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Antioxidant Supplement Coenzyme Q10 Looks Promising for Bipolar Depression

Coenzyme Q10 (CoQ10) is an antioxidant that occurs naturally in the human body, but its levels decline with age, medical illness, and depression. In a randomized, controlled trial that was published in the *Journal of Clinical Psychopharmacology* in 2018, researcher Maryam Mehrpooya and colleagues found that **adding coenzyme Q10 supplements to a treatment regimen improved bipolar depression compared to adding placebo.**

The pathophysiology of bipolar disorder involves mitochondrial dysfunction, oxidative stress, and inflammation, and coenzyme Q10 can affect all of these pathways. It is also neuroprotective, and may help prevent the degeneration of neurons in people with Alzheimer's, Parkinson's, or Huntington's diseases.

The study included a final total of 69 participants who were randomly assigned to receive either 200 mg/day of coenzyme Q10 supplements or placebo in addition to their normal treatment regimen, which had been stable for at least two months at the time of the study. Participants' bipolar depression was rated at the beginning of the study, after four weeks, and after eight weeks. **At the eight-week mark, coenzyme Q10 showed a statistically significant benefit over placebo with a large effect size.** Three participants who received coenzyme Q10 experienced full remission of their depression, and 72% of those in the coenzyme Q10 group improved compared to only 12% of those who received placebo.

The study had some limitations. It was small, and twenty participants dropped out of the study before its completion, which may have inflated the findings.

Previous research found that coenzyme Q10 had benefits in specific populations. In two non-blind studies (studies in which participants know that they are receiving the treatment in question rather than possibly a placebo), 29 older patients with bipolar disorder improved when taking 800 mg to 1200 mg/day of coenzyme Q10. A randomized, controlled trial of coenzyme Q10 in people with multiple sclerosis and depression found that 500 mg/day reduced fatigue symptoms and depression. Coenzyme Q10 has also improved well-being and energy in small, controlled trials in people with breast cancer, Gulf War veterans, and elderly populations.

Taking coenzyme Q10 is low-risk. It had no adverse effects in the study by Mehrpooya and colleagues. Gastrointestinal reactions are possible, but can be managed by taking coenzyme Q10 with food and spreading out dosing throughout the day. Insomnia is also possible, but is less likely when coenzyme Q10 is taken early in the day. One effect to note is that coenzyme Q10 can interact badly with the blood-thinner warfarin.

Editor's Note: The study by Mehrpooya and colleagues is interesting. Another antioxidant, N-acetylcysteine (NAC), also took 2 months to work in trichotillomania and bipolar depression, so patients should be warned not to expect a quick response with either coenzyme Q10 or NAC. Other potentially useful supplements include: Vitamin D3 (1500–5000 IU/day), folate or L-methylfolate, and acetyl-L-carnitine. Acetyl-L-carnitine may work more quickly, based on its presumed mechanism (increasing the production of the inhibitory metabotrophic glutamate receptor mGluR-2, which inhibits glutamate release).

Eating Beef Jerky and Other Nitrate-Cured Meats Linked to Increased Mania Risk

In a 2018 article in the journal *Molecular Psychiatry*, researcher Seva G. Khambadkone and colleagues reported that a history of eating nitrated dry cured meat, such as beef jerky, was associated with a more than threefold increase in the risk of current mania. Eating other types of meat and fish products was not linked to mania.

The study included 217 people with mania, 91 with bipolar depression, 79 with unipolar depression, and 371 with schizophrenia, plus 343 control participants without a psychiatric disorder. Each participant responded to a questionnaire assessing whether they had ever eaten certain foods. The researchers had the idea that eating foods such as undercooked meat or fish, which might carry infectious agents, could be connected with mania, since inflammation seems to be linked to psychiatric illness. To the researchers' surprise, **their analysis found an independent link between eating nitrated dry cured meat (such as beef jerky, turkey jerky, or meat sticks) and being admitted to a hospital with acute mania.** Having eaten other cured meats such as salami or

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Prenatal Prevention of Psychiatric Illness with Nutritional Supplements

In a 2018 article in the *American Journal of Psychiatry*, researcher Robert Freedman and colleagues shared the results of a systematic review of data on nutritional supplements during pregnancy for the primary prevention of psychiatric illness in the child. Freedman and colleagues concluded that the evidence is robust that prenatal **folic acid** supplementation plus multivitamins not only can prevent birth defects such as cleft palate, spina bifida, and microcephaly, but also social withdrawal, decreased attention, and aggression at age 18 months. They wrote, "Supplements of up to 4 mg [of folic acid] before 12 weeks gestation have been found to be safe and effective."

The effects of **omega-3 fatty acid** supplementation depended on when the supplements were taken. Taking omega-3 fatty acid supplements early in pregnancy was linked to an increase in schizophrenia and more symptoms of attention deficit hyperactivity disorder (ADHD) in the offspring. However, supplementation after 20 weeks of pregnancy decreased preterm delivery, low birth weight, and asthma.

As of 2017, **choline** supplementation during pregnancy is recommended by the American Medical Association. Their recommendation is based on research in which the choline precursor phosphatidylcholine (5,000-6,300 mg/day) was given to mothers beginning in the 18th week of pregnancy and continued in the newborn for two weeks to three months after birth in the form of 100mg of liquid phosphatidylcholine. This supplementation regimen normalized the P50 auditory evoked potential, a measure of inhibitory sensory gating that is abnormal in patients with schizophrenia and bipolar disorder and infants whose parents had psychosis, depression, or smoked (all risk factors for a later diagnosis of schizophrenia).

Healthy individuals show a reduced response to an auditory cue when it is repeated 50 milliseconds after the initial cue. In people with schizophrenia, response to the repeated cue is not suppressed. Not only did the P50 auditory evoked potential normalize with phosphatidylcholine supplementation, but at 3.5 years of age, those who received phosphatidylcholine supplements in utero and as newborns had fewer problems with attention and social interactions. The findings were even more robust in those with the CHRNA7 genotype (a genetic variation in the alpha 7 nicotinic receptor), which is a risk factor for schizophrenia.

Supplementation with **vitamins A and D** during gestation also decreased the risk for schizophrenia and autism spectrum disorders in offspring. Recommendations include Vitamin D at doses of 600 to 4,000 IU for pregnant mothers and 400 to 1,000 IU for infants. Because of potential toxicity, vitamin A should be limited to 8,000 units from diet and supplements combined. (Supplements typically contain 2,500 units.)

While there are some methodological limitations to the findings, Freedman and colleagues conclude, "As part of comprehensive maternal and fetal care, prenatal nutrient interventions should be further considered as uniquely effective first steps in decreasing risk for future psychiatric and other illnesses in newborn children."

Editor's Note: Given the high risk of psychiatric illness (74%) in the offspring of a parent with bipolar disorder and the finding of abnormal P50 auditory evoked potential in patients with bipolar disorder, the recommended nutritional supplements should be given special consideration during gestation of a child who has a parent with bipolar disorder. According to the 2018 article by Freedman and colleagues, this would include folate, phosphatidylcholine, vitamin A and vitamin D.

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Nitrated Meats Linked To Mania Risk (cont.)

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prosciutto was not linked to mania, nor was having eaten any other food.

Following these findings, Khambadkone and colleagues designed a study in which rats were given meat with added nitrate. The rats showed hyperactivity that resembled human mania, alterations in brain pathways that have been linked to bipolar disorder, and changes to gut microbes.

Preventing Illness in the Offspring of a Parent with Bipolar Disorder

A 2018 article by researcher Robert Freedman and colleagues in the *American Journal of Psychiatry* (described at left) reported that prenatal nutritional supplements can reduce mental illness in at-risk offspring. The article made a good case for supplementation with folate, phosphatidylcholine, and vitamins A and D.

Here we describe some additional ways to minimize risk of mental illness in children who are at risk for bipolar disorder or other mental illnesses.

Some efforts at prevention can begin even before a child is conceived. Avoiding smoking or drinking alcohol and maintaining a nutritious diet to prevent inflammation and excessive weight gain before conception could reduce adverse epigenetic effects on the offspring. Epigenetics refers to environmental influences on gene transcription. The impact of life experiences such as a mother or father's substance use is not registered in their child's DNA sequence, but can influence the structure of the child's DNA or its packaging.

Maternal good health and wellbeing during pregnancy has also been shown to improve neonatal health and functioning.

Once a child is born, they can be encouraged in healthy habits, including a nutritious diet, good sleeping habits, regular vigorous exercise, and mindfulness/meditation training (which pediatric psychiatrist James Hudziak has suggested should be universal).

For a child who is beginning to develop mood or behavioral symptoms, more intensive intervention may be prudent. Research supports the effectiveness of family interventions such as family-focused therapy (FFT) for youth with depression, cyclothymia, or bipolar disorder not otherwise specified (BP-NOS) and a family history of bipolar disorder. Researcher David J. Miklowitz described the effects of this intervention in a 2013 article in the *Journal of the American Academy of Child and Adolescent Psychiatry*.

Depression in children 3 to 6 years of age is as common as depression in older children (with rates around 1–2%), and robust improvements have been observed when families engage in parent child interaction therapy (PCIT) with a focus on emotional development. In PCIT, parents are coached while interacting with their children and encouraged to establish warm interactions while setting appropriate limits. In a study by Joan L. Luby and colleagues published in the *American Journal of Psychiatry* in 2018, using PCIT modified to include an emotional development component improved depression and associated symptoms in children aged 3 to 11, and it also improved mothers' mood and behavior.

Data on nutritional supplements for children as an active intervention for early psychiatric symptoms are less well delineated, but deserve consideration. Many ill children have low vitamin D or an outright deficiency, and one study found that vitamin D supplementation improved behavior. The antioxidant N-acetylcysteine (NAC) improves depression and anxiety in adults and irritability in children with autism (at 2,700mg/day). It is also effective in a variety of habit-related and substance abuse disorders. Dosing for a child at risk for psychiatric illness might begin with 500mg/day and increase 500mg/week to a maximum of about 2,500–3000mg/day.

For children who face some trauma or adversity such as abuse or neglect, acetyl-L-carnitine (ACL) might be considered. ACL is low in depressed adults who had an early onset of their depression and in those with a history of abuse in childhood. There is evidence that ACL improves depression in adults. In animal models of depression, ACL works faster than antidepressants and has an epigenetic mechanism that rapidly normalizes low levels of the metabotrophic glutamate receptor mGluR-2, which decrease with stress, allowing too much release of the neurotransmitter glutamate.

For children with bipolar not otherwise specified (BP-NOS), more traditional medications might be contemplated in addition to family-focused therapy. High on the list would be the antipsychotic lurasidone, which is now approved by the US Food and Drug Administration for bipolar depression in 10- to 17-year-olds. Anticonvulsants such as lamotrigine or oxcarbazepine (and valproate in boys only) might also be considered, as well as lithium. Lithium should be given strong consideration if there is a family history of bipolar disorder, and especially if there is a family history of responsiveness to lithium. BP-NOS can be difficult to stabilize, and 35-50% of those diagnosed with it convert to a diagnosis of bipolar I or II after several years of follow up, especially if there is a family history of bipolar disorder.

Ideally, treating risk factors and/or early symptoms of psychiatric illness would prevent the development of full-blown illness. Efforts at prevention might be most important in a child with a parent who had an early onset of bipolar disorder, as this is an additional risk factor for early-onset illness in the child. Further risk factors for early-onset illness are: 1) a loaded family history in parents and grandparents, not only of bipolar disorder but also of depression, suicide attempts, alcohol abuse or substance abuse, and 2) experiencing verbal, physical, or sexual abuse in childhood. Another risk factor is the family living in the US (as opposed to Europe), where a quarter of those who develop bipolar disorder do so prior to age 13, and two-thirds prior to age 18.

The data are striking that early comprehensive intervention after a first or

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Meta-Analysis Finds Omega-3 Fatty Acids Do Not Reduce Cardiovascular Disease Risk

In a 2018 meta-analysis published in the journal *JAMA Cardiology*, researcher Theingi Aung and colleagues found that **across 10 studies including a total of 77,197 participants, omega-3 fatty acid supplementation did not reduce risk of coronary heart disease in people at high risk.** This newer finding conflicts with a 2017 advisory from the American Heart Association that suggested omega-3 fatty acid supplementation might prevent cardiovascular disease.

When it comes to mood disorders, it has been similarly difficult to pin down whether omega-3 fatty acids are helpful. Data on omega-3 fatty acid supplements for the prevention of depression have been ambiguous, with small numbers of studies and variations in study design that make it difficult to draw strong conclusions about whether these supplements can improve or prevent depression.

A 2016 systematic review by Paola Bozzatello and colleagues in the *Journal of Clinical Psychiatry* found only seven studies of omega-3 fatty acid supplementation in bipolar disorder. The studies had small sample sizes and widely varying dosage parameters, so the evidence that can be drawn from them is not strong, but the review did find a modest benefit on bipolar depression (but not mania) when omega-3 fatty acids were added to a treatment regimen, compared to treatment as usual.

The same review found that studies of omega-3 fatty acid supplementation in unipolar depression also varied widely, and thus it was difficult to draw inferences from them. Some meta-analyses found no benefit to omega-3 fatty acid supplementation, while others suggested that omega-3s could improve depression. The review found that the type of omega-3 fatty acids used might matter. Supplementation with EPA seemed to improve depression more than supplementation with DHA. The review also cited a 2014 comprehensive meta-analysis by Giuseppe Grosso and colleagues in the journal *PLoS One* that analyzed the findings from 19 studies in people with depression or depressive symptoms. Grosso and colleagues found that people with more severe depression seemed to benefit more from omega-3s.

Immune Benefits of Eating Cranberries

Decades ago, researchers found that a compound in cranberries called proanthocyanidins (PACs) helps prevent bacteria from sticking to the urinary tract, so they are unable to multiply and cause infections. More recently, **researchers have explored whether cranberries can protect against other bacterial infections, reducing the need for antibiotics.** Overuse of antibiotics is leading to a worldwide problem of antibiotic resistance, in which even simple infections may no longer respond to antibiotics. Consuming cranberries also seems to suppress the bacteria that causes stomach ulcers.

Cranberries have other benefits. They are full of antioxidants, which help to lower oxidative stress and inflammation and boost the immune system. These effects are helpful in preventing bacterial infections, but they also improve heart health. Antioxidants can reduce the oxidation of LDL ("bad") cholesterol while increasing HDL ("good") cholesterol. They also keep arteries flexible. These effects all reduce risk factors for heart disease.

Preventing Illness in Children at High Risk for Bipolar Disorder (cont.)

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second manic episode in adolescents or adults reduces episode recurrences compared to treatment as usual. **Comprehensive intervention includes psychotherapy, psycho-education, mood charting, and pharmacotherapy**. The randomized intervention described by researcher Lars V. Kessing and colleagues in a 2013 article in the *British Journal of Psychiatry* lasted two years, but the benefits continued over the subsequent four years, indicating that early intervention could greatly improve the trajectory of the illness over a period of six years.

Stopping the transgenerational transmission of psychiatric illness with comprehensive therapeutic intervention might be taken on as a goal for each family with children at high risk, even if data for the effectiveness of prevention strategies are not ironclad. This would meet an accepted standard for evidence-based medicine: when direct gold-standard evidence is lacking, physicians and families need to go with the next-best data available, especially when treatment options are safe and the likely outcomes of untreated illness are serious or even disastrous.

Until early intervention studies in children with early signs of psychiatric illness or those who are at high risk for psychiatric illness prove otherwise, families and physicians would be justified in presuming that the robust data from Kessing's study would also apply to these younger patients. Early intervention studies in young people with schizophrenia have been conducted over the past two decades, and it is too bad that there have been few efforts to conduct these for bipolar and related disorders. Parents whose own bipolar illness started early and/or was compounded by other psychiatric illnesses could thus reasonably consider intervening early in their child in an effort to minimize the risk of later serious psychiatric illness.

Adolescents with Bipolar Disorder May Have Higher Levels of Vitamin D–Binding Protein

A 2018 article by Brawnie Petrov and colleagues in the journal *Translational Psychiatry* suggests that adolescents with bipolar disorder have higher levels of vitamin D–binding protein than adolescents without a mood disorder. The researchers wrote that **vitamin D–binding protein "responds early to cellular damage by binding…structural proteins and activating inflammatory cells."**

This pilot study suggests that measuring levels of vitamin D–binding protein could be a useful marker of bipolar disorder. The study was small, with only 12 participants who had bipolar disorder, 11 who had unipolar depression, and 13 with no mood disorder. The researchers hope to follow up with larger studies in adolescents and adults using blood that has already been collected from people with bipolar disorder.

Vitamin D–binding protein is not measured by a standard blood test. The study authors used a technique where they "fished" for inflammatory factors that might be linked to mood disorders. The researchers began by looking for a link between other inflammatory markers in the blood and bipolar disorder, which have repeatedly been found in other studies, but they did not find any such association. There also did not seem to be a link between bipolar illness and vitamin D levels in the blood, only vitamin D–binding protein levels.

It can be especially difficult to distinguish early bipolar disorder from unipolar depression, and if the results of this small study are replicated, a blood test might eventually help to identify people with bipolar disorder earlier.

Vitamin D Deficiency in Newborns Linked to Higher Risk of Schizophrenia in Adulthood

A 2018 study by Darryl W. Eyles in the journal *Scientific Reports* found that newborns with vitamin D deficiency were more likely to develop schizophrenia later in life. The study made use of several Danish data depositories and had a large sample size of 2,602 participants. In this case control study, registries of patients treated for schizophrenia were matched up to preserved dried blood samples collected at their births, and these were compared to other dried blood samples from people without schizophrenia who shared the same sex and birthdate.

The researchers divided participants into quintiles based on vitamin D levels at birth. Compared to those who fell into the fourth quintile, those in the lowest quintile were 44% more likely to be diagnosed with schizophrenia in adulthood. The researchers also determined polygenic risk scores for each participant, that is, they calculated schizophrenia risk based on the presence of various genes. The two processes together explained 1.2% of the variance in schizophrenia diagnoses.

Risk factors for vitamin D deficiency include being born in the winter or spring, living in high-latitude locations, spending early life in an urban setting, and being darker-skinned (especially in high-latitude locations). These risk factors are all correlated with decreased skin absorption of UV rays from the sun, which is how the human body produces vitamin D. The vitamin D receptor is expressed in the brain in areas that are relevant to schizophrenia, such as areas with a lot of dopamine activity, and each of the above risk factors also applies to schizophrenia.

As expected, participants born in the winter and spring had lower vitamin D levels. Participants whose parents had immigrated to Denmark had lower vitamin D than those with parents native to Denmark.

Newborns' vitamin D levels depend completely on their mothers' vitamin D levels, so Eyles and colleagues suggest that ensuring pregnant women have adequate vitamin D levels could prevent some cases of schizophrenia.

Vitamin D Has More Benefits Than Previously Thought

Vitamin D has long been known as an important vitamin for bone health, preventing conditions such as osteoporosis and rickets. More recently, research suggests that vitamin D may also protect against conditions such as cancer, heart failure, diabetes, respiratory tract infections, and autoimmune disease.

Many Americans have low vitamin D or a vitamin D deficiency. The human body produces vitamin D in large amounts when the skin is exposed to ultraviolet B rays in sunlight. Vitamin D can also be absorbed from vitamin D–fortified foods such as dairy products, some orange juice, and cereals. Some foods such as fatty fish, beef liver, and egg yolks naturally contain some vitamin D, but it is difficult to get enough vitamin D just from consuming these foods.

Low mood or seasonal affective disorder (SAD), in which people feel depressed during winter periods of limited exposure to sunshine, have been linked to low vitamin D.

Other symptoms of low vitamin D vary but can include pain in the joints, bones, or muscles; fatigue; and breathing problems.

Editor's Note: ***A few small studies have suggested that 1,500 IU per day of vitamin D supplements can help depressed mood, even in those with normal vitamin D levels.*** *Several studies have indicated that children or adolescents with psychiatric disorders are especially likely to be vitamin D–deficient. Another study found that higher amounts of vitamin D (4,000 IU) could improve cognition in healthy volunteers more than lower doses could. Vitamin D also improved cognition in people with multiple sclerosis and in those with the autoimmune disease Hashimoto's thyroiditis.*

Vitamin Methyl B12 Improved Autism Symptoms in Randomized, Placebo-Controlled Study

In a 2016 article in the *Journal of the American Academy of Child and Adolescent Psychiatry*, Robert L. Hendren and colleagues described an 8-week study in which the vitamin methyl B12 improved symptoms of autism spectrum disorders in children. **Fifty-seven children were randomized to receive either 75 µg/kg of methyl B12 injected under the skin every three days or saline injections as a placebo instead. Methyl B12 improved the children's autism symptoms compared to placebo. The improvements correlated with increases in levels of the amino acid methionine in the blood and improvements in cellular methylation capacity.** Children with autism spectrum disorders have reduced ability to methylate (i.e. add methyl groups to) DNA. The methylation process helps convert the toxic amino acid homocysteine into beneficial methionine. The children who received methyl B12 showed a reduction in homocysteine and a better ratio of methionine to homocysteine.

Homocysteine is bad for the heart, for cognition, and for fetal development, while methionine can help improve depression and is important to many cellular reactions. Converting homocysteine to methionine requires vitamin B12 and folate, another B vitamin found in foods such as green vegetables and beans.

Taking folate supplements can help make antidepressants more effective by aiding the methylation process. However, some people have a common variation in the MTHFR gene that makes it difficult for the body to make use of folate. These people would need to take the nutritional supplement L-methylfolate instead of regular folate to help in the conversion of homocysteine to s-adenosylmethionine (SAMe, which acts as an antidepressant).

Rich Diet Reprograms Immune Cells in Mice

A 2018 article by Anette Christ and colleagues in the journal *Cell* describes the process by which a Western diet can trigger changes to the immune system in mice. **The mice fed a calorically rich Western diet started to show systemic inflammation. Blood measures of inflammation returned to normal after the mice resumed their regular diet, but their immune responses remained heightened, as if the immune system had been trained to overreact.**

The vast majority of deaths in Western cultures are caused by non-communicable diseases such as type 2 diabetes and cardiovascular disease, which have been linked to lifestyle factors such as diet and exercise. The immune system has two wings: one that responds to specific pathogens, and one that mounts general protection against infection and is triggered by immune signaling receptors. However, according to Christ and colleagues, in addition to reacting when microbes are present, this second wing may also respond to "sterile" danger signs, such as consumption of a Western diet. The immune system may become trained to react this way chronically, something that the

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Eating Walnuts and Other Tree Nuts May Lower Cholesterol

In a 2018 meta-analysis and systematic review published in the *American Journal of Clinical Nutrition*, researcher Marta Guasch-Ferré and colleagues shared their analysis of 26 studies of the effects of diets rich in walnuts on blood lipids and cardiovascular health. The studies included a total of 1059 participants. **The walnut-heavy diets were associated with lower total cholesterol, lower LDL ("bad") cholesterol, and lower triglyceride concentrations. They were also associated with lower apolipoprotein B, a component of LDL.**

When walnut-enriched diets were compared to American diets and Western diets, the benefits of the added walnuts on total cholesterol and LDL cholesterol were even more dramatic. The researchers described a Western diet as high in red and processed meats, high-fat dairy products, processed and artificially sweetened foods, and with little intake of fruits, vegetables, fish, legumes, or whole grains.

Compared to control diets, the diets rich in walnuts did not cause weight gain or an increase in body mass index (BMI), and they also did not affect blood pressure.

The studies included in the meta-analysis lasted from four weeks to one year, with a mean length of 8 weeks. The amount of walnuts ranged from 15 to 108 grams per day. In most cases, participants were given whole walnuts to incorporate into whatever daily meal plan they were following, which in some cases was their usual diet and in others was an intervention diet such as a Mediterranean diet or a low-fat diet.

Another meta-analysis published in the *American Journal of Clinical Nutrition* in 2015 by Liana C. Del Gobbo and colleagues analyzed 61 studies about the effects of tree nuts on cholesterol and related measures, and similarly found that **eating tree nuts lowers total cholesterol, LDL cholesterol, ApoB, and triglycerides.** Del Gobbo and colleagues wrote, "The major determinant of cholesterol lowering appears to be nut dose rather than nut type." **Tree nuts include walnuts, pistachios, macadamia nuts, pecans, cashews, almonds, hazelnuts, and Brazil nuts.**

Study in Mice Suggests that Compound in Turmeric May Reduce Anxiety and Promote Resilience to Stress

Chronic stress is a risk factor for the development of mood and anxiety disorders. Researchers have begun to focus on how to promote resilience to stress. **Curcumin is a micronutrient found in turmeric that has anti-inflammatory and antidepressant effects and may promote such resilience.**

Researchers studying human depression often design studies to see how mice with chronic social defeat stress respond to various interventions. Mice who are repeatedly menaced by a larger mouse begin to show symptoms that resemble human depression, such as social avoidance, lack of interest in saccharin compared to plain water (a stand-in for loss of enjoyment or anhedonia in humans), and anxiety.

In a 2018 article in the journal *Neuropsychopharmacology*, researcher Antonio V. Aubry and colleagues described the effects of curcumin on mice undergoing chronic social defeat stress. Mice who were given a diet that consisted of 1.5% curcumin showed a 4.5-fold increase in resilience to social defeat stress, measured by their performance during a test of social interaction. Among the 129 mice in the study, 64% showed the increase in resilience, the remaining 36% did not respond to the curcumin diet and had the normal 'depressed' response. The mice who responded well to curcumin released less of the stress hormone corticosterone, and they also had lower levels of the inflammatory marker IL-6.

All of the mice on the curcumin diet showed reduced anxiety during tests that forced them to travel through open spaces (when they prefer to stay in more enclosed spaces or move along the edges of an enclosure).

Western Diet Reprograms Immune Cells in Mice

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researchers believe may trigger inflammation in noncommunicable diseases.

The Western diet triggered epigenetic changes to the mice's immune system. Epigenetic changes are ones that affect the structure of DNA, for example how tightly it is packaged. In the case of the Western diet, these changes resulted in a heightened immune system that launched strong inflammatory responses in reaction to even small stimuli. Myeloid cells from bone marrow were reprogrammed to proliferate and provide a stronger immune response.

The researchers also took human monocyte cells trained with LDL ("bad") cholesterol and stimulated them with lipopolysaccharide (an inflammatory compound made of fat and sugar). The cells showed a heightened immune reaction similar to that seen in the mice.

Mice genetically engineered to lack the inflammasome NLRP3, which activates inflammatory responses, did not show the systemic inflammation or the enhanced myeloid activity when fed the Western diet, so Christ and colleagues believe NLRP3 may play an important role in mediating the immune response to the Western diet.

Red Meat Interacts with Bacteria in the Gut to Raise Heart Disease Risk

A 2018 study by a group of researchers at the Cleveland Clinic have clarified the way that a diet heavy in red meat may lead to heart disease. The research centers on trimethylamine N-oxide (TMAO), a gut bacteria byproduct that is formed during digestion. **When gut bacteria digest choline, lecithin, and carnitine, nutrients that are common in certain animal products and red meat, TMAO is produced.**

In an article by Robert A. Koeth and colleagues in the *European Heart Journal*, the researchers show that diets that rely on red meat as the main protein source lead to more circulating TMAO than diets in which white meat or something other than meat is the primary source of protein. They found that in people who eat a lot of red meat, the kidneys are less efficient at expelling TMAO, and levels creep even higher. **High levels of TMAO have been linked to hardening and narrowing of the arteries (atherosclerosis) and heart disease complications.** High levels of TMAO in the blood can be a predictor of heart attack, stroke, and death.

The study of 113 participants consisted of three different diets that each participant followed in random order (with a washout period in between each diet). A month of eating a diet in which red meat was responsible for at least 25% of participants' daily calories led to higher levels of TMAO in the blood and urine. TMAO increased threefold during the red meat diet periods compared to periods in which white meat or non-meat protein were the source of those calories, and in certain participants, TMAO increased as much as tenfold. When participants stopped eating the red meat diet, their TMAO levels fell over the following month.

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