ahead of print).

129 Oxenkrug GF. Interferon-γ-inducible kynurenines/pteridines inflammation cascade: implications for aging and aging-associated psychiatric and medical disorders. *J. Neural Transm.* 118(1), 75–85 (2011).

130 O'Connor JC, Lawson MA, Andre C *et al.* Induction of IDO by bacille Calmette–Guerin is responsible for development of murine depressive-like behavior. *J. Immunol.* 182(5), 3202–3212 (2009).

131 Capuron L, Ravaud A, Neveu PJ, Miller AH, Maes M, Dantzer R. Association between decreased serum tryptophan concentrations and depressive symptoms in cancer patients undergoing cytokine therapy. *Mol. Psychiatr.* 7(5), 468–473 (2002).

132 Breum L, Rasmussen MH, Hilsted J, Fernstrom JD. Twenty-four-hour plasma tryptophan concentrations and ratios are below normal in obese subjects and are not normalized by substantial weight reduction. *Am. J. Clin. Nutr.* 77(5), 1112–1118 (2003).

133 Brandacher G, Hoeller E, Fuchs D, Weiss HG. Chronic immune activation underlies morbid obesity: is IDO a key player? *Curr. Drug. Metab.* 8(3), 289–295 (2007).

134 Surendar J, Mohan V, Rao MM, Babu S, Aravindhan V. Increased levels of both Th1 and Th2 cytokines in subjects with metabolic syndrome (CURES-103). *Diabet. Technol. Ther.* 13(4), 477–482 (2011).

135 Brandacher G, Winkler C, Aigner F *et al.* Bariatric surgery cannot prevent tryptophan depletion due to chronic immune activation in morbidly obese patients. *Obes. Surg.* 16(5), 541–548 (2006).

136 Hennings JM, Ising M, Grautoff S, Himmerich H, Pollmacher T, Schaaf L. Glucose tolerance in depressed inpatients, under treatment with mirtazapine and in healthy controls. *Exp. Clin. Endocrinol. Diabet.* 118(2), 98–100 (2010).

137 Okamura F, Tashiro A, Utumi A *et al.* Insulin resistance in patients with depression and its changes during the clinical course of depression: minimal model analysis. *Metabolism* 49(10), 1255–1260 (2000).

138 Wagner J, Allen NA, Swalley LM, Melkus GD, Whittemore R. Depression, depression treatment, and insulin sensitivity in adults at risk for Type 2 diabetes. *Diabet. Res. Clin. Pract.* 86(2), 96–103 (2009).

139 Weber-Hamann B, Gilles M, Lederbogen F, Heuser I, Deuschle M. Improved insulin sensitivity in 80 nondiabetic patients with MDD after clinical remission in a double-blind, randomized trial of amitriptyline and paroxetine. *J. Clin. Psychiatr.* 67(12), 1856–1861 (2006).

140 Eissa Ahmed AA, Al-Rasheed NM. Antidepressant-like effects of rosiglitazone, a PPARγ agonist, in the rat forced swim and mouse tail suspension tests. *Behav. Pharmacol.* 20(7), 635–642 (2009).

141 Kemp DE, Ismail-Beigi F, Calabrese JR. Antidepressant response associated with pioglitazone: support for an overlapping pathophysiology between major depression and metabolic syndrome. *Am. J. Psychiatr.* 166(5), 619 (2009).

142 Rasgon NL, Kenna HA, Williams KE, Powers B, Wroolie T, Schatzberg AF. Rosiglitazone add-on in treatment of depressed patients with insulin resistance: a pilot study. *Scientific World J.* 10, 321–328 (2010).

143 Eller T, Vasar V, Shlik J, Maron E. Pro-inflammatory cytokines and treatment response to escitalopram in major depressive disorder. *Prog. Neuropsychopharmacol. Biol. Psychiatr.* 32(2), 445–450 (2008).

144 Lanquillon S, Krieg JC, Bening-Abu-Shach U, Vedder H. Cytokine production and treatment response in major depressive disorder. *Neuropsychopharmacology* 22(4), 370–379 (2000).

145 Narita K, Murata T, Takahashi T, Kosaka H, Omata N, Wada Y. Plasma levels of adiponectin and tumor necrosis factor-α in patients with remitted major depression receiving long-term maintenance antidepressant therapy. *Prog. Neuropsychopharmacol. Biol. Psychiatr.* 30(6), 1159–1162 (2006).

146 Tyring S, Gottlieb A, Papp K *et al.* Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised Phase III trial. *Lancet* 367(9504), 29–35 (2006).

147 Ertenli I, Ozer S, Kiraz S *et al.* Infliximab, a TNF-α antagonist treatment in patients with ankylosing spondylitis: the impact on depression, anxiety and quality of life level. *Rheumatol. Int.* doi: 10.1007/s00296-010-1616-x (2010) (Epub ahead of print).

148 Stanley TL, Zanni MV, Johnsen S *et al.* TNF-α antagonism with etanercept decreases glucose and increases the proportion of high molecular weight adiponectin in obese subjects with features of the metabolic syndrome. *J. Clin. Endocrinol. Metab.* 96(1), E146–E150 (2011).

149 Laaksonen DE, Lindstrom J, Lakka TA *et al.* Physical activity in the prevention of Type 2 diabetes: the Finnish diabetes prevention study. *Diabetes* 54(1), 158–165 (2005).

150 Zanuso S, Jimenez A, Pugliese G, Corigliano G, Balducci S. Exercise for the management of Type 2 diabetes: a review of the evidence. *Acta Diabetol.* 47(1), 15–22 (2010).

151 Trivedi MH, Greer TL, Grannemann BD *et al.* TREAD: Treatment with Rxercise Augmentation for Depression: study rationale and design. *Clin. Trials* 3(3), 291–305 (2006).

152 Trivedi MH, Greer TL, Grannemann BD, Chambliss HO, Jordan AN. Exercise as an augmentation strategy for treatment of major depression. *J. Psychiatr. Pract.* 12(4), 205–213 (2006).

153 Dunn AL, Jewell JS. The effect of exercise on mental health. *Curr. Sports Med. Rep.* 9(4), 202–207 (2010).

154 Trivedi MH, Greer TL, Church TS *et al.* Exercise as an augmentation treatment for nonremitted major depressive disorder: a randomized, parallel dose comparison. *J. Clin. Psychiatr.* 72(5), 677–684 (2011).