HHS Public Access

Author manuscript

Am J Psychiatry. Author manuscript; available in PMC 2019 May 13.

Published in final edited form as:

Am J Psychiatry. 2015 November 01; 172(11): 1075–1091. doi:10.1176/appi.ajp.2015.15020152.

Inflammation: Depression Fans the Flames and Feasts on the Heat

Janice K. Kiecolt-Glaser, PhD, **Heather M. Derry, MA**, and **Christopher P. Fagundes, PhD**

Institute for Behavioral Medicine Research, The Ohio State University College of Medicine, Columbus, USA (Kiecolt-Glaser, Derry); Department of Psychiatry and Behavioral Health, The Ohio State University College of Medicine, Columbus, USA (Kiecolt-Glaser); Department of Health Disparities Research, University of Texas MD Anderson Cancer Center, Houston, USA (Fagundes)

Abstract

Depression and inflammation fuel one another. Inflammation plays a key role in depression's pathogenesis for a subset of depressed individuals; depression also primes larger cytokine responses to stressors and pathogens that do not appear to habituate. Accordingly, treatment decisions may be informed by attention to questions of 'how' (pathways) and 'for whom' (predispositions) these links exist, which are the focus of the current article. When combined with predisposing factors (moderators such as childhood adversity and obesity), stressors and pathogens can lead to exaggerated or prolonged inflammatory responses. The resulting sickness behaviors (e.g., pain, disturbed sleep), depressive symptoms, and negative health behaviors (e.g., poor diet, a sedentary lifestyle) may act as mediating pathways that lead to further unrestrained inflammation and depression. Depression, childhood adversity, stressors, and diet can all influence the gut microbiome and promote intestinal permeability, another pathway to enhanced inflammatory responses. Larger, more frequent, or more prolonged inflammatory responses could have negative mental and physical health consequences. In clinical practice, inflammation provides a guide to potential targets for symptom management by signaling responsiveness to certain therapeutic strategies. For example, a theme across research with cytokine antagonists, omega-3 polyunsaturated fatty acids, celecoxib, and exercise is that anti-inflammatory interventions have a substantially greater impact on mood among individuals with heightened inflammation. Thus, when inflammation and depression co-occur, treating them in tandem may enhance recovery and reduce risk of recurrence. The bidirectional links among depression, inflammation, and disease suggest that effective depression treatments could have a far-reaching impact on mood, inflammation, and health.

Keywords

depression; inflammation; cytokines; obesity; childhood adversity

*Corresponding Author: Janice K. Kiecolt-Glaser, Institute for Behavioral Medicine Research, The Ohio State University College of Medicine, 460 Medical Center Drive, Columbus, OH 43210, Janice.Kiecolt-Glaser@osumc.edu.

Depression and inflammation are intertwined, fueling and feeding off each other. This bidirectional loop in which depression facilitates inflammatory responses and inflammation promotes depression has clear health consequences. Heightened inflammation characterizes a number of disorders and systemic diseases including cardiovascular disease, diabetes, metabolic syndrome, rheumatoid arthritis, asthma, multiple sclerosis, chronic pain, and psoriasis; each of these also features an elevated risk for depression (1, 2).

Three meta-analyses have highlighted proinflammatory cytokine differences between patients with major depressive disorder (MDD) and controls including interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-α), IL-1β, the soluble IL-2 receptor (sIL2R), the IL-1 receptor antagonist (IL-1ra), and C-reactive protein (CRP) (3–5). The stronger associations in clinically-based samples compared to community samples provide evidence of dose-response relationships (3). Supporting a causal pathway, higher IL-6 and CRP predicted the subsequent development of depressive symptoms (6). Relatedly, prospective studies also showed that depression predicted later IL-6 and CRP (7–10).

The pediatric literature also demonstrates bidirectional pathways between inflammation and depression (11). Data from two population-based prospective studies provided evidence for depression-inflammation relationships early in life. Children with higher IL-6 at age 9 were more likely to be depressed at age 18 compared to those with low IL-6; importantly, IL-6 was measured prior to onset, thus suggesting that high IL-6 is indeed a risk factor (12). In another study with children who were 9, 11, or 13 years old at intake, depression predicted subsequent CRP, with higher CRP following multiple depressive episodes (7).

However, depression is complex, and inflammation may only contribute in a subpopulation. NHANES data provide a rough estimate of the prevalence of heightened inflammation among depressed people; 47% of those whose depression inventory scores were above the clinical threshold had a CRP ≥ 3.0 mg/L, and 29% had a CRP ≥ 5.0 mg/L (13). Raison and Miller (14) suggest that about a third of depressed patients have inflammatory values that are noticeably higher than the majority of nondepressed comparison subjects. Thus, inflammation is neither necessary nor sufficient to induce or sustain depression (14, 15), but it clearly plays an important role in a substantial subpopulation (16). It follows that positive clinical responses to anti-inflammatory interventions may only occur among the subset with heightened inflammation (17, 18). Accordingly, we address mechanistic pathways between depression and inflammation, and then turn to questions of ‘how’ (pathways) and ‘for whom’ (predispositions) these links exist, with a focus on integrating newer research relevant to MDD initiation, treatment response, and risk for recurrence (Figure 1).

Mechanistic Pathways

Cytokines induce depressive symptoms by impacting diverse mood-related processes. Elevated inflammatory signaling dysregulates neurotransmitter metabolism, impairs neuronal health, and alters neural activity in mood-relevant brain regions (2, 19).

Peripherally-released cytokines send signals via molecular, cellular, and neural routes, which ultimately reach the brain and enhance central nervous system (CNS) inflammation (2, 19,

20). Cytokines alter production, metabolism, and transport of neurotransmitters that synergistically affect mood, including dopamine, glutamate, and serotonin (21). For example, cytokines stimulate indoleamine 2,3-dioxygenase (IDO), an enzyme that impacts tryptophan metabolism. This well-established pathway promotes depression by simultaneously slowing serotonin production and enhancing levels of kynurenine, a tryptophan metabolite (22).

Inflammation also affects neuronal growth and survival. Cytokines contribute to oxidative stress, which damages glial cells in mood-relevant brain regions, such as the prefrontal cortex and amygdala (23). Cytokine-induced glutamate dysregulation can lead to excitotoxicity, thereby decreasing production of neurotrophic factors (e.g., brain-derived neurotrophic factor, BDNF) that typically support neuronal health, neuroplasticity, and neurogenesis (24). Notably, these neurotransmitter and cellular changes alter brain activity and neurocircuits underlying distress, motivation, and motor function (16, 19).

In addition to their effects on neural processes, cytokines promote dysregulated HPA axis functioning, a key characteristic of depression (25, 26). Abnormal glucocorticoid signaling can influence the maintenance and progression of depression (27). Briefly, glucocorticoids typically dampen inflammation via a negative feedback loop. However, inflammation can cause glucocorticoid resistance in immunocytes and their cellular targets by inducing MAP kinases c-jun N-terminal kinase (JNK) and p38 (1). In this way, cytokine signal transduction pathways (e.g., nuclear factor- kB, NF-kB) disrupt glucocorticoid receptor function and expression, leading to unrestrained inflammatory responses that could further fuel depressive symptoms (2, 26, 28). Cytokine-dependent glucocorticoid receptor resistance decreases inhibitory feedback on production of CRH and cytokines, intensifying the stress-response system (29). The glucocorticoid receptor protein is abundantly expressed throughout the main neuronal subregions of the human hippocampus. BDNF functions as a powerful modulator of structural plasticity in the hippocampus and mediates protective influences by enhancing neuronal survival (30). Sustained GC exposure leads to dendritic atrophy in hippocampal subfields and decreases neuronal cell survival by evoking a decline in BDNF expression in hippocampal and cortical regions (31, 32).

Inflammation may impact people differently depending on their individual physiology such that some people have bodily systems that protect them from developing inflammatory based depression, while other people do not. Mechanistically, even lower levels of inflammation could be depressogenic among vulnerable individuals; Raison and Miller (14) call this phenomenon “immune response element amplification.” These might include lower parasympathetic activity, poorer sensitivity to glucocorticoid inhibitory feedback, lower BDNF production, larger responses to social threat in the anterior cingulate cortex or amygdala, and smaller hippocampal volume. Indeed, these are all MDD correlates that would impact sensitivity to inflammatory stimuli’s depressogenic consequences.

Traveling Companions: Inflammation and Depression

The bidirectional links between inflammation and depression have received considerable attention (1, 2, 16, 33–36). Heightened inflammation alerts the (CNS to induce or intensify

"sickness behaviors," including negative mood, fatigue, anhedonia, increased pain sensitivity, loss of appetite, and cognitive deficits, a cluster of symptoms resembling human depression (29, 34, 37). For example, administration of cytokines, endotoxin, or vaccines worsened mood, fatigue, and pain sensitivity, and boosted proinflammatory cytokine production in healthy volunteers (34).

Inflammatory mediators can also induce clinical depression, bolstering support for inflammation's role in depression's pathophysiology. These effects can be substantial; for example, cytokine therapies, used for treating some cancers and chronic viral infections, provoke the onset of MDD in up to 45% of patients (21, 38–40). Most people who receive interferon alpha (IFN-α) treatment develop neurovegetative symptoms including fatigue, sleep problems, anorexia, and psychomotor retardation; these symptoms persist throughout treatment (21). However, mood and cognitive symptoms develop primarily in vulnerable patients, including those with a mood disorder history or higher initial levels of depressive symptoms, chronic inflammatory exposure, higher baseline levels of inflammation, or genetic polymorphisms associated with risk for depression or inflammation (21, 38, 39).

Antidepressant medication responsiveness may be poorer among MDD patients with heightened plasma inflammatory markers, as well as those with polymorphisms in inflammation-related genes and proinflammatory gene expression profiles (17, 41–51). In a provocative trial with 60 MDD patients who were at least moderately medication resistant, the efficacy of the monoclonal antibody infliximab, a TNF-α antagonist, was assessed (17). Despite the absence of any overall benefit for infliximab vs. placebo, patients with high baseline CRP had substantially greater reductions in depressive symptoms than those with low CRP.

The Gut Microbiota, Inflammation, and Depression

The gut-brain axis involves bidirectional communication between the CNS and gastrointestinal tract via neurocrine and endocrine signaling pathways (52). Physical and psychological stressors can alter the gut microbiota's composition and metabolic activities, and signals produced by the gut microbiota can, in turn, impact the brain and emotional responses (52). Alterations in the gut microbiota shape physiology through contributions to inflammation, obesity, and mood, among many others (53). For example, both rodent and human studies provide causal evidence linking obesity and the gut microbiome (53).

Depression can promote intestinal permeability, i.e., greater inflammation-inducing endotoxin translocation, described as a "leaky gut." Indeed, depressed patients had higher antibody against gut bacteria than controls (54). In another study, MDD patients had elevated expression of 16S rDNA, a marker of bacterial translocation, compared to nondepressed controls, and the magnitude was correlated with depressive symptom severity (55). Among alcohol-dependent patients, those with higher depression, anxiety, and craving symptoms also had greater gut permeability and gut-bacterial dysbiosis than those with normal gut permeability (56).

Targeting the gut-brain axis may offer novel treatment options with benefits mediated through the vagus nerve, spinal cord, or neuroendocrine system (57). Diet plays a key role in the gut's microbiota composition, and thus represents one potential therapeutic avenue, as do supplements (particularly probiotics and prebiotics), and medications, including antibiotics (52). In rats, probiotic pretreatment attenuated gut leakiness following a restraint stressor (58). Limited human data suggest that selected probiotics may reduce depressive symptoms due to their anti-inflammatory properties as well as their ability to reduce HPA axis activity (57).

Rodent studies show how the microbiota's composition has potent effects on brain biochemistry and behavior early in development (53). Early life maternal separation in mice can produce both long-lasting changes in HPA stress responses as well as persistent microbiome alterations (57), evidence for one pathway through which early adversity induces depression and inflammatory responses in adults.

Early Adversity

Adults who experienced abuse or neglect as children are more likely to develop psychiatric disorders (59). Indeed, childhood maltreatment is a particularly potent risk factor for depression in adults, especially when individuals encounter stressful life events (2, 59). Early adversity also predicts a greater risk for recurrent, treatment-resistant depressive episodes (59).

Convergent evidence shows that childhood adversity can have longer-term inflammatory consequences (60–64). Among adults with MDD, those with a history of early maltreatment had higher CRP than those without a similar history (60). Additionally, early life adversity was still associated with heightened IL-6 and TNF-α among an older adult sample with a mean age of 70 (61). Adult survivors of childhood abuse also have maladaptive alterations in the HPA axis and autonomic stress responses compared to similar individuals without an abuse history (65). For example, those with a history of early life stress have lower heart rate variability, reflecting lower parasympathetic activity (62), which is linked to inflammation. Trauma survivors have enhanced glucocorticoid resistance and increased central corticotropin-releasing factor (CRF) activity, further supporting neuroendocrine stress response sensitization among those with early adversity (65). Furthermore, inflammation-relevant epigenetic alterations associated with early adversity include alterations in glucocorticoid receptor expression (62).

Early adversity can enhance inflammatory responsiveness to stressors. IL-6 levels rose higher after a laboratory stressor among those who were depressed and reported childhood trauma compared with those without a trauma history (66). These laboratory stress data parallel differences observed in response to daily stressors: IL-6 levels were 2.35 times greater among individuals with a childhood abuse history who experienced multiple stressors in the past 24 hours compared to participants with multiple daily stressors but no abuse history (67).

Sickness Behaviors: Paving the Way to Inflammation and Depression

Sickness behaviors serve an adaptive function by conserving energy during an acute illness (1). However, these symptoms can, in turn, fuel inflammation and depression, and thus it is not surprising that they can also predict treatment resistance and poorer treatment outcomes (68).

Pain generates an inflammatory response (69, 70), and amplified pain sensitivity serves as an additional inflammatory source that in turn provokes depressive symptoms (71, 72). The association appears to be reciprocal: greater pain is associated with a higher prevalence of depression, and improvements in depression are correlated with declines in pain (73). Pain increases the risk for depression's recurrence by worsening subthreshold depressive symptoms (74). Greater pain severity is associated with poorer treatment outcomes in depression, including poorer responses to antidepressant medications (73, 74).

Disturbed sleep, a cardinal symptom of depression, also has a contributory role, producing a twofold increased risk for depression (75). Sleep loss stimulates production of proinflammatory cytokines and cellular inflammatory signaling, thus facilitating depression (75). In turn, heightened inflammation disrupts sleep regulation (76, 77); pharmacologic cytokine blockers can normalize sleep (75). In a longitudinal study, sleep disturbance increased risk for systemic inflammation at the five-year follow-up (78).

Thus, sleep and pain are additional, independent accelerators for depression and inflammation that also act in tandem, building on each other. Disturbed sleep exacerbates pain and fatigue (79). Conversely, pain clearly impairs sleep (79). Changes in appetite, another key symptom of both inflammation and depression, can be triggered by sleep loss and fatigue (76, 79). The poorer mood-related dietary choices that typically follow serve to promote inflammation and depression.

Diet as a Road to Depression and Inflammation

Observational studies have linked healthier diets with a lower risk for depression (80, 81). Prospective studies suggest that healthier diets offer some protection against the development of both depressive symptoms and depressive disorders (82, 83).

In addition to altering the risk for depression, diet quality also influences inflammation. Metabolic syndrome patients who were randomized to a Mediterranean-style diet for two years had significant reductions in CRP and IL-6 (84). In a twin study, adherence to a Mediterranean diet was associated with lower IL-6, and results were not a function of shared environmental variance or genetic factors (85).

An innovative prospective study addressed the question of whether a Mediterranean-style diet lowered the risk of increased inflammation over time among older adults with depressive symptoms at study entry (86). At the six year follow-up, the average IL-6 increase was larger among depressed participants who had not followed a Mediterranean-style diet than in all other groups; in contrast, IL-6 did not change among those who were

depressed but followed a Mediterranean-style diet, suggesting that the healthier diet buffered the impact of depression on inflammation (86).

To assess the question of whether inflammation serves as a mediator between diet and depression, researchers employed an empirically-derived inflammatory dietary pattern score related to CRP, IL-6, and TNF-RII (87). Using food frequency questionnaire data collected 6 times over 18 years in the large Nurses' Health Study, the risk for depression increased with higher inflammatory scores among women who were not depressed at baseline (87).

Along with diet quality, quantity and timing matter. Caloric restriction produces powerful anti-inflammatory effects over periods of months to years (88). Intriguingly, caloric restriction is also strongly antidepressant in rodent depression models (89).

Even intermittent fasting or time-restricted feeding can reduce inflammation. Comparisons of IL-6 and CRP in observant Muslims one week before the month of Ramadan (no eating or drinking during daylight), during the final week, and 20 days after Ramadan showed that daytime fasting decreased IL-6 and CRP levels by about 50% compared to pre-Ramadan values, a dramatic reduction in the absence of weight change; a non-fasting group assessed at the same times showed no IL-6 or CRP changes (90). Time-restricted feeding also reduced inflammation in mice (91). Additionally, TNF-α and IL-1ra responses to endotoxin were attenuated in rats that fasted for 48 hours compared to non-fasted rats (92).

Short-term fasting can also benefit mood. Clinical observational studies have reported reductions in depressive symptoms that appear between days 2–7 of fasting (93). Accordingly, anorexia may serve an adaptive function in both clinical depression and inflammation-induced sickness behavior by reducing inflammation (94).

Thus, cross-sectional, prospective, and RCT research demonstrates how diet quality, quantity, and timing influence both depression and inflammation. Diet-related inflammation can promote depression—and diet-linked depression, in turn, heightens inflammation. One dietary component, fish oil, has generated considerable interest.

Omega-3 Polyunsaturated Fatty Acids (PUFAs)

Fish oil is the prime source for two key omega-3 PUFAs, eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA). Patients with depression have, on average, lower plasma levels of omega-3 PUFAs than nondepressed controls; furthermore, there are relationships within these populations between depressive symptom severity and lower omega-3 PUFA plasma levels (95, 96).

Five RCT meta-analyses have reached different conclusions about omega-3 PUFA's efficacy for treatment of depression. The first concluded that omega-3 PUFA supplementation benefited clinically depressed individuals, but not those with less severe depressed mood (97). In contrast, a second that focused only on MDD argued that omega-3 PUFAs had a small, non-significant effect (98). A third determined that omega-3 supplementation was effective in both MDD patients as well as those with subclinical depressive symptoms (99). Two further meta-analyses suggested that EPA, not DHA, was the key PUFA related to

efficacy in treating depression (100, 101), consistent with the evidence for EPA's stronger anti-inflammatory properties compared with DHA (102, 103).

Epidemiological and observational studies have demonstrated that lower omega-3 PUFA levels are associated with higher serum IL-6, TNF-α, and CRP (104–106). In contrast, most RCTs have not produced reliable serum cytokine changes (107); the strongest support for the omega-3 PUFA's anti-inflammatory properties in vivo has come from studies with older, hypertriglyceridemic or diabetic individuals with elevated inflammatory markers(102), as well as an RCT with sedentary, overweight middle-aged and older adults (108).

However, inflammatory challenge studies provide compelling evidence of protective effects. The omega-3 PUFAs attenuated both endotoxin and IFN-α-induced inflammation and sickness behavior in rodents and humans (109–113). In an RCT in which patients received EPA, DHA, or placebo for only two weeks prior to initiation of IFN-α treatment, EPA significantly reduced the incidence of IFN-α-induced depression, and both EPA and DHA substantially delayed MDD onset (42). EPA was more effective than DHA, consistent with two meta-analyses (100, 101). Importantly, the population was subjected to an inflammatory insult that carried a high risk for depression, providing a backdrop that highlighted the reduction in risk.

Both the results of inflammatory challenge studies and meta-analyses suggest that heightened pretreatment inflammation and/or clinical depression enhance the odds of demonstrating omega-3 PUFA-related improvements. The IFN-α RCT clearly identified important benefits of omega-3 PUFA treatment (42).

Exercise

Considerable evidence supports the value of exercise in treating depression and preventing its onset (76, 114, 115). Physically active individuals have lower levels of inflammatory biomarkers than their sedentary counterparts (116); reductions in inflammation provide one potential explanation for exercise's antidepressant benefits (117).

In the TREAD study, MDD patients who did not achieve remission following an adequate trial of a single SSRI were randomized to two exercise augmentation groups (118). The higher-dose exercise augmentation group had a 28.3% remission rate, compared to 15.5% for the lower-dose group, and effect sizes were the same or larger than those observed in pharmacologic treatment augmentation studies (118). Although four cytokines did not change significantly during the 12 week intervention, higher pre-intervention TNF-α levels were associated with larger decreases in depressive symptoms, and changes in IL-1β were correlated with changes in depressive symptoms (119).

These TREAD study data are consistent with a paradox in the exercise literature. Despite the fact that observational studies reliably show that more active people have lower inflammation than their sedentary counterparts (117, 120), RCT data demonstrating that exercise training reduces inflammation are sparse and inconsistent (121, 122). In fact, two reviews concluded that exercise RCTs produce little or no change in inflammatory markers in healthy people who do not lose weight (121, 122).

However, just as higher pretreatment inflammation predicted a better response to a TNF-α blocker (17), the TREAD study data suggest that exercise's antidepressant effects may be greater among those who have higher pretreatment inflammation (119). Similarly, the IFN-α RCT demonstrated that omega-3 PUFA treatment was efficacious when individuals faced a major inflammatory challenge. In each case, the initial inflammatory profile made a difference.

Obesity

Depression promotes obesity, and, in turn, obesity promotes depression (1, 123). Depressed people have a 58% increased risk of becoming obese; the risk for developing depression over time is 55% among persons with obesity (123). Longitudinal studies suggest that depressive symptoms promote the development of the metabolic syndrome, which has central obesity as its cornerstone (124, 125).

Depression and obesity have key inflammatory mechanisms in common. Obesity has been characterized as a state of chronic inflammation due to elevated plasma IL-6, TNF-α, and CRP levels (1). What is more, the pathways are bidirectional; visceral adipose tissue's secretion of proinflammatory cytokines can function as a stimulus for HPA axis activation, such that hypercortisolemia enhances adipocyte accumulation, and vice versa (124).

Adiposity appears to fuel inflammatory stress responses. Women with greater central adiposity produced larger inflammatory responses to a laboratory stress task than their leaner counterparts (126). Other authors reported that both higher BMI and greater body fat were associated with larger stress-induced IL-6 responses that did not habituate with repeated stress (127).

Interactive influence of obesity and age in mice.

A recent mouse study highlighted the joint impact of obesity and age on inflammatory responsiveness. Because the decrease in lean body mass and the increase in adiposity that occurs with advancing years plays a role in the age-associated increases in inflammation (128), it was not surprising that immunotherapy induced a lethal cytokine storm in aged mice, but not young mice (129). However, in young *obese* mice, immunotherapy induced the same cytokine overresponsiveness, organ pathology, and mortality as seen in the aged mice (129).

Together, these convergent lines of evidence show how stress and depression can act synergistically with obesity to potentiate larger inflammatory responses that could, in turn, further fuel depression. In addition to higher baseline levels of inflammation, these data suggest that obesity also confers risk by generating larger inflammatory responses to stress or pathogens. Higher baseline inflammation provides an important substrate for subsequent exaggerated inflammatory responses to challenge.

Priming: Cross-Sensitization Among Cytokines, Stressors, and Depression

In addition to early life stress, other major life stressors function as proximal risk factors for MDD (2). Both currently and formerly depressed people experience more major and minor stressors than those who do not have a depression history, and current and past depression can also boost emotional reactivity to stressors (130–132). Furthermore, depression can damage close personal relationships, a key stress buffer; both current and formerly depressed men and women had poorer family functioning than those who had no depression history, even years after their depression had remitted (133). A history of depression may indicate a high-risk phenotype for stress responsiveness (134). Accordingly, a past or current mood disorder could act synergistically with stress to heighten inflammation.

Cross-sensitization in rodents and monkeys.

The close tie between depression and stress has implications for inflammation; cross-sensitization between stressors and cytokines has been well-documented in rats (135, 136). For example, exposure to a novel environment, foot or tail shock, or even exposure to conditioned stimuli that were present during foot shock all served to enhance IL-6 production (70, 135). Furthermore, rats that had previously been stressed produced larger and more rapid proinflammatory responses to a bacterial endotoxin than rats without a prior stress exposure (135).

The rats' endotoxin exposure mimics the immune challenges that occur frequently in daily life. For example, high fat meals can provoke mild postprandial endoxemia (137, 138), as well as alterations in gut microbiota and intestinal permeability (139).

These data are important because the physiological systems that respond to endotoxin also respond to behavioral challenges, and this shared responsivity is particularly detrimental when endotoxin exposure occurs in proximity to psychological stress (140). In rodents, when endotoxin was paired with stressors such as tail shock or restraint, it synergistically increased production of proinflammatory cytokines, exceeding the effect of endotoxin or the stressor alone (141). The situational context also substantially affected behavioral and immunological responses to low dose endotoxin in rhesus monkeys; the potency of the stressor influenced the magnitude and nature of endotoxin responses (140).

Recent mouse studies provide provocative evidence that higher IL-6 production may influence behavioral responses to social stress (48). Both *in vivo* and *in vitro* IL-6 responses predicted subsequent behavioral responses to repeated social defeat. Mice with larger IL-6 responses to initial aggressor exposure later displayed a stress-susceptible behavioral phenotype (depressive-like behavior) and more persistent stress-related IL-6 elevations (48). Those with smaller initial IL-6 responses were more likely to display subsequent resilient or dominant behaviors. There were also pre-existing immune differences in stimulated IL-6 production between mice that would later display stress-susceptible versus resilient behavioral profiles. In further studies a pharmacologic IL-6 blockade prevented the development of social avoidance behavior, highlighting its key role (48).

Accordingly, pre-existing individual differences in IL-6 responsivity predict stress vulnerability (48). Importantly, because these differences occurred within an inbred, genetically similar strain, both epigenetic and environmental factors (e.g., parental transmission of stress sensitivity, differences in the stability of the home cage's social hierarchy, or postnatal microbial exposures) likely played a prominent role in developing these profiles (142–144).

Depression primes inflammatory responsiveness.

In accord with the animal literature, human studies show that depression primes inflammatory responses, promoting larger cytokine increases in reaction to stressors and pathogens. For example, mild depressive symptoms were associated with amplified and prolonged inflammatory responses following influenza vaccination among older adults as well as pregnant women (145, 146). Among women who had just given birth, those who had a lifetime MDD history showed greater increases in both serum IL-6 and the soluble IL-6 receptor after delivery than women without a depression history (147). Similarly, MDD patients had larger increases in inflammatory markers than non-depressed controls in response to a laboratory stressor (148, 149). In another study individuals with more depressive symptoms had larger stress-induced increases in IL-6 following laboratory stressors than those with fewer depressive symptoms (150).

Studies that have addressed the impact of repeated laboratory stressors on IL-6 production do not show evidence of habituation (127, 151). Thus, if both currently and formerly depressed people experience more stressors than those without a history (130–132), they would likely continue to experience repeated exaggerated inflammatory responses.

Just as individual differences in IL-6 responsivity predict stress vulnerability in mice, the IL-6 overresponsiveness among people with depression, childhood adversity, and obesity also reflects risk. Larger, more frequent, or more prolonged inflammatory responses have negative mental and physical health consequences.

Assessing Inflammation in Research and Clinical Practice

Inflammation signals responsiveness to certain therapies and provides a guide to potential targets for clinical symptom management. For example, a meta-analysis revealed that nonsteroidal anti-inflammatory drugs (NSAIDs) reduced depressive symptoms compared to placebo, particularly the selective COX-2 inhibitor celecoxib; patients with higher inflammation benefited most (152). Similarly, a clear theme across research with omega-3 PUFAs, exercise, and cytokine antagonists is that anti-inflammatory interventions have a substantially greater impact on mood among individuals with heightened inflammation. Higher CRP was associated with a better response to escitalopram than nortriptyline (153). The antidepressant effects of anti-inflammatories may be magnified among patients with comorbid pain-related or inflammatory disorders -- a very wide spectrum from psoriasis to cardiovascular disease to obesity. Furthermore, individuals who have relevant inflammatory genetic polymorphisms or gene expression profiles may be more responsive to these treatments (38, 39, 46, 49, 109, 154). It follows that substantial inflammatory changes (and

benefits) may not be observed among those with lower inflammation who undergo the same treatment.

Indeed, highlighting the importance of heightened inflammation for treatment choice, patients with lower inflammation who received a placebo improved more than patients assigned to active treatment in both infliximab and omega-3 trials (17, 18). These findings led to the suggestion that anti-inflammatory therapy might be harmful for patients without inflammation-driven MDD (17, 18).

Identification of patients who can benefit from anti-inflammatory interventions is clearly important. Table 1 lists risk factors for heightened inflammation, an indirect way to evaluate a patient's inflammatory phenotype.

For objective confirmation, the optimal strategy would be to determine treatment based on a set of biomarkers, with IL-6, TNF-α, and CRP having the strongest relationships with depression (3, 4). Differences in inflammatory patterns are likely, given the heterogeneity of the MDD population (155), and thus multiple biomarkers could provide a clearer picture of inflammatory status than a single assay, facilitating identification of the best candidates for anti-inflammatory interventions (18). For example, in an omega-3 trial, patients with high values on any one of five biomarkers were more responsive to EPA than to placebo, and the EPA-placebo differences were larger among those who had multiple heightened inflammatory markers (18). After identification of anti-inflammatory treatment candidates, additional inflammatory assessments can provide useful treatment response data.

For routine clinical use, a biomarker needs to provide accurate and reproducible data with well-validated norms (156). Hospital labs need standardized assays that provide replicable data across sites (156). CRP meets these criteria, but none of the cytokines do, limiting their utility for clinical practice at present, despite their obvious value (Table 2).

Anti-inflammatory treatment trials should preselect patients with heightened inflammation, and routinely assess inflammatory change (157). Surprisingly, in anti-inflammatory depression trials to date, heightened inflammation has not been part of the inclusion criteria (157). Using baseline inflammation to predict treatment response has provided provocative data, substantially expanding our understanding of who may benefit (17, 18), a worthwhile approach for future studies. In addition, researchers should examine the extent of inflammatory change and relate it to changes in depression to better understand how lowering inflammation influences depression.

Inflammation's Implications for MDD Treatment

Inflammation is not ubiquitous among people with depression, but when the two conditions co-occur, treating inflammation in tandem with depression can enhance recovery and reduce risk of recurrence. Pharmacological interventions for inflammation in depression supported by research studies are currently available (Table 3). A meta-analysis of the effects of anti-depressant medication on cytokines showed an average 50% reduction in depressive symptoms across antidepressants, but only SSRIs appeared to affect cytokine production (158).

Other interventions also can have benefit. Alcohol dependence and smoking are often comorbid with depression, and both have notable inflammatory consequences (159, 160); successful treatment of either can produce durable positive changes in both inflammation and depression. Lifestyle interventions (Table 3) including weight loss, dietary change, exercise, and some integrative medicine interventions can provide significant positive long-term benefits for patients who make an ongoing commitment.

Early interventions may be particularly important as a prophylaxis for those with predispositions toward depression and heightened inflammation. For example, inflammation was lower among 17-year-old youth who had been randomized to a brief family intervention eight years earlier compared to controls (161).

Cognitive-behavioral therapy's (CBT) efficacy in depression treatment is well-documented, and CBT may concurrently reduce inflammation (55, 162). In fact, one non-randomized trial found post-treatment decreases in an indicator of intestinal bacterial translocation as well as other inflammatory markers (55).

Both pain and disturbed sleep boost inflammation (69, 70, 75). Improvements in pain and sleep can enhance treatment outcomes and reduce the risk for recurrent depression (73–75). CBT has well-documented efficacy in the long-term remission of insomnia, and the addition of CBT for insomnia to a standard antidepressant regimen can produce a more rapid and longer-lasting remission than antidepressant treatment by itself (163). What is more, CBT for sleep disturbances can also reduce inflammation as well as depressive symptoms (164, 165). For example, CBT for insomnia produced greater positive change (improvements in sleep, daytime fatigue, depressive symptoms, and CRP) when compared to either Tai Chi or a sleep education control, and remission of insomnia was associated with lower CRP 16 months posttreatment (164).

CBT treatments for pain and pain-related problems have improved pain, physical disability, and mood across a range of chronic pain syndromes (166). In addition, CBT also produced larger decrements in IL-6 among rheumatoid arthritis patients compared to those randomized to mindfulness meditation or education-only (167).

We have highlighted the impact of over-responsiveness to daily stressors as an important pathway deserving of greater attention. Indeed, exaggerated stress-induced inflammatory responses mark a number of conditions that increase depression risk—e.g., fatigue, loneliness, lower subjective social status, smoking history, and marital discord (168–172). Accordingly, exaggerated inflammatory responses could reflect a greater risk for depression. Inflammatory overresponsiveness may stem in part from decreased glucocorticoid stress responses (26, 154, 168), and blunted glucocorticoid signaling in concert with increased NF-κB signaling may provide one functional fingerprint for chronic stress (154). Consequently, interventions targeting over-responsivity may benefit mood and inflammation. For example, cognitive-behavioral treatments that mute affective overresponsiveness to stressors could have important protective effects. In addition, some evidence suggests that meditation and yoga may reduce inflammatory responsiveness (173–175).

We have focused on how depression and inflammation are intertwined, but the implications extend to other health outcomes. Depression and inflammation are both linked to a number of disorders and systemic diseases, and the processes we described clearly impact those diseases as well. Depression has a substantial global disease burden, and excess depression-related mortality has been documented in multiple diseases (176). The bidirectional links among depression, inflammation, and disease make this research complex; they also suggest that effective depression treatments can have a far-reaching impact on mood, inflammation, and health.

Acknowledgments

Work on this manuscript was supported in part by NIH grants CA172296, CA186720, and CA186251, as well as a Pelotonia Predoctoral Fellowship from the Ohio State University Comprehensive Cancer Center. The sponsors had no role in the design and conduct of the studies reviewed, or preparation, review, or approval of the manuscript. The authors have no potential conflicts of interest. We thank Angie Leroy for producing the figure.

References

1. Shelton RC, Miller AH. Eating ourselves to death (and despair): The contribution of adiposity and inflammation to depression. Prog Neurobiol. 2010;91:275–299. [PubMed: 20417247]
2. Slavich GM, Irwin MR. From stress to inflammation and major depressive disorder: A social signal transduction theory of depression. Psychol Bull. 2014;140:774–815. [PubMed: 24417575]
3. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: A meta-analysis. Psychosom Med. 2009;71:171–186. [PubMed: 19188531]
4. Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, Lanctot KL. A meta-analysis of cytokines in major depression. Biol Psychiatry. 2010;67:446–457. [PubMed: 20015486]
5. Liu Y, Ho RC, 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. [PubMed: 21872339]
6. Valkanova V, Ebmeier KP, Allan CL. CRP, IL-6 and depression: A systematic review and meta-analysis of longitudinal studies. J Affect Disord. 2013;150:736–744. [PubMed: 23870425]
7. Copeland WE, Shanahan L, Worthman C, Angold A, Costello EJ. Cumulative depression episodes predict later C-reactive protein levels: A prospective analysis. Biol Psychiatry. 2012;71:15–21. [PubMed: 22047718]
8. Matthews KA, Schott LL, Bromberger JT, Cyranowski JM, Everson-Rose SA, Sowers M. Are there bi-directional associations between depressive symptoms and C-reactive protein in mid-life women? Brain Behav Immun. 2010;24:96–101. [PubMed: 19683568]
9. Deverts DJ, Cohen S, DiLillo VG, Lewis CE, Kiefe C, Whooley M, Matthews KA. Depressive symptoms, race, and circulating C-reactive protein: The Coronary Artery Risk Development in Young Adults (CARDIA) study. Psychosom Med. 2010;72:734–741. [PubMed: 20668285]
10. Duivis HE, de Jonge P, Penninx BW, Na BY, Cohen BE, Whooley MA. Depressive symptoms, health behaviors, and subsequent inflammation in patients with coronary heart disease: Prospective findings from the Heart and Soul Study. Am J Psychiatry. 2011;168:913–920. [PubMed: 21724664]
11. Kim JW, Szigethy EM, Melhem NM, Saghafi EM, Brent DA. Inflammatory markers and the pathogenesis of pediatric depression and suicide: A systematic review of the literature. J Clin Psychiatry. 2014;75:1242–1253. [PubMed: 25470085]
12. Khandaker GM, Pearson RM, Zammit S, Lewis G, Jones PB. Association of serum interleukin 6 and C-reactive protein in childhood with depression and psychosis in young adult life: A population-based longitudinal study. JAMA Psychiatry. 2014;71:1121–1128. [PubMed: 25133871]
13. Rethorst CD, Bernstein I, Trivedi MH. Inflammation, obesity, and metabolic syndrome in depression: Analysis of the 2009–2010 National Health and Nutrition Examination Survey (NHANES). J Clin Psychiatry. 2014;75:E1428–E1432. [PubMed: 25551239]

14. Raison CL, Miller AH. Is depression an inflammatory disorder? Current Psychiatry Reports. 2011;13:467–475. [PubMed: 21927805]
15. Glassman AH, Miller GE. Where there is depression, there is inflammation… Sometimes! Biol Psychiatry. 2007;62:280–281. [PubMed: 17678943]
16. Haroon E, Raison CL, Miller AH. Psychoneuroimmunology meets neuropsychopharmacology: Translational implications of the impact of inflammation on behavior. Neuropsychopharmacology. 2012;37:137–162. [PubMed: 21918508]
17. Raison CL, Rutherford RE, Woolwine BJ, Shuo C, Schettler P, Drake DF, Haroon E, Miller AH. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: The role of baseline inflammatory biomarkers. JAMA Psychiatry. 2013;70:31–41. [PubMed: 22945416]
18. Rapaport MH, Nierenberg AA, Schettler PJ, Kinkead B, Cardoos A, Walker R, Mischoulon D. Inflammation as a predictive biomarker for response to omega-3 fatty acids in major depressive disorder: A proof-of-concept study. Mol Psychiatry. 2015.
19. Miller AH, Haroon E, Raison CL, Felger JC. Cytokine targets in the brain: Impact on neurotransmitters and neurocircuits. Depress Anxiety. 2013;30:297–306. [PubMed: 23468190]
20. Irwin MR, Cole SW. Reciprocal regulation of the neural and innate immune systems. Nat Rev Immunol. 2011;11:625–632. [PubMed: 21818124]
21. Capuron L, Miller AH. Immune system to brain signaling: Neuropsychopharmacological implications. Pharmacol Ther. 2011;130:226–238. [PubMed: 21334376]
22. Dantzer R, O'Connor JC, Lawson MA, Kelley KW. Inflammation-associated depression: From serotonin to kynurenine. Psychoneuroendocrinology. 2011;36:426–436. [PubMed: 21041030]
23. Leonard B, Maes M. Mechanistic explanations how cell-mediated immune activation, inflammation and oxidative and nitrosative stress pathways and their sequels and concomitants play a role in the pathophysiology of unipolar depression. Neurosci Biobehav Rev. 2012;36:764–785. [PubMed: 22197082]
24. Eyre H, Baune BT. Neuroplastic changes in depression: A role for the immune system. Psychoneuroendocrinology. 2012;37:1397–1416. [PubMed: 22525700]
25. Stetler C, Miller GE. Depression and hypothalamic-pituitary-adrenal activation: A quantitative summary of four decades of research. Psychosom Med. 2011;73:114–126. [PubMed: 21257974]
26. Pace TWW, Hu F, Miller AH. Cytokine-effects on glucocorticoid receptor function: Relevance to glucocorticoid resistance and the pathophysiology and treatment of major depression. Brain Behav Immun. 2007;21:9–19. [PubMed: 17070667]
27. Conway-Campbell BL, Pooley JR, Hager GL, Lightman SL. Molecular dynamics of ultradian glucocorticoid receptor action. Mol Cell Endocrinol. 2012;348:383–393. [PubMed: 21872640]
28. Zunszain PA, Anacker C, Cattaneo A, Carvalho LA, Pariante CM. Glucocorticoids, cytokines and brain abnormalities in depression. Prog Neuropsychopharmacol Biol Psychiatry. 2011;35:722–729. [PubMed: 20406665]
29. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: When the immune system subjugates the brain. Nat Rev Neurosci. 2008;9:46–56. [PubMed: 18073775]
30. Suri D, Vaidya VA. Glucocorticoid regulation of brain-derived neurotrophic factor: Relevance to hippocampal structural and functional plasticity. Neuroscience. 2013;239:196–213. [PubMed: 22967840]
31. Tata DA, Anderson BJ. The effects of chronic glucocorticoid exposure on dendritic length, synapse numbers and glial volume in animal models: Implications for hippocampal volume reductions in depression. Physiology & Behavior. 2010;99:186–193. [PubMed: 19786041]
32. Anacker C, Cattaneo A, Luoni A, Musaelyan K, Zunszain PA, Milanesi E, Rybka J, Berry A, Cirulli F, Thuret S, Price J, Riva MA, Gennarelli M, Pariante CM. Glucocorticoid-related molecular signaling pathways regulating hippocampal neurogenesis. Neuropsychopharmacology. 2013;38:872–883. [PubMed: 23303060]
33. Raison CL, Miller AH. Malaise, melancholia and madness: The evolutionary legacy of an inflammatory bias. Brain Behav Immun. 2013;31:1–8. [PubMed: 23639523]

34. Raison CL, Capuron L, Miller AH. Cytokines sing the blues: Inflammation and the pathogenesis of depression. Trends Immunol. 2006;27:24–31. [PubMed: 16316783]
35. Miller AH, Maletic V, Raison CL. Inflammation and its discontents: The role of cytokines in the pathophysiology of major depression. Biol Psychiatry. 2009;65:732–741. [PubMed: 19150053]
36. Berk M, Williams LJ, Jacka FN, O'Neil A, Pasco JA, Moylan S, Allen NB, Stuart AL, Hayley AC, Byrne ML, Maes M. So depression is an inflammatory disease, but where does the inflammation come from? BMC Medicine. 2013;11.
37. DellaGioia N, Hannestad J. A critical review of human endotoxin administration as an experimental paradigm of depression. Neurosci Biobehav Rev. 2010;34:130–143. [PubMed: 19666048]
38. Bull SJ, Huezo-Diaz P, Binder EB, Cubells JF, Ranjith G, Maddock C, Miyazaki C, Alexander N, Hotopf M, Cleare AJ, Norris S, Cassidy E, Aitchison KJ, Miller AH, Pariante CM. Functional polymorphisms in the interleukin-6 and serotonin transporter genes, and depression and fatigue induced by interferon-alpha and ribavirin treatment. Mol Psychiatry. 2009;14:1095–1104. [PubMed: 18458677]
39. Udina M, Moreno-Espana J, Navines R, Gimenez D, Langohr K, Gratacos M, Capuron L, de la Torre R, Sola R, Martin-Santos R. Serotonin and interleukin-6: The role of genetic polymorphisms in IFN-induced neuropsychiatric symptoms. Psychoneuroendocrinology. 2013;38:1803–1813. [PubMed: 23571152]
40. Udina M, Castellvi P, Moreno-Espana J, Navines R, Valdes M, Forns X, Langohr K, Sola R, Vieta E, Martin-Santos R. Interferon-induced depression in chronic hepatitis C: A systematic review and meta-analysis. J Clin Psychiatry. 2012;73:1128–1138. [PubMed: 22967776]
41. Eller T, Vasar V, Shlik J, Maron E. Pro-inflammatory cytokines and treatment response to escitalopram in major depressive disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32:445–450. [PubMed: 17976882]
42. Su KP, Lai HC, Yang HT, Su WP, Peng CY, Chang JP, Chang HC, Pariante CM. Omega-3 fatty acids in the prevention of interferon-alpha-induced depression: Results from a randomized, controlled trial. Biol Psychiatry. 2014;76:559–566. [PubMed: 24602409]
43. O'Brien S, Scully P, Fitzgerald P, Scott L, Dinan T. Plasma cytokine profiles in depressed patients who fail to respond to selective serotonin reuptake inhibitor therapy. J Psychiatr Res. 2007;41:326–331. [PubMed: 16870211]
44. Carvalho LA, Torre JP, Papadopoulos AS, Poon L, Juruena MF, Markopoulou K, Cleare AJ, Pariante CM. Lack of clinical therapeutic benefit of antidepressants is associated overall activation of the inflammatory system. J Affect Disord. 2013;148:136–140. [PubMed: 23200297]
45. Yoshimura R, Hori H, Ikenouchi-Sugita A, Umene-Nakano W, Ueda N, Nakamura J. Higher plasma interleukin-6 (IL-6) level is associated with SSRI- or SNRI-refractory depression. Prog Neuropsychopharmacol Biol Psychiatry. 2009;33:722–726. [PubMed: 19332097]
46. Baune BT, Dannlowski U, Domschke K, Janssen DG, Jordan MA, Ohrmann P, Bauer J, Biros E, Arolt V, Kugel H, Baxter AG, Suslow T. The interleukin 1 beta (IL1B) gene is associated with failure to achieve remission and impaired emotion processing in major depression. Biol Psychiatry. 2010;67:543–549. [PubMed: 20044070]
47. Vogelzangs N, Comijs HC, Oude Voshaar RC, Stek ML, Penninx BWJH. Late-life depression symptom profiles are differentially associated with immunometabolic functioning. Brain Behav Immun. 2014;41:109–115. [PubMed: 24838021]
48. Hodes GE, Pfau ML, Leboeuf M, Golden SA, Christoffel DJ, Bregman D, Rebusi N, Heshmati M, Aleyasin H, Warren BL, Lebonte B, Horn S, Lapidus KA, Stelzhammer V, Wong EH, Bahn S, Krishnan V, Bolanos-Guzman CA, Murrough JW, Merad M, Russo SJ. Individual differences in the peripheral immune system promote resilience versus susceptibility to social stress. Proc Natl Acad Sci U S A. 2014.
49. Yu YW, Chen TJ, Hong CJ, Chen HM, Tsai SJ. Association study of the interleukin-1 beta (c-511t) genetic polymorphism with major depressive disorder, associated symptomatology, and antidepressant response. Neuropsychopharmacology. 2003;28:1182–1185. [PubMed: 12700687]
50. Cattaneo A, Gennarelli M, Uher R, Breen G, Farmer A, Aitchison KJ, Craig IW, Anacker C, Zunsztain PA, McGuffin P, Pariante CM. Candidate genes expression profile associated with

antidepressants response in the GENDEP study: Differentiating between baseline 'predictors' and longitudinal 'targets'. Neuropsychopharmacology. 2013;38:377–385. [PubMed: 22990943]

51. Wong ML, Dong C, Maestre-Mesa J, Licinio J. Polymorphisms in inflammation-related genes are associated with susceptibility to major depression and antidepressant response. Mol Psychiatry. 2008;13:800–812. [PubMed: 18504423]
52. Mayer EA, Knight R, Mazmanian SK, Cryan JF, Tillisch K. Gut microbes and the brain: Paradigm shift in neuroscience. J Neurosci. 2014;34:15490–15496. [PubMed: 25392516]
53. Cryan JF, Dinan TG. Mind-altering microorganisms: The impact of the gut microbiota on brain and behaviour. Nature Reviews Neuroscience. 2012;13:701–712. [PubMed: 22968153]
54. Maes M, Kubera M, Leunis JC. The gut-brain barrier in major depression: Intestinal mucosal dysfunction with an increased translocation of LPS from gram negative enterobacteria (leaky gut) plays a role in the inflammatory pathophysiology of depression. Neuroendocrinol Lett. 2008;29:117–124. [PubMed: 18283240]
55. Keri S, Szabo C, Kelemen O. Expression of toll-like receptors in peripheral blood mononuclear cells and response to cognitive-behavioral therapy in major depressive disorder. Brain Behavior and Immunity. 2014;40:235–243.
56. Leclercq S, Matamoros S, Cani PD, Neyrinck AM, Jamar F, Staerkel P, Windey K, Tremaroli V, Backhed F, Verbeke K, de Timary P, Delzenne NM. Intestinal permeability, gut-bacterial dysbiosis, and behavioral markers of alcohol-dependence severity. Proc Natl Acad Sci U S A. 2014;111:E4485–E4493. [PubMed: 25288760]
57. Dinan TG, Stanton C, Cryan JF. Psychobiotics: A novel class of psychotropic. Biol Psychiatry. 2013;74:720–726. [PubMed: 23759244]
58. Ait-Belgnaoui A, Durand H, Cartier C, Chaumaz G, Eutamene H, Ferrier L, Houdeau E, Fioramonti J, Bueno L, Theodorou V. Prevention of gut leakiness by a probiotic treatment leads to attenuated HPA response to an acute psychological stress in rats. Psychoneuroendocrinology. 2012;37:1885–1895. [PubMed: 22541937]
59. Nanni V, Uher R, Danese A. Childhood maltreatment predicts unfavorable course of illness and treatment outcome in depression: A meta-analysis. Am J Psychiatry. 2012;169:141–151. [PubMed: 22420036]
60. Danese A, Moffitt TE, Pariante CM, Ambler A, Poulton R, Caspi A. Elevated inflammation levels in depressed adults with a history of childhood maltreatment. Arch Gen Psychiatry. 2008;65:409–415. [PubMed: 18391129]
61. Kiecolt-Glaser JK, Gouin JP, Weng NP, Malarkey WB, Beversdorf DQ, Glaser R. Childhood adversity heightens the impact of later-life caregiving stress on telomere length and inflammation. Psychosom Med. 2011;73:16–22. [PubMed: 21148804]
62. Miller GE, Chen E, Parker KJ. Psychological stress in childhood and susceptibility to the chronic diseases of aging: Moving toward a model of behavioral and biological mechanisms. Psychol Bull. 2011;137:959–997. [PubMed: 21787044]
63. Fagundes CP, Glaser R, Kiecolt-Glaser JK. Stressful early life experiences and immune dysregulation across the lifespan. Brain Behav Immun. 2013;27:8–12. [PubMed: 22771426]
64. Tursich M, Neufeld RW, Frewen PA, Harricharan S, Kibler JL, Rhind SG, Lanius RA. Association of trauma exposure with proinflammatory activity: A transdiagnostic meta-analysis. Translational psychiatry. 2014;4:e413. [PubMed: 25050993]
65. Heim C, Newport DJ, Mletzko T, Miller AH, Nemeroff CB. The link between childhood trauma and depression: Insights from HPA axis studies in humans. Psychoneuroendocrinology. 2008;33:693–710. [PubMed: 18602762]
66. Carpenter LL, Gawuga CE, Tyrka AR, Lee JK, Anderson GM, Price LH. Association between plasma IL-6 response to acute stress and early-life adversity in healthy adults. Neuropsychopharmacology. 2010;35:2617–2623. [PubMed: 20881945]
67. Gouin JP, Glaser R, Malarkey WB, Beversdorf D, Kiecolt-Glaser JK. Childhood abuse and inflammatory responses to daily stressors. Ann Behav Med. 2012;44:287–292. [PubMed: 22714139]
68. Huijbregts KML, van der Feltz-Cornelis CM, van Marwijk HWJ, de Jong FJ, van der Windt DAWM, Beekman ATF. Negative association of concomitant physical symptoms with the course

of major depressive disorder: A systematic review. J Psychosom Res. 2010;68:511–519. [PubMed: 20488267]

69. Griffis CA, Breen EC, Compton P, Goldberg A, Witarama T, Kotlerman J, Irwin MR. Acute painful stress and inflammatory mediator production. Neuroimmunomodulation. 2013;20:127–133. [PubMed: 23407214]
70. Zhou D, Kusnecov AW, Shurin MR, DePaoli M, Rabin BS. Exposure to physical and psychological stressors elevates plasma interleukin 6: Relationship to the activation of hypothalamic-pituitary-adrenal axis. Endocrinology. 1993;133:2523–2530. [PubMed: 8243274]
71. Benson S, Kattoor J, Wegner A, Hammes F, Reidick D, Grigoleit JS, Engler H, Oberbeck R, Schedlowski M, Elsenbruch S. Acute experimental endotoxemia induces visceral hypersensitivity and altered pain evaluation in healthy humans. Pain. 2012;153:794–799. [PubMed: 22264996]
72. Watkins LR, Maier SF. Immune regulation of central nervous system functions: From sickness responses to pathological pain. J Intern Med. 2005;257:139–155. [PubMed: 15656873]
73. Fishbain DA, Cole B, Lewis JE, Gao JR. Does pain interfere with antidepressant depression treatment response and remission in patients with depression and pain? An evidence-based structured review. Pain Medicine. 2014;15:1522–1539. [PubMed: 25139618]
74. Gerrits M, van Oppen P, Leone SS, van Marwijk HWJ, van der Horst HE, Penninx BW. Pain, not chronic disease, is associated with the recurrence of depressive and anxiety disorders. BMC Psychiatry. 2014;14.
75. Irwin MR. Why sleep is important for health: A psychoneuroimmunology perspective. Annual Review of Psychology, Vol 66. 2015;66:143–172.
76. Lopresti AL, Hood SD, Drummond PD. A review of lifestyle factors that contribute to important pathways associated with major depression: Diet, sleep and exercise. J Affect Disord. 2013;148:12–27. [PubMed: 23415826]
77. Raison CL, Rye DB, Woolwine BJ, Vogt GJ, Bautista BM, Spivey JR, Miller AH. Chronic interferon-alpha administration disrupts sleep continuity and depth in patients with hepatitis c: Association with fatigue, motor slowing, and increased evening cortisol. Biol Psychiatry. 2010;68:942–949. [PubMed: 20537611]
78. Cho HJ, Seeman TE, Kiefe CI, Lauderdale DS, Irwin MR. Sleep disturbance and longitudinal risk of inflammation: Moderating influences of social integration and social isolation in the Coronary Artery Risk Development in Young Adults (CARDIA) study. Brain Behav Immun. 2015;46:319–326. [PubMed: 25733101]
79. Irwin MR, Olmstead R, Carrillo C, Sadeghi N, FitzGerald JD, Ranganath VK, Nicassio PM. Sleep loss exacerbates fatigue, depression, and pain in rheumatoid arthritis. Sleep. 2012;35:537–543. [PubMed: 22467992]
80. Rahe C, Unrath M, Berger K. Dietary patterns and the risk of depression in adults: A systematic review of observational studies. Eur J Nutr. 2014;53:997–1013. [PubMed: 24468939]
81. Lai JS, Hiles S, Bisquera A, Hure AJ, McEvoy M, Attia J. A systematic review and meta-analysis of dietary patterns and depression in community-dwelling adults. Am J Clin Nutr. 2014;99:181–197. [PubMed: 24196402]
82. Sanchez-Villegas A, Delgado-Rodriguez M, Alonso A, Schlatter J, Lahortiga F, Majem LS, Martinez-Gonzalez MA. Association of the Mediterranean dietary pattern with the incidence of depression: The Seguimiento Universidad de Navarra/University of Navarra Follow-up (SUN) cohort. Arch Gen Psychiatry. 2009;66:1090–1098. [PubMed: 19805699]
83. Rienks J, Dobson AJ, Mishra GD. Mediterranean dietary pattern and prevalence and incidence of depressive symptoms in mid-aged women: Results from a large community-based prospective study. Eur J Clin Nutr. 2013;67:75–82. [PubMed: 23212131]
84. Esposito K, Marfella R, Ciotola M, Di Palo C, Giugliano F, Giugliano G, D'Armiento M, D'Andrea F, Giugliano D. Effect of a Mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: A randomized trial. JAMA. 2004;292:1440–1446. [PubMed: 15383514]
85. Dai J, Miller AH, Bremner JD, Goldberg J, Jones L, Shallenberger L, Buckham R, Murrah NV, Veledar E, Wilson PW, Vaccarino V. Adherence to the Mediterranean diet is inversely associated

with circulating interleukin-6 among middle-aged men: A twin study. Circulation. 2008;117:169–175. [PubMed: 18086924]

86. Milaneschi Y, Bandinelli S, Penninx BW, Vogelzangs N, Corsi AM, Lauretani F, Kisialiou A, Vazzana R, Terracciano A, Guralnik JM, Ferrucci L. Depressive symptoms and inflammation increase in a prospective study of older adults: A protective effect of a healthy (Mediterranean-style) diet. Mol Psychiatry. 2011;16:589–590. [PubMed: 21042319]
87. Lucas M, Chocano-Bedoya P, Shulze MB, Mirzaei F, O'Reilly EJ, Okereke OI, Hu FB, Willett WC, Ascherio A. Inflammatory dietary pattern and risk of depression among women. Brain Behav Immun. 2014;36:46–53. [PubMed: 24095894]
88. Fontana L Neuroendocrine factors in the regulation of inflammation: Excessive adiposity and calorie restriction. Exp Gerontol. 2009;44:41–45. [PubMed: 18502597]
89. Lutter M, Krishnan V, Russo SJ, Jung S, McClung CA, Nestler EJ. Orexin signaling mediates the antidepressant-like effect of calorie restriction. J Neurosci. 2008;28:3071–3075. [PubMed: 18354010]
90. Aksungar FB, Topkaya AE, Akyildiz M. Interleukin-6, C-reactive protein and biochemical parameters during prolonged intermittent fasting. Ann Nutr Metab. 2007;51:88–95. [PubMed: 17374948]
91. Chaix A, Zarrinpar A, Miu P, Panda S. Time-restricted feeding is a preventative and therapeutic intervention against diverse nutritional challenges. Cell Metabolism. 2014;20:991–1005. [PubMed: 25470547]
92. Inoue W, Somay G, Poole S, Luheshi GN. Immune-to-brain signaling and central prostaglandin E2 synthesis in fasted rats with altered lipopolysaccharide-induced fever. Am J Physiol Regul Integr Comp Physiol. 2008;295:R133–143. [PubMed: 18480240]
93. Fond G, Macgregor A, Leboyer M, Michalsen A. Fasting in mood disorders: Neurobiology and effectiveness. A review of the literature. Psychiatry Res. 2013;209:253–258. [PubMed: 23332541]
94. Maes M, Berk M, Goehler L, Song C, Anderson G, Galecki P, Leonard B. Depression and sickness behavior are Janus-faced responses to shared inflammatory pathways. BMC Med. 2012;10:66. [PubMed: 22747645]
95. Lin PY, Huang SY, Su KP. A meta-analytic review of polyunsaturated fatty acid compositions in patients with depression. Biol Psychiatry. 2010;68:140–147. [PubMed: 20452573]
96. Giles GE, Mahoney CR, Kanarek RB. Omega-3 fatty acids influence mood in healthy and depressed individuals. Nutr Rev. 2013;71:727–741. [PubMed: 24447198]
97. Appleton KM, Rogers PJ, Ness AR. Updated systematic review and meta-analysis of the effects of n-3 long-chain polyunsaturated fatty acids on depressed mood. Am J Clin Nutr. 2010;91:757–770. [PubMed: 20130098]
98. Bloch MH, Hannestad J. Omega-3 fatty acids for the treatment of depression: Systematic review and meta-analysis. Mol Psychiatry. 2012;17:1272–1282. [PubMed: 21931319]
99. Grosso G, Pajak A, Marventano S, Castellano S, Galvano F, Bucolo C, Drago F, Caraci F. Role of omega-3 fatty acids in the treatment of depressive disorders: A comprehensive meta-analysis of randomized clinical trials. PLoS One. 2014;9:e96905. [PubMed: 24805797]
100. Sublette ME, Ellis SP, Geant AL, Mann JJ. Meta-analysis of the effects of eicosapentaenoic acid (EPA) in clinical trials in depression. J Clin Psychiatry. 2011;72:1577–1584. [PubMed: 21939614]
101. Martins JG. EPA but not DHA appears to be responsible for the efficacy of omega-3 long chain polyunsaturated fatty acid supplementation in depression: Evidence from a meta-analysis of randomized controlled trials. J Am Coll Nutr. 2009;28:525–542. [PubMed: 20439549]
102. Sijben JWC, Calder PC. Differential immunomodulation with long-chain n-3 pufa in health and chronic disease. Proc Nutr Soc. 2007;66:237–259. [PubMed: 17466105]
103. Ariel A, Serhan CN. Resolvins and protectins in the termination program of acute inflammation. Trends Immunol. 2007;28:176–183. [PubMed: 17337246]
104. Ferrucci L, Cherubini A, Bandinelli S, Bartali B, Corsi A, Lauretani F, Martin A, Andres-Lacueva C, Senin U, Guralnik JM. Relationship of plasma polyunsaturated fatty acids to circulating inflammatory markers. J Clin Endocrinol Metab. 2006;91:439–446. [PubMed: 16234304]

105. Farzaneh-Far R, Harris WS, Garg S, Na B, Whooley MA. Inverse association of erythrocyte n-3 fatty acid levels with inflammatory biomarkers in patients with stable coronary artery disease: The Heart and Soul Study. Atherosclerosis. 2009;205:538–543. [PubMed: 19185299]
106. Kalogeropoulos N, Panagiotakos DB, Pitsavos C, Chrysohoou C, Rousinou G, Toutouza M, Stefanadis C. Unsaturated fatty acids are inversely associated and n-6/n-3 ratios are positively related to inflammation and coagulation markers in plasma of apparently healthy adults. Clin Chim Acta. 2010;411:584–591. [PubMed: 20097190]
107. Rangel-Huerta OD, Aguilera CM, Mesa MD, Gil A. Omega-3 long-chain polyunsaturated fatty acids supplementation on inflammatory biomakers: A systematic review of randomised clinical trials. Br J Nutr. 2012;107 Suppl 2:S159–170. [PubMed: 22591890]
108. Kiecolt-Glaser JK, Belury MA, Andridge R, Malarkey WB, Hwang BS, Glaser R. Omega-3 supplementation lowers inflammation in healthy middle-aged and older adults: A randomized controlled trial. Brain Behav Immun. 2012;26:988–995. [PubMed: 22640930]
109. Su KP, Huang SY, Peng CY, Lai HC, Huang CL, Chen YC, Aitchison KJ, Pariante CM. Phospholipase a2 and cyclooxygenase 2 genes influence the risk of interferon-alpha-induced depression by regulating polyunsaturated fatty acids levels. Biol Psychiatry. 2010;67:550–557. [PubMed: 20034614]
110. Carlezon WAJ, Mague SD, Parow AM, Stoll AL, Cohen BM, Renshaw PF. Antidepressant-like effects of uridine and omega-3 fatty acids are potentiated by combined treatment in rats. Biol Psychiatry. 2005;57:343–350. [PubMed: 15705349]
111. Pittet YK, Berger MM, Pluess TT, Voirol P, Revelly JP, Tappy L, Chiolero RL. Blunting the response to endotoxin in healthy subjects: Effects of various doses of intravenous fish oil. Intensive Care Med. 2010;36:289–295. [PubMed: 19844694]
112. Pluess TT, Hayoz D, Berger MM, Tappy L, Revelly JP, Michaeli B, Carpentier YA, Chiolero RL. Intravenous fish oil blunts the physiological response to endotoxin in healthy subjects. Intensive Care Med. 2007;33:789–797. [PubMed: 17377770]
113. Song C, Li X, Leonard BE, Horrobin DF. Effects of dietary n-3 or n-6 fatty acids on interleukin-1 beta-induced anxiety, stress, and inflammatory responses in rats. J Lipid Res. 2003;44:1984–1991. [PubMed: 12837849]
114. Da Silva MA, Singh-Manoux A, Brunner EJ, Kaffashian S, Shipley MJ, Kivimaki M, Nabi H. Bidirectional association between physical activity and symptoms of anxiety and depression: The Whitehall II study. Eur J Epidemiol. 2012;27:537–546. [PubMed: 22623145]
115. Mammen G, Faulkner G. Physical activity and the prevention of depression: A systematic review of prospective studies. Am J Prev Med. 2013;45:649–657. [PubMed: 24139780]
116. Lancaster GI, Febbraio MA. The immunomodulating role of exercise in metabolic disease. Trends Immunol. 2014;35:262–269. [PubMed: 24680647]
117. Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Mastana SS, Nimmo MA. The anti-inflammatory effects of exercise: Mechanisms and implications for the prevention and treatment of disease. Nat Rev Immunol. 2011;11:607–615. [PubMed: 21818123]
118. Trivedi MH, Greer TL, Church TS, Carmody TJ, Grannemann BD, Galper DI, Dunn AL, Earnest CP, Sunderajan P, Henley SS, Blair SN. Exercise as an augmentation treatment for nonremitted major depressive disorder: A randomized, parallel dose comparison. J Clin Psychiatry. 2011;72:677–684. [PubMed: 21658349]
119. Rethorst CD, Toups MS, Greer TL, Nakonezny PA, Carmody TJ, Grannemann BD, Huebinger RM, Barber RC, Trivedi MH. Pro-inflammatory cytokines as predictors of antidepressant effects of exercise in major depressive disorder. Mol Psychiatry. 2013;18:1119–1124. [PubMed: 22925832]
120. Nicklas BJ, Brinkley TE. Exercise training as a treatment for chronic inflammation in the elderly. Exerc Sport Sci Rev. 2009;37:165–170. [PubMed: 19955865]
121. Calder PC, Ahluwalia N, Brouns F, Buetler T, Clement K, Cunningham K, Esposito K, Jonsson LS, Kolb H, Lansink M, Marcos A, Margioris A, Matusheski N, Nordmann H, O'Brien J, Pugliese G, Rizkalla S, Schalkwijk C, Tuomilehto J, Warnberg J, Watzl B, Winklhofer-Roob BM. Dietary factors and low-grade inflammation in relation to overweight and obesity. Br J Nutr. 2011;106 Suppl 3:S5–78. [PubMed: 22133051]

122. Beavers KM, Brinkley TE, Nicklas BJ. Effect of exercise training on chronic inflammation. Clin Chim Acta. 2010;411:785–793. [PubMed: 20188719]
123. Luppino FS, de Wit LM, Bouvy PF, Stijnen T, Cuijpers P, Penninx BW, Zitman FG. Overweight, obesity, and depression: A systematic review and meta-analysis of longitudinal studies. Arch Gen Psychiatry. 2010;67:220–229. [PubMed: 20194822]
124. Kyrou I, Chrousos GP, Tsigos C. Stress, visceral obesity, and metabolic complications. Ann N Y Acad Sci. 2006;1083:77–110. [PubMed: 17148735]
125. 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. Diabetes Care. 2007;30:872–877. [PubMed: 17392548]
126. Brydon L, Wright CE, O'Donnell K, Zachary I, Wardle J, Steptoe A. Stress-induced cytokine responses and central adiposity in young women. Int J Obes. 2008;32:443–450.
127. McInnis CM, Thoma MV, Gianferante D, Hanlin L, Chen X, Breines JG, Hong S, Rohleder N. Measures of adiposity predict interleukin-6 responses to repeated psychosocial stress. Brain Behav Immun. 2014;42:33–40. [PubMed: 25107874]
128. Franceschi C, Bonafe M, Valensin S, Olivieri F, De Luca M, Ottaviani E, De Benedictis G. Inflamm-aging. An evolutionary perspective on immunosenescence. Ann N Y Acad Sci. 2000;908:244–254. [PubMed: 10911963]
129. Mirsoian A, Bouchlaka MN, Sckisel GD, Chen M, Pai CC, Maverakis E, Spencer RG, Fishbein KW, Siddiqui S, Monjazeb AM, Martin B, Maudsley S, Hesdorffer C, Ferrucci L, Longo DL, Blazar BR, Wiltrout RH, Taub DD, Murphy WJ. Adiposity induces lethal cytokine storm after systemic administration of stimulatory immunotherapy regimens in aged mice. J Exp Med. 2014;211:2373–2383. [PubMed: 25366964]
130. Hammen C Generation of stress in the course of unipolar depression. J Abnorm Psychol. 1991;100:555–561. [PubMed: 1757669]
131. Husky M, Mazure C, Maciejewski P, Swendsen J. Past depression and gender interact to influence emotional reactivity to daily life stress. Cognit Ther Res. 2009;33:264–271.
132. O'Grady MA, Tennen H, Armeli S. Depression history, depression vulnerability and the experience of everyday negative events. J Soc Clin Psychol. 2010;29:949–974. [PubMed: 21170154]
133. Herr NR, Hammen C, Brennan PA. Current and past depression as predictors of family functioning: A comparison of men and women in a community sample. J Fam Psychol. 2007;21:694–702. [PubMed: 18179341]
134. Kiecolt-Glaser JK, Jaremka L, Andridge R, Peng J, Habash D, Fagundes CP, Glaser R, Malarkey WB, Belury MA. Marital discord, past depression, and metabolic responses to high-fat meals: Interpersonal pathways to obesity. Psychoneuroendocrinology. 2015;52:239–250. [PubMed: 25506778]
135. Johnson JD, O'Connor KA, Deak T, Stark M, Watkins LR, Maier SF. Prior stressor exposure sensitizes LPS-induced cytokine production. Brain Behav Immun. 2002;16:461–476. [PubMed: 12096891]
136. Dantzer R, Wollman E, Vitkovic L, Yirmiya R. Cytokines and depression: Fortuitous or causative association? Mol Psychiatry. 1999;4:328–332. [PubMed: 10483048]
137. Erridge C The capacity of foodstuffs to induce innate immune activation of human monocytes in vitro is dependent on food content of stimulants of toll-like receptors 2 and 4. Br J Nutr. 2011;105:15–23. [PubMed: 20849668]
138. Herieka M, Erridge C. High-fat meal induced postprandial inflammation. Mol Nutr Food Res. 2014;58:136–146. [PubMed: 23847095]
139. Moreira APB, Texeira TFS, Ferreira AB, Peluzio MDG, Alfenas RDG. Influence of a high-fat diet on gut microbiota, intestinal permeability and metabolic endotoxaemia. Br J Nutr. 2012;108:801–809. [PubMed: 22717075]
140. Willette AA, Lubach GR, Coe CL. Environmental context differentially affects behavioral, leukocyte, cortisol, and interleukin-6 responses to low doses of endotoxin in the rhesus monkey. Brain Behav Immun. 2007;21:807–815. [PubMed: 17336039]

141. Anisman H, Merali Z, Poulter MO, Hayley S. Cytokines as a precipitant of depressive illness: Animal and human studies. Curr Pharm Des. 2005;11:963–972. [PubMed: 15777247]
142. Dietz DM, Laplant Q, Watts EL, Hodes GE, Russo SJ, Feng J, Oosting RS, Vialou V, Nestler EJ. Paternal transmission of stress-induced pathologies. Biol Psychiatry. 2011;70:408–414. [PubMed: 21679926]
143. Shanks N, Lightman SL. The maternal-neonatal neuro-immune interface: Are there long-term implications for inflammatory or stress-related disease? J Clin Invest. 2001;108:1567–1573. [PubMed: 11733549]
144. McDade TW, Hoke M, Borja JB, Adair LS, Kuzawa C. Do environments in infancy moderate the association between stress and inflammation in adulthood? Initial evidence from a birth cohort in the philippines. Brain Behav Immun. 2013;31:23–30. [PubMed: 22960631]
145. Glaser R, Robles T, Sheridan J, Malarkey WB, Kiecolt-Glaser JK. Mild depressive symptoms are associated with amplified and prolonged inflammatory responses following influenza vaccination in older adults. Arch Gen Psychiatry. 2003;60:1009–1014. [PubMed: 14557146]
146. Christian LM, Franco A, Iams JD, Sheridan J, Glaser R. Depressive symptoms predict exaggerated inflammatory responses to an in vivo immune challenge among pregnant women. Brain Behav Immun. 2010;24:49–53. [PubMed: 19464358]
147. Maes M, Ombelet W, De Jongh R, Kenis G, Bosmans E. The inflammatory response following delivery is amplified in women who previously suffered from major depression, suggesting that major depression is accompanied by a sensitization of the inflammatory response system. J Affect Disord. 2001;63:85–92. [PubMed: 11246084]
148. Pace TWW, Mletzko TC, Alagbe O, Musselman DL, Nemeroff CB, Miller AH, Heim CM. Increased stress-induced inflammatory responses in male patients with major depression and increased early life stress. Am J Psychiatry. 2006;163:1630–1632. [PubMed: 16946190]
149. Weinstein AA, Deuster PA, Francis JL, Bonsall RW, Tracy RP, Kop WJ. Neurohormonal and inflammatory hyper-responsiveness to acute mental stress in depression. Biol Psychol. 2010;84:228–234. [PubMed: 20117167]
150. Fagundes CP, Glaser R, Hwang BS, Malarkey WB, Kiecolt-Glaser JK. Depressive symptoms enhance stress-induced inflammatory responses. Brain Behav Immun. 2013;31:172–176. [PubMed: 22634107]
151. von Kanel R, Kudielka BM, Preckel D, Hanebuth D, Fischer JE. Delayed response and lack of habituation in plasma interleukin-6 to acute mental stress in men. Brain Behav Immun. 2006;20:40–48. [PubMed: 15890495]
152. Kohler O, Benros ME, Nordentoft M, Farkouh ME, Iyengar RL, Mors O, Krogh J. Effect of anti-inflammatory treatment on depression, depressive symptoms, and adverse effects: A systematic review and meta-analysis of randomized clinical trials. JAMA Psychiatry. 2014;71:1381–1391. [PubMed: 25322082]
153. Uher R, Tansey KE, Dew T, Maier W, Mors O, Hauser J, Dernovsek MZ, Henigsberg N, Souery D, Farmer A, McGuffin P. An inflammatory biomarker as a differential predictor of outcome of depression treatment with escitalopram and nortriptyline. Am J Psychiatry. 2014;171:1278–1286. [PubMed: 25017001]
154. Miller GE, Chen E, Sze J, Marin T, Arevalo JM, Doll R, Ma R, Cole SW. A functional genomic fingerprint of chronic stress in humans: Blunted glucocorticoid and increased NF-kappa B signaling. Biol Psychiatry. 2008;64:266–272. [PubMed: 18440494]
155. Lamers F, Vogelzangs N, Merikangas KR, de Jonge P, Beekman ATF, Penninx BWJH. Evidence for a differential role of HPA-axis function, inflammation and metabolic syndrome in melancholic versus atypical depression. Mol Psychiatry. 2013;18:692–699. [PubMed: 23089630]
156. Ueland T, Gullestad L, Nymo SH, Yndestad A, Aukrust P, Askevold ET. Inflammatory cytokines as biomarkers in heart failure. Clin Chim Acta. 2015;443:71–77. [PubMed: 25199849]
157. Miller AH, Raison CL. Are anti-inflammatory therapies viable treatments for psychiatric disorders?: Where the rubber meets the road. JAMA Psychiatry. 2015.
158. Hannestad J, DellaGioia N, Bloch M. The effect of antidepressant medication treatment on serum levels of inflammatory cytokines: A meta-analysis. Neuropsychopharmacology. 2011;36:2452–2459. [PubMed: 21796103]

159. Levitzky YS, Guo CY, Rong J, Larson MG, Walter RE, Keaney JF, Sutherland PA, Vasan A, Lipinska I, Evans JC, Benjamin EJ. Relation of smoking status to a panel of inflammatory markers: The Framingham offspring. Atherosclerosis. 2008;201:217–224. [PubMed: 18289552]

160. Leclercq S, De Saeger C, Delzenne N, de Timary P, Starkel P. Role of inflammatory pathways, blood mononuclear cells, and gut-derived bacterial products in alcohol dependence. Biol Psychiatry. 2014;76:725–733. [PubMed: 24629538]

161. Miller GE, Brody GH, Yu TY, Chen E. A family-oriented psychosocial intervention reduces inflammation in low-SES African American youth. Proc Natl Acad Sci U S A. 2014;111:11287–11292. [PubMed: 25049403]

162. Gazal M, Souza LD, Fucolo BA, Wiener CD, Silva RA, Pinheiro RT, Jansen K, Ghislene G, Oses JP, Kaster MP. The impact of cognitive behavioral therapy on IL-6 levels in unmedicated women experiencing the first episode of depression: A pilot study. Psychiatry Res. 2013;209:742–745. [PubMed: 23541242]

163. Manber R, Edinger JD, Gress JL, Pedro-Salcedo MGS, Kuo TF, Kalista T. Cognitive behavioral therapy for insomnia enhances depression outcome in patients with comorbid major depressive disorder and insomnia. Sleep. 2008;31:489–495. [PubMed: 18457236]

164. Irwin MR, Olmstead R, Carrillo C, Sadeghi N, Breen EC, Witarama T, Yokomizo M, Lavretsky H, Carroll JE, Motivala SJ, Bootzin R, Nicassio P. Cognitive behavioral therapy vs. Tai chi for late life insomnia and inflammatory risk: A randomized controlled comparative efficacy trial. Sleep. 2014;37:1543–U1361. [PubMed: 25142571]

165. Chen H-Y, Cheng IC, Pan Y-J, Chiu Y-L, Hsu S-P, Pai M-F, Yang J-Y, Peng Y-S, Tsai T-J, Wu K-D. Cognitive-behavioral therapy for sleep disturbance decreases inflammatory cytokines and oxidative stress in hemodialysis patients. Kidney Int. 2011;80:415–422. [PubMed: 21654719]

166. Ehde DM, Dillworth TM, Turner JA. Cognitive-behavioral therapy for individuals with chronic pain efficacy, innovations, and directions for research. Am Psychol. 2014;69:153–166. [PubMed: 24547801]

167. Zautra AJ, Davis MC, Reich JW, Tennen H, Irwin MR, Nicassio P, Finan P, Kratz A, Parrish B. Comparison of cognitive behavioral and mindfulness meditation interventions on adaptation to rheumatoid arthritis for patients with and without history of recurrent depression. J Consult Clin Psychol. 2008;76:408–421. [PubMed: 18540734]

168. Bower JE, Ganz PA, Aziz N, Olmstead R, Irwin MR, Cole SW. Inflammatory responses to psychological stress in fatigued breast cancer survivors: Relationship to glucocorticoids. Brain Behav Immun. 2007;21:251–258. [PubMed: 17008048]

169. Jaremka LM, Fagundes CP, Peng J, Bennett JM, Glaser R, Malarkey WB, Kiecolt-Glaser JK. Loneliness promotes inflammation during acute stress. Psychol Sci. 2013;24:1089–1097. [PubMed: 23630220]

170. Derry HM, Fagundes CP, Andridge R, Glaser R, Malarkey WB, Kiecolt-Glaser JK. Lower subjective social status exaggerates interleukin-6 responses to a laboratory stressor. Psychoneuroendocrinology. 2013;38:2676–2685. [PubMed: 23849596]

171. Bennett JM, Glaser R, Andridge RR, Peng J, Malarkey WB, Kiecolt-Glaser JK. Long lasting effects of smoking: Breast cancer survivors' inflammatory responses to acute stress differ by smoking history. Psychoneuroendocrinology. 2013;38:179–187. [PubMed: 22727479]

172. Kiecolt-Glaser JK, Loving TJ, Stowell JR, Malarkey WB, Lemeshow S, Dickinson SL, Glaser R. Hostile marital interactions, proinflammatory cytokine production, and wound healing. Arch Gen Psychiatry. 2005;62:1377–1384. [PubMed: 16330726]

173. Kox M, van Eijk LT, Zwaag J, van den Wildenberg J, Sweep FC, van der Hoeven JG, Pickkers P. Voluntary activation of the sympathetic nervous system and attenuation of the innate immune response in humans. Proc Natl Acad Sci U S A. 2014.

174. Kiecolt-Glaser JK, Christian L, Preston H, Houts CR, Malarkey WB, Emery CF, Glaser R. Stress, inflammation, and yoga practice. Psychosom Med. 2010;72:113–121. [PubMed: 20064902]

175. Bower JE, Greendale G, Crosswell AD, Garet D, Sternlieb B, Ganz PA, Irwin MR, Olmstead R, Arevalo J, Cole SW. Yoga reduces inflammatory signaling in fatigued breast cancer survivors: A randomized controlled trial. Psychoneuroendocrinology. 2014;43:20–29. [PubMed: 24703167]

176. Cuijpers P, Vogelzangs N, Twisk J, Kleiboer A, Li J, Penninx BW. Comprehensive meta-analysis of excess mortality in depression in the general community versus patients with specific illnesses. Am J Psychiatry. 2014;171:453–462. [PubMed: 24434956]

177. Franceschi C Inflammaging as a major characteristic of old people: Can it be prevented or cured? Nutr Rev. 2007;65:S173–S176. [PubMed: 18240544]

178. Vogelzangs N, Kritchevsky SB, Beekman ATF, Newman AB, Satterfield S, Simonsick EM, Yaffe K, Harris TB, Penninx BWJH. Depressive symptoms and change in abdominal obesity in older persons. Arch Gen Psychiatry. 2008;65:1386–1393. [PubMed: 19047525]

179. Alexopoulos GS, Morimoto SS. The inflammation hypothesis in geriatric depression. Int J Geriatr Psychiatry. 2011;26:1109–1118. [PubMed: 21370276]

180. Danese A, Moffitt TE, Harrington H, Milne BJ, Polanczyk G, Pariante CM, Poulton R, Caspi A. Adverse childhood experiences and adult risk factors for age-related disease: Depression, inflammation, and clustering of metabolic risk markers. Arch Pediatr Adolesc Med. 2009;163:1135–1143. [PubMed: 19996051]

181. Penninx BWJH, Milaneschi Y, Lamers F, Vogelzangs N. Understanding the somatic consequences of depression: Biological mechanisms and the role of depression symptom profile. BMC Medicine. 2013;11.

182. Vogelzangs N, Beekman ATF, Dortland A, Schoevers RA, Giltay EJ, de Jonge P, Penninx B. Inflammatory and metabolic dysregulation and the 2-year course of depressive disorders in antidepressant users. Neuropsychopharmacology. 2014;39:1624–1634. [PubMed: 24442097]

183. Choi J, Joseph L, Pilote L. Obesity and C-reactive protein in various populations: A systematic review and meta-analysis. Obesity Reviews. 2013;14:232–244. [PubMed: 23171381]

184. Irwin MR, Wang M, Ribeiro D, Cho HJ, Olmstead R, Breen EC, Martinez-Maza O, Cole S. Sleep loss activates cellular inflammatory signaling. Biol Psychiatry. 2008;64:538–540. [PubMed: 18561896]

185. Grandner MA, Buxton OM, Jackson N, Sands-Lincoln M, Pandey A, Jean-Louis G. Extreme sleep durations and increased C-reactive protein: Effects of sex and ethnoracial group. Sleep. 2013;36:769–779. [PubMed: 23633760]

186. Lopez-Garcia E, Schulze MB, Fung TT, Meigs JB, Rifai N, Manson JE, Hu FB. Major dietary patterns are related to plasma concentrations of markers of inflammation and endothelial dysfunction. Am J Clin Nutr. 2004;80:1029–1035. [PubMed: 15447916]

187. Kasapis C, Thompson PD. The effects of physical activity on serum C-reactive protein and inflammatory markers: A systematic review. J Am Coll Cardiol. 2005;45:1563–1569. [PubMed: 15893167]

188. Jaremka LM, Fagundes CP, Glaser R, Bennett JM, Malarkey WB, Kiecolt-Glaser JK. Loneliness predicts pain, depression, and fatigue: Understanding the role of immune dysregulation. Psychoneuroendocrinology. 2013;38:1310–1317. [PubMed: 23273678]

189. Valentine RJ, Woods JA, McAuley E, Dantzer R, Evans EM. The associations of adiposity, physical activity and inflammation with fatigue in older adults. Brain Behav Immun. 2011;25:1482–1490. [PubMed: 21693185]

190. Wegner A, Elsenbruch S, Maluck J, Grigoleit J-S, Engler H, Jäger M, Spreitzer I, Schedlowski M, Benson S. Inflammation-induced hyperalgesia: Effects of timing, dosage, and negative affect on somatic pain sensitivity in human experimental endotoxemia. Brain Behav Immun. 2014;41:46–54. [PubMed: 24814500]

191. O'Connor MF, Bower JE, Cho HJ, Creswell JD, Dimitrov S, Hamby ME, Hoyt MA, Martin JL, Robles TF, Sloan EK, Thomas KS, Irwin MR. To assess, to control, to exclude: Effects of biobehavioral factors on circulating inflammatory markers. Brain Behav Immun. 2009;23:887–897. [PubMed: 19389469]

192. Yang Y, Kozloski M. Sex differences in age trajectories of physiological dysregulation: Inflammation, metabolic syndrome, and allostatic load. J Gerontol A Biol Sci Med Sci. 2011;66:493–500. [PubMed: 21350248]

193. Moieni M, Irwin MR, Jevtic I, Olmstead R, Breen EC, Eisenberger NI. Sex differences in depressive and socioemotional responses to an inflammatory challenge: Implications for sex differences in depression. Neuropsychopharmacology. 2015.

194. Tyring S, Gottlieb A, Papp K, Gordon K, Leonardi C, Wang A, Lalla D, Woolley M, Jahreis A, Zitnik R, Cella D, Krishnan R. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: Double-blind placebo-controlled randomised phase III trial. Lancet. 2006;367:29–35. [PubMed: 16399150]

195. Langley RG, Feldman SR, Han C, Schenkel B, Szapary P, Hsu MC, Ortonne JP, Gordon KB, Kimball AB. Ustekinumab significantly improves symptoms of anxiety, depression, and skin-related quality of life in patients with moderate-to-severe psoriasis: Results from a randomized, double-blind, placebo-controlled phase III trial. J Am Acad Dermatol. 2010;63:457–465. [PubMed: 20462664]

196. Monk JP, Phillips G, Waite R, Kuhn J, Schaaf L, Otterson G, Guttridge D, Rhoades C, Shah M, Criswell T, Caliguiri M, Villalona-Calero M. Assessment of tumor necrosis factor alpha blockade as an intervention to improve tolerability of dose-sensitive chemotherapy in cancer patients. J Clin Oncol. 2006;24:1852–1859. [PubMed: 16622259]

197. Persoons P, Vermeire S, Demyttenaere K, Fischler B, Vandenberghe J, Van Oudenhove L, Pierik M, Hlavaty T, Van Assche G, Noman M, Rutgeerts P. The impact of major depressive disorder on the short- and long-term outcome of Crohn's disease treatment with infliximab. Aliment Pharm Therap. 2005;22:101–110.

198. Selvin E, Paynter NP, Erlinger TP. The effect of weight loss on C-reactive protein - a systematic review. Arch Intern Med. 2007;167:31–39. [PubMed: 17210875]

199. Kiecolt-Glaser JK, Bennett JM, Andridge R, Peng J, Shapiro CL, Malarkey WB, Emery CF, Layman R, Mrozek EE, Glaser R. Yoga's impact on inflammation, mood, and fatigue in breast cancer survivors: A randomized controlled trial. J Clin Oncol. 2014;32:1040–1049. [PubMed: 24470004]

200. Vitiello MV, McCurry SM, Shortreed SM, Baker LD, Rybarczyk BD, Keefe FJ, Von Koff M. Short-term improvement in insomnia symptoms predicts long-term improvements in sleep, pain, and fatigue in older adults with comorbid osteoarthritis and insomnia. Pain. 2014;155:1547–1554. [PubMed: 24793909]

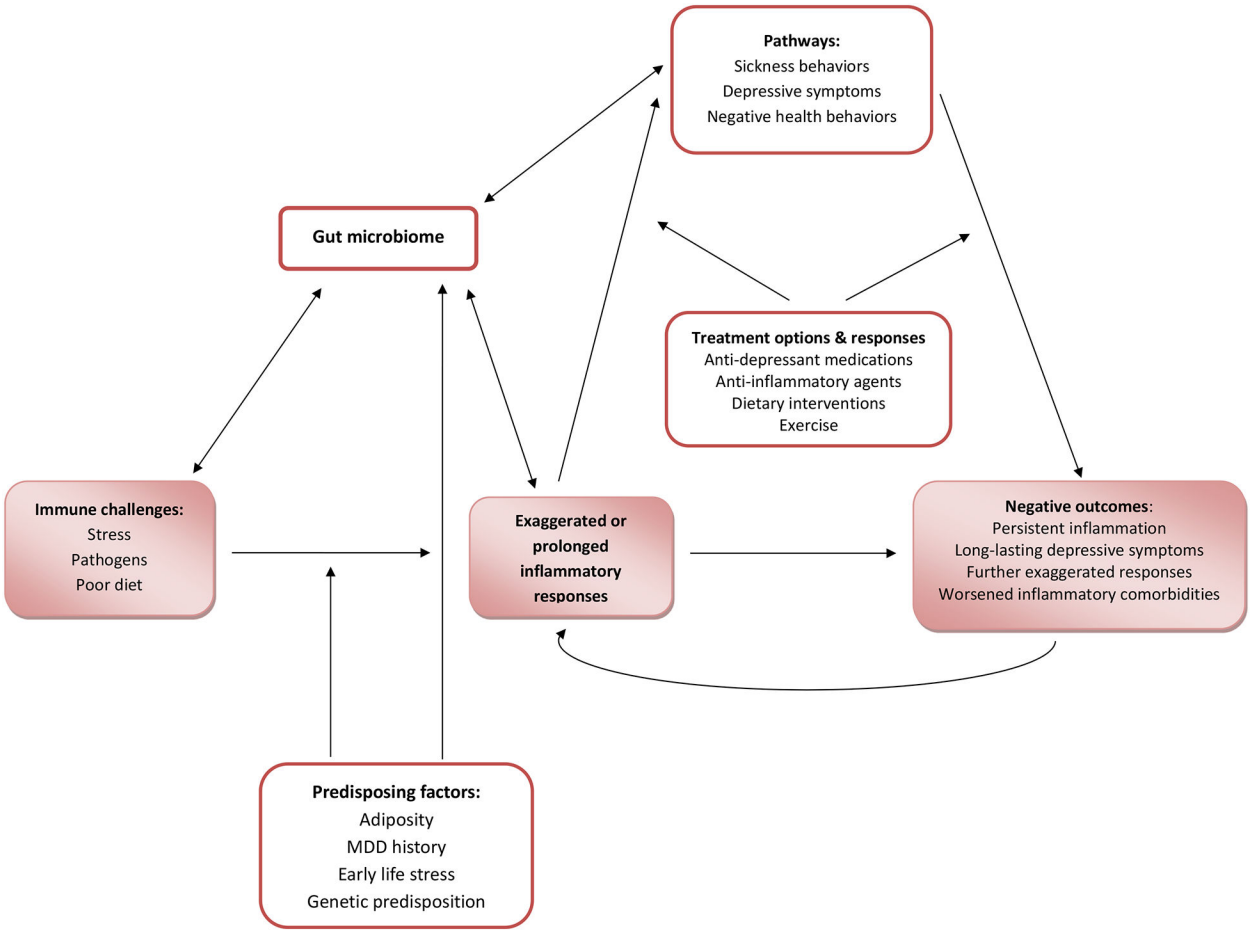

Figure 1.

This illustration depicts factors that increase risk for inflammatory overresponsiveness, as well as pathways leading to heightened inflammation, depression, and health risks. When combined with predisposing factors (moderators), immune challenges can lead to exaggerated or prolonged inflammatory responses. The resulting sickness behaviors (e.g., pain, fatigue, sleep disturbance), depressive symptoms, and negative health behaviors (e.g., poor diet) may act as mediating pathways that lead to further unrestrained inflammation. Depression, childhood adversity, stressors, and diet can all influence the gut microbiome and promote intestinal permeability, another pathway to enhanced inflammatory responses. Ultimately, this overresponsiveness could carry important physical and mental health risks, and could amplify inflammatory responses to subsequent immune challenges. This pattern suggests novel treatment options that could halt both exaggerated inflammation and depressive symptoms, and may also help to pinpoint which patients are expected to benefit from certain treatments.

Table 1.

Assessing the likelihood of heightened inflammation: Risk factors that raise the index of suspicion

Risk factor	Comments
Older age	• Inflammation rises with age (177) • A large prospective study showed that older depressed adults gained visceral fat over five years, while non–depressed adults lost visceral fat (178) • Among the genes upregulated during late life, more than half regulate inflammation-related processes, one mechanism for exaggerated proinflammatory responses (179)
Early life stress	• Adults who experienced abuse or neglect as children have a substantially heightened risk for inflammation as well as depression (60, 61) • Low childhood socioeconomic status confers enduring risk for depression and elevated inflammation, independent of concurrent risk factors such as abuse and neglect (180)
Comorbidities	• Both the number and the severity of comorbid inflammatory disorders or diseases influence inflammation and risk of depression; risk is further heightened by the pain and sleep disturbances that often occur in tandem with the comorbidities (181)
Atypical depression	• Atypical MDD with features including hypersomnia, fatigue, increased appetite, and weight gain is associated with greater inflammatory dysregulation than melancholic depression (181)
Chronic/recurrent depression	• A more chronic course of depression is associated with higher inflammation (7, 182)
Obesity	• Adipocytes (fat cells) produce and secrete IL-6 and TNF-α, and abdominal fat is a major inflammatory source (129) • Central adiposity and greater body fat are associated with larger stress-induced inflammatory responses(126, 127) • There is a medium-sized relationship between BMI and CRP in adults (r = 0.36) (183)
Poor sleep	• Sleep loss stimulates production of proinflammatory cytokines and cellular inflammatory signaling. (184) • Disturbed sleep accompanies many inflammation-associated comorbidities • Both decreased sleep (<5 hours) and increased sleep (> 9 hours) share a medium-sized relationship with CRP, d = 0.29 and d = 0.34 respectively (185)
Unhealthy diet	• “Western” diets (e.g., high in red and processed meats, sweets, desserts, French fries, and refined grains) have higher associated inflammation than healthier diets, e.g., Mediterranean diets (186) • Adherence to a Mediterranean diet was associated with lower IL-6 (85)
Sedentary lifestyle	• Physically active individuals have lower inflammation than their sedentary counterparts (116) • Better cardiorespiratory fitness is associated with lower inflammation (187)
Fatigue	• Fatigue, pain, and depression function as a troublesome symptom cluster across multiple medical and community populations (188). • Like pain and depression, fatigue has strong inflammatory ties (189)
Pain	• Pain generates inflammatory responses (69, 70) • Amplified pain sensitivity serves as an additional inflammatory source that in turn provokes negative affect (69, 71, 72, 190)
Smoking	• Current smokers have higher values across multiple inflammatory markers than non-smokers (159)

Risk factor	Comments
	• Some former smokers have persistently elevated inflammation compared to those who never smoked (159)
Alcohol dependence	• CRP and proinflammatory cytokines are higher among heavy drinkers and abstainers than moderate drinkers (191)
Female sex	• More women than men have elevated CRP levels (192) • IL-6 and TNF-α responses to low-dose endotoxin did not differ between men and women, but women's reports of depressed mood and social disconnection increased more than those of men, suggesting women may be more sensitive to heightened inflammation (193) • Obesity and CRP are more strongly related in women than in men (183) • Sleep loss stimulates longer-lasting elevations in inflammation in women compared to men (75)

Table 2.

Inflammatory biomarkers commonly used in depression research

Inflammatory biomarker	Advantages	Disadvantages	Comments
CRP	• Routinely assayed by local clinical labs • No diurnal variation • > 5 (mg/L) risk stratification value suggested by literature (17)	• Less responsive to acute stress than cytokines • Less reliably linked to psychosocial stressors compared with other markers	• Synthesized in the liver, secreted in response to IL-6 • 15–19 hour half-life • Well-established risk stratification values and clear clinical relevance for cardiovascular disease
IL-6	• Biomarker most strongly associated with depression (3) • Most widely used inflammatory biomarker in depression research because of its sensitivity • Responsive to both acute and chronic stressors	• Limited availability in local clinical labs • Values dependent on assay type and assay procedures within and between labs (4) • No risk stratification norms, values not comparable across labs • Values can differ 3 to 50+ fold based on diurnal variation, recent sleep, and the duration and intensity of recent exercise (191)	• Can be ordered through national labs (e.g., Quest, LabCorp) • Half-life is <6 hours • Rises within ~30–45 minutes of lab stressors; catecholamines increase IL-6 levels • Fasting morning blood draws reduce variability
TNF-α	• Positively associated with depression in clinical and community samples (3) • Reliably elevated in MDD (4)	• Limited availability in local clinical labs • Values dependent on assay type and assay procedures within and between labs(4) • No risk stratification norms, values not comparable across labs	• Can be ordered through national labs • Fasting morning blood draws reduce variability • Targeted by cytokine inhibitor treatments
IL-1ra	• Positively associated with depression in clinical and community samples (3)	• Limited availability in local clinical labs • Values dependent on assay type and assay procedures within and between labs (4) • No risk stratification norms, values not comparable across labs	• Can be ordered through national labs • Fasting morning blood draws reduce variability
IL-1β	• Positively associated with depression in a meta-analysis of clinical and community samples (3)	• Not associated with MDD in a meta-analysis of MDD studies (4) • Highly skewed distribution, many samples below limits of detection	• Can be ordered through national labs • Fasting morning blood draws reduce variability

Inflammatory biomarker	Advantages	Disadvantages	Comments
		• Limited availability in local clinical labs • Values dependent on assay type and assay procedures within and between labs (4) • No risk stratification norms, values not comparable across labs	

CRP= C-reactive protein; IL-1β=interleukin 1 beta; IL-1ra=interleukin 1 receptor antagonist; IL-6=interleukin 6; TNF-α = tumor necrosis factor alpha

Table 3.

Anti-inflammatory treatment strategies.

Intervention type	Advantages	Disadvantages	Comments
Pharmacological interventions			
Celecoxib and other NSAIDs	• May be useful as a monotherapy, or in combination with antidepressant medication (152) • Celecoxib is associated with better antidepressant efficacy (response and remission) than other NSAIDs (152)	• Risk for gastrointestinal bleeding with chronic use, especially for older adults or those who use alcohol • Increased risk of cardiovascular events • Affects other pathways in addition to inflammation (e.g., glucocorticoid receptors, adhesion molecules)	• Patients with higher initial inflammation experienced greater benefit from celecoxib than those with lower inflammation (152) • Patients with comorbid pain- or inflammatory-related disorders responded better to NSAID treatment than those without similar disorders (152)
Cytokine inhibitors (e.g., infliximab)	• Specifically targets individual inflammatory cytokines • Treatment response can be monitored by assessing change in the targeted cytokine • Can normalize sleep (75) • Cytokine inhibitors have reduced depressive symptoms in people with psoriasis (194, 195), lessened fatigue during cancer treatment (196), and resolved MDD in Crohn's disease patients (197)	• Reduces the ability to fight infection; increases risk of death and reactivation of tuberculosis • Not suitable for those with immunosuppressive conditions • Patients with lower CRP responded better to placebo than infliximab, suggesting infliximab may not be appropriate for patients without inflammation-driven MDD (17)	• Treatment-resistant MDD patients with high baseline CRP had substantially greater reductions in depressive symptoms than those with low CRP • Cytokine antagonists and anti-inflammatory cytokines have reversed or reduced cytokine-induced sickness behaviors in rodents (34)
Omega-3 PUFAs	• Higher fish consumption is associated with a lower prevalence of depression • Few side effects • Benefits extend to cardiovascular system (e.g.,	• Less beneficial among individuals without an inflammatory profile (42, 102)	• Omega-3 PUFAs attenuated both endotoxin and IFN-α-induced inflammation and sickness behavior in rodents and humans (109–113)

Intervention type	Advantages	Disadvantages	Comments
	lowering triglycerides)		• EPA appears more beneficial than DHA (42, 100, 101) • Patients with a lower inflammatory profile responded better to placebo than to EPA (42)
Prebiotics, probiotics, and antibiotics	• Probiotics reduce gut leakiness and neuroinflammation in animal models • May also impact obesity (53) • Initial studies in humans suggest that probiotics improve mood among healthy adults and those with IBS and chronic fatigue syndrome (57)	• More information is needed on the particular microbiota alterations in depressed patients that need to be addressed	• Most of the treatment data comes from animal models
Lifestyle/behavioral interventions			
Healthy diets (e.g., Mediterranean diet)	• May confer additional benefits such as reduced cardiovascular disease risk • Healthier diets offer some protection against the development of both depressive symptoms and depressive disorders (82, 83)	• Dietary change and adherence can be a substantial obstacle • Some people may have limited availability of nutritious foods due to cost and access	• A Mediterranean diet may reduce inflammation among individuals with health risks (84) • Can buffer the impact of depression on inflammation (86)
Caloric restriction/time restricted eating	• Caloric restriction can simultaneously attenuate production of proinflammatory cytokines while enhancing anti-inflammatory pathways (88) • Low-cost intervention	• Implementation can be challenging • Quite difficult to maintain long-term adherence • Diet must be nutrient-dense to compensate for caloric restriction	• Aged mice subjected to caloric restriction had the lower cytokine responses characteristic of young mice following immunotherapy, and were similarly protected from mortality (129)
Weight loss	• Reduces multiple obesity-related health risks, including depression	• A minority of people maintain a substantially lower weight long-term after weight loss	• Weight loss reduces inflammation; those with greater weight loss have greater CRP

Intervention type	Advantages	Disadvantages	Comments
			reductions (198)
Exercise	• Can result in substantial long-term benefits for morbidity and mortality	• Regular exercise is required for continued benefit	• When assessed objectively by maximal exercise testing, fitness is inversely associated with inflammation, even after adjusting for confounds including age, smoking, medications, and visceral fat (187)
Integrative medicine interventions	• Can be adapted for those with physical limitations. • May reduce inflammatory over-responsiveness to stressors (173–175) • Yoga, tai chi, and mindfulness-based meditation improve sleep, another path to reduced inflammation (164, 199, 200)	• Regular practice required for efficacy	• Benefits are proportional to the time invested (174, 199) • The specific active anti-inflammatory components of yoga, tai chi, meditation, and other integrative therapies are not known (e.g., the relative importance of breathing, meditation, movement, etc.)
Family intervention	• Benefits may be long-lasting and could extend to parents and other siblings	• Significant parental investment • Can be costly • Access may be limited (e.g., by lack of family support)	• Family therapy buffered against elevated inflammation in at-risk youth (161)
Cognitive-behavioral therapy (CBT)	• Can address multiple behaviors leading to inflammation (e.g., depression, sleep habits, pain, negative health behaviors) • Long-lasting benefit possible	• Requires the patient's investment in change • Significant time commitment • Poorer outcomes among those with comorbid conditions • Risk of relapse	• CBT interventions addressing depression, sleep, and pain also lowered inflammation (55, 162, 164, 165, 167)