

Mechanisms of Psychiatric Illness

Inflammation: Depression Fans the Flames and Feasts on the Heat

American Journal of Psychiatry
November 2015; Vol. 172; No. 11; pp. 1075-1091

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 This article has 200 references.

KEY POINTS FROM THIS ARTICLE:

- 1) "Depression and inflammation fuel one another." "Depression and inflammation are intertwined, fueling and feeding off each other."
- 2) The depression-inflammation relationship begins early in life.
[This is why children should also have an anti-inflammatory diet and supplements]
- 3) Inflammation plays a key role in depression's pathogenesis. There is a bidirectional link between depression, inflammation, and disease.
- 4) "Stress and infection can lead to exaggerated or prolonged inflammatory responses," increasing the incidence and depth of depression.
- 5) "Larger, more frequent, or more prolonged inflammatory responses could have negative mental and physical health consequences."
- 6) "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."
- 7) "Elevated inflammatory signaling dysregulates neurotransmitter metabolism, impairs neuronal health, and alters neural activity in mood-relevant brain regions."
- 8) "Peripherally released cytokines send signals via molecular, cellular, and neural routes, which ultimately reach the brain and enhance CNS inflammation."
- 9) "Cytokines alter production, metabolism, and transport of neurotransmitters that synergistically affect mood, including dopamine, glutamate, and serotonin."
- 10) Cytokines inhibit the enzyme that converts tryptophan to serotonin, slowing serotonin production and promoting depression.
- 11) "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.”

12) Cytokines dysregulate the hypothalamic-pituitary-adrenal (HPA) axis function, a key characteristic of depression.

13) Vaccines cause a pro-inflammatory response, and as such can heighten depression. “Mild depressive symptoms were associated with amplified and prolonged inflammatory responses following influenza vaccination in older adults as well as pregnant women.”

THE GUT MICROBIOTA, INFLAMMATION, AND DEPRESSION

14) “The gut-brain axis involves bidirectional communication between the CNS and the gastrointestinal tract.” “Alterations in the gut microbiota shape physiology through contributions to inflammation, obesity, and mood, among other things.”

15) Depression promotes intestinal permeability (a “leaky gut”), increasing systemic inflammation. Targeting the gut-brain axis benefits the vagus nerve, spinal cord, and neuroendocrine system. **[prebiotics / probiotics]**

16) “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).” “Probiotics may reduce depressive symptoms as a result of their anti-inflammatory properties as well as their ability to reduce HPA axis activity.”

17) Disturbed sleep doubles one’s risk of depression. Sleep loss stimulates production of pro-inflammatory cytokines. Also, heightened inflammation disrupts sleep regulation.

DIET AS A ROAD TO DEPRESSION AND INFLAMMATION

18) Healthier diets are linked with a lower risk for depression. Studies indicate that healthier diets offer protection against the development of depressive symptoms and depressive disorders.

19) Diet quality influences inflammation. The risk for depression increases with higher inflammation.

20) “Caloric restriction produces powerful anti-inflammatory effects over periods of months to years.” Caloric restriction is also strongly antidepressant. Even intermittent fasting can reduce inflammation.

21) “Cross-sectional, prospective, and randomized controlled-trial 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-3s].”

OMEGA-3 FATTY ACIDS

- 22) "Fish oil is the prime source for two key omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)."
- 23) Patients with depression have lower plasma levels of omega-3 fatty acids than non-depressed comparison subjects. Depressive symptom severity correlates with omega-3 fatty acid plasma levels.
- 24) Omega-3 fatty acid supplementation benefits clinically depressed individuals.
- 25) "A [study] determined that omega-3 fatty acid supplementation was effective in both patients with major depression and those with subclinical depressive symptoms."
- 26) "EPA, not DHA, was the key omega-3 fatty acid related to efficacy in treating depression, consistent with the evidence for EPA's stronger anti-inflammatory properties compared with DHA." **[Important]**
- 27) "Lower omega-3 fatty acid levels are associated with higher serum IL-6, TNF- α , and CRP." "Inflammatory challenge studies provide compelling evidence of protective effects [with higher omega-3s]."
- 28) "Both EPA and DHA substantially delayed onset of major depression," and "EPA was more effective than DHA." **[Important]**
- 29) For depression, studies "clearly identified important benefits of omega-3 fatty acid treatment."

EXERCISE

- 30) "Considerable evidence supports the value of exercise in treating depression and preventing its onset."
- 31) "Physically active individuals have lower levels of inflammatory biomarkers than their sedentary counterparts." "Reductions in inflammation provide one potential explanation for the antidepressant benefits of exercise."

OBESITY

- 32) "Depression promotes obesity, and obesity in turn promotes depression."
- 33) "A clear theme across research with omega-3 fatty acids, exercise, and cytokine antagonists is that anti-inflammatory interventions have a substantially greater impact on mood in individuals with heightened inflammation."

Anti-Inflammatory Treatment Strategies

- 34) Anti-inflammatory treatment with NSAIDs is associated with increased risk for gastrointestinal bleeding (especially for older adults or those who use alcohol), and increased risk of cardiovascular events.
- 35) Anti-inflammatory treatment with cytokine inhibitors reduces the ability to fight infection, and increases risk of death and reactivation of tuberculosis.
- 36) Anti-inflammatory treatment with omega-3 fatty acids and higher fish consumption is associated with a lower prevalence of depression and few side effects. "EPA appears to be more beneficial than DHA." **[Important]**
- 37) Probiotics reduce gut leakiness and neuro-inflammation. In humans, probiotics can improve mood.
- 38) "Healthier diets offer some protection against the development of both depressive symptoms and depressive disorders."
- 39) "Both pain and disturbed sleep boost inflammation."
- 40) "Depression and inflammation are both linked to a number of disorders and systemic diseases, and the processes we described clearly have an impact on those diseases as well."
- 41) Treating inflammation can have a far-reaching impact on mood and health.

COMMENTS FROM DAN MURPHY

The central message is that inflammation drives depression, and vice versa. Depression drives other poor health issues.

Anti-inflammation approaches both prevent and treat depression.

The non-drug anti-inflammatory approach advocated in this article includes:

- Improved Diet
- Omega-3 Supplementation, especially EPA
- Probiotics and Prebiotics
- Exercise
- Sleep Hygiene
- Stress Reduction

Factors Associated with Heightened Inflammation and Depression

- **Older Age**

Inflammation rises with age. Among the genes up-regulated as we age, more than half regulate inflammation-related processes.

- **Obesity**

"Adipocytes (fat cells) produce and secrete IL-6 and TNF- α , and abdominal fat is a major inflammatory source. Central adiposity and greater body fat are associated with larger stress-induced inflammatory responses."

- **Poor Sleep**

"Sleep loss stimulates production of pro-inflammatory cytokines and cellular inflammatory signaling."

"Disturbed sleep accompanies many inflammation-associated comorbidities."

Both decreased sleep (<5 hours) and increased sleep (>9 hours) increase inflammation.

- **Unhealthy Diet "Western" Diets**

Diets high in red and processed meats, sweets and desserts, French fries and refined grains, increase inflammation.

- **Omega-6/Omega-3 Ratio**

High levels of Omega-6 fatty acids and low levels of Omega-3 fatty acids (especially EPA) are associated with inflammation and depression.

- **Sedentary lifestyle**

"Physically active individuals have lower inflammation than their sedentary counterparts."

"Better cardiorespiratory fitness is associated with lower inflammation."

- **Pain and Fatigue**

Pain and Fatigue have strong ties with inflammation and depression.

- **Smoking**

Smokers have higher inflammation markers than nonsmokers.

- **Alcohol**

Heavy drinkers are more inflamed than abstainers or moderate drinkers.

- **Female Sex**

More women than men have elevated inflammation, and women appear to be more sensitive to heightened inflammation.

- **Prebiotics and Probiotics**

"Probiotics reduce gut leakiness and neuro-inflammation."

- **Caloric restriction**

"Caloric restriction can simultaneously attenuate production of pro-inflammatory cytokines while enhancing anti-inflammatory pathways."

- **Weight loss**

Reduces multiple obesity-related health risks, including depression.

"Weight loss reduces inflammation."

- **Exercise**

"Can result in substantial long-term benefits for morbidity and mortality."

"Fitness is inversely associated with inflammation."

- **Yoga, tai chi, and mindfulness-based meditation**

Improve sleep and reduced inflammation.