

Low Cholesterol May Raise Your Alzheimer's Risk

STORY AT-A-GLANCE

- Cholesterol is found in your bloodstream and cells, and is necessary for the production of cell membranes. Cholesterol also plays an important role in the formation of memories and is vital for healthy neurological function
- Higher cholesterol levels are associated with better brain health; low cholesterol levels have been shown to increase your risk of depression and suicide
- A 2014 study found higher levels of HDL and lower levels of LDL were associated with a reduced risk for amyloid plaque deposits in the brain, independently of age and presence of the APOE4 gene, which raises your risk for Alzheimer's
- Research published in 2008 found elderly individuals who were not genetically predisposed to Alzheimer's disease who had the highest levels of cholesterol — including the highest levels of LDL — had the best memory
- Another study published in 2018 came to a similar, although more complex, conclusion. While having higher total cholesterol at midlife was associated with a reduced risk for cognitive decline after the age of 85, those whose cholesterol levels increased between midlife and late life were at increased risk

While cholesterol has been vilified as something that should be as low as possible to prevent heart disease, it's actually a crucial component for good health and too low a level can have serious repercussions for your health.

Cholesterol is found not only in your bloodstream but also in every cell in your body, and is necessary for the production of cell membranes, virtually every steroid hormone, vitamin D and bile acids that help you digest fat.

Cholesterol also plays an important role in the formation of memories and is vital for healthy neurological function. For example, low cholesterol levels have been shown to increase your risk of depression and suicide,¹ in some cases rather dramatically.

As noted by neurologist Dr. David Perlmutter, a quarter of all the cholesterol in your body is found in your brain, where it performs the function of an antioxidant.² A number of studies have demonstrated that, contrary to popular belief, higher cholesterol levels are associated with better brain health.

According to senior research scientist Stephanie Seneff, Ph.D., insufficient fat and cholesterol in your brain play a crucial role in the Alzheimer's disease process, detailed in her 2009 paper³ "APOE-4: The Clue to Why Low Fat Diet and Statins May Cause Alzheimer's."

Cholesterol 101

As noted by nutritional researcher Zoe Harcombe, a researcher in dietary fat who has a Ph.D. in public health nutrition, "It is virtually impossible to explain how vital cholesterol is to the human body. If you had no cholesterol in your body you would be dead."⁴

Your liver manufactures most, about 80 percent, of the cholesterol your body requires, which in and of itself suggests your body cannot survive without it. The remaining 20% comes from your diet. However, dietary cholesterol is absorbed at a rate of 20% to 60% depending on the individual, and if you consume less, your body will compensate by making more and vice versa.

In order to be transported through your bloodstream, the cholesterol is encapsulated in a lipoprotein, which is where the terms LDL (low-density lipoprotein), HDL (high-density lipoprotein) and VLDL (very-low-density lipoprotein) come from. Whether LDL is truly as hazardous as many in the medical community insist, however, is still up for debate.

According to Harcombe, the notion that there is good (referring to HDL) and bad (LDL) cholesterol is incorrect, as technically LDL and HDL are not even cholesterol; they're carriers and transporters of cholesterol, triglycerides (fat), phospholipids and proteins. "LDL would more accurately be called the carrier of fresh cholesterol and HDL would more accurately be called the carrier of recycled cholesterol," Harcombe explains.⁵

Now, HDL is indeed beneficial in that it acts as a master manager, helping protect LDL against oxidation and transporting triglycerides and cholesterol in and out of the VLDL. In a healthy person, the LDL will be reabsorbed by the liver after about two days, where it gets broken up and recycled. As a general rule, a high-sugar diet will cause damaged LDLs to rise, beneficial HDLs to drop, triglycerides and, often, total cholesterol to rise.

How Cholesterol Impacts Neurological Function, Disease Risk

Getting back to Alzheimer's, a number of studies have demonstrated the importance of higher cholesterol for the prevention of this devastating neurodegenerative disease. In 2014, a study⁶ in JAMA Neurology investigated the impact of cholesterol levels on the deposition of beta-amyloid plaque in the brains of 74 seniors with a mean age of 78. Three of them had mild dementia, 33 were clinically normal and 38 had mild cognitive impairment. As explained by the authors:⁷

"Cholesterol, vital to neuronal structure and function, has important roles in the synthesis, deposition, and clearance of β -amyloid ($A\beta$) and may have a pathogenic role in Alzheimer disease (AD) ... There are also important connections among apolipoprotein E (APOE), $A\beta$, and cholesterol.

A strong genetic risk factor for AD, the APOE ϵ 4 allele is associated with earlier and higher deposition of $A\beta$. APOE is the primary transporter of cholesterol in the brain, and its isoforms differentially modulate brain cholesterol levels."

Here, the researchers found that higher levels of HDL and lower levels of LDL were associated with a reduced risk for amyloid plaque deposits in the brain, and these findings were independent of age and presence of the APOE4 gene. Study coauthor Dr. Charles DeCarli, a professor of neurology at UC Davis and director of the UC Davis Alzheimer's Disease Center, commented on the results:⁸ *"If you have an LDL above 100 or an HDL that is less than 40 ... you want to make sure that you're getting those numbers into alignment. You have to get the HDL up and the LDL down."*

That said, research⁹ published in 2008 found that elderly individuals who were not genetically predisposed to Alzheimer's disease who had the highest levels of cholesterol — including the highest levels of LDL — had the best memory, so the verdict is still out on whether high LDL is a significant risk factor.

Another study^{10,11} published in 2018 similarly came to a similar, although more complex, conclusion. In this study, the researchers evaluated the total cholesterol levels of participants in the Framingham Heart Study at midlife (around the age of 40) and late-life (around the age of 75). They also assessed mean total cholesterol between midlife and late life, and the total change in cholesterol since midlife.

Here, they found that having higher total cholesterol at midlife was associated with a reduced risk for cognitive decline after the age of 85. However, those whose cholesterol levels increased between midlife and late life were at increased risk, suggesting there are likely other unknown variables at play as well.

New Theory Proposed

In related news, researchers at Florida Atlantic University's (FAU) Brain Institute and Vanderbilt University have proposed a new theory to help explain the link between cholesterol, beta-amyloid and Alzheimer's. The study,¹² published in *Neurobiology of Disease* in July 2019, tracked the location and mobility of amyloid precursor protein to assess its function in neurons.

Amyloid precursor protein is strongly associated with Alzheimer's, but its distribution across various brain membranes and neuronal functions are still unclear. As reported by Science Daily:¹³

"In the case of more common sporadic Alzheimer's disease, the highest genetic risk factor is a protein that is involved in cholesterol transportation and not this amyloid precursor protein ... For the study, [Qi] Zhang [Ph.D., senior author and researcher at FAU Brain Institute] and collaborators genetically disrupted the interaction between cholesterol and amyloid precursor protein.

Surprisingly, by disengaging the two, they discovered that this manipulation not only disrupts the trafficking of amyloid precursor protein but also messes up cholesterol distribution at the neuronal surface.

Neurons with an altered distribution of cholesterol exhibited swollen synapses and fragmented axons and other early signs of neurodegeneration. 'Our study is intriguing because we noticed a peculiar association between amyloid precursor protein and cholesterol that resides in the cell membrane of synapses, which are points of contact among neurons and the biological basis for learning and memory,' said Zhang.

'Amyloid precursor protein may just be one of the many accomplices partially contributing to cholesterol deficiency. Strangely, the heart and brain seem to meet again in the fight against bad cholesterol.'

High-Fat Ketogenic Diet Protects Your Brain Health

As noted by Seneff in her 2009 paper¹⁴ on Alzheimer's:

"ApoE-4 ... is a known risk factor [for Alzheimer's disease]. Since apoE plays a critical role in the transport of cholesterol and fats to the brain, it can be hypothesized that insufficient fat and cholesterol in the brain play crucial role in the disease process.

In a remarkable ... study, it was found that Alzheimer's patients have only 1/6 of the concentration of free fatty acids in the cerebrospinal fluid compared to individuals without Alzheimer's. In parallel, it is becoming very clear that cholesterol is pervasive in the brain, and that it plays a critical role both in nerve transport in the synapse and in maintaining the health of the myelin sheath coating nerve fibers ...

Throughout a person's life, the myelin sheath has to be constantly maintained and repaired. This is something that researchers are only beginning to appreciate, but two related properties of Alzheimer's are poor quality myelin sheath alongside a

drastically reduced concentration of fatty acids and cholesterol in the cerebrospinal fluid ...

An extremely high-fat (ketogenic) diet has been found to improve cognitive ability in Alzheimer's patients. These and other observations ... lead me to conclude that both a low-fat diet and statin drug treatment increase susceptibility to Alzheimer's."

Indeed, I've previously written about how a ketogenic diet, high in healthy fats, helps protect against neurodegenerative diseases such as Alzheimer's. One of the most striking studies¹⁵ showing the effects of a high-fat/low-carb versus high-carb diets on brain health revealed that high-carb diets increase your risk of dementia by a whopping 89 percent, while high-fat diets lower it by 44 percent. According to the authors, "A dietary pattern with relatively high caloric intake from carbohydrates and low caloric intake from fat and proteins may increase the risk of mild cognitive impairment or dementia in elderly persons." A ketogenic diet benefits your brain in a number of different ways. For example, it:

- Triggers ketone production** — A cyclical ketogenic diet will help you convert from carb-burning mode to fat-burning mode, which in turn triggers your body to produce ketones, an important source of energy (fuel) for your brain¹⁶ that have been shown to help prevent brain atrophy and alleviate symptoms of Alzheimer's.¹⁷ They may even restore and renew neuron and nerve function in your brain after damage has set in.

- Improves your insulin sensitivity** — A cyclical ketogenic diet will also improve your insulin sensitivity, which is an important factor in Alzheimer's.¹⁸ The link between insulin sensitivity and Alzheimer's is so strong, the disease is sometimes referred to as Type 3 diabetes. Even mild elevation of blood sugar is associated with an elevated risk for dementia.¹⁹ Diabetes and heart disease²⁰ are also known to elevate your risk, and both are rooted in insulin resistance.

The connection between high-sugar diets and Alzheimer's was also highlighted in a longitudinal study published in the journal *Diabetologia* in January 2018.²¹ Nearly 5,190 individuals were followed over a decade, and the results showed that the higher an individual's blood sugar, the faster their rate of cognitive decline.

Studies have also confirmed that the greater an individual's insulin resistance, the less sugar they have in key parts of their brain, and these areas typically correspond to the areas affected by Alzheimer's.^{22,23}

•**Reduces free radical damage and lowers inflammation in your brain** — Ketones not only burn very efficiently and are a superior fuel for your brain, but also generate fewer reactive oxygen species and less free radical damage. A ketone called beta hydroxybutyrate is also a major epigenetic player, stimulating radical decreases in oxidative stress by decreasing NF-kB, thus reducing inflammation and increase NADPH levels along with beneficial changes in DNA expression that improve your detoxification and antioxidant production.

I explain the ins and outs of implementing this kind of diet, and its many health benefits, in my book, "[KetoFast](#)." In it, I also explain why cycling through stages of feast and famine, opposed to continuously remaining in nutritional ketosis, is so important.

Phospholipid-Bound DHA Is Particularly Important

A type of fat that is of particular importance for your brain health and prevention of neurodegeneration is the marine-based omega-3 fat docosahexaenoic acid (DHA), found in fatty fish, fish oil and krill oil.

Research²⁴ by a biomedical research scientist on aging, Rhonda Patrick, Ph.D., highlights the benefits of DHA bound to phospholipids — such as that found in krill oil — showing this particular form may actually reduce the risk of Alzheimer's in those with the APOE4 gene, which is thought to be present in about one-quarter of the population.

Having a single copy of the gene raises your risk two- to threefold. For those with two copies, the risk of Alzheimer's is as much as 15 times higher than those without this genetic predisposition.

Two hallmarks of Alzheimer's are amyloid beta plaques and tau tangles, both of which impair normal brain functioning. Alzheimer's patients also have reduced glucose transport into their brains, and this is one of the reasons why plaque and tangles form and accumulate. As explained by Patrick in her press release:²⁵ *"DHA promotes brain glucose uptake by regulating the structure and function of special proteins called glucose transporters located at the blood-brain barrier, the tightly bound layer of cells that limits passage of substances into the brain ...*

DHA ... naturally occurs in a triglyceride form and a phospholipid form. Eating DHA-rich fish slows the progression of Alzheimer's disease and improves symptoms in APOE4 carriers. However, some evidence suggests that taking DHA supplements, which largely lack the phospholipid form, does not."

According to Patrick, this variation in response appears to be related to the different ways in which the two forms of DHA are metabolized and ultimately transported into your brain.

Phospholipid DHA May Be Ideal for High-Risk Individuals

When the triglyceride form of DHA is metabolized, most of it turns into non-esterified DHA, while the phospholipid form is metabolized primarily into DHA-lysophosphatidylcholine (DHA-lysoPC). While both of these forms can cross the blood-brain barrier to reach your brain, the phospholipid form does so far more efficiently. Patrick explains:²⁶

"Whereas non-esterified DHA passes through the blood-brain barrier via passive diffusion, the phospholipid form, DHA-lysoPC, enters via a special transporter called Mfsd2a."

Previous studies have found APOE4 disrupts the tight junctions of the blood-brain barrier, leading to a breakdown in the barrier's outer membrane leaflet and a subsequent loss of barrier integrity. One end result of this loss is impaired diffusion of non-esterified DHA."

According to Patrick, people with APOE4 have a faulty non-esterified DHA transport system, and this may be why they're at increased risk for Alzheimer's. The good news is that DHA-lysoPC can bypass the tight junctions, thereby improving DHA transport, and for those with one or two APOE4 variants, taking the phospholipid form of DHA may therefore lower their risk of Alzheimer's more effectively.

"When looking at the effects of DHA on cognitive function in people with APOE4-related Alzheimer's disease, it's important that researchers consider the effects of DHA in phospholipid form, especially from rich sources such as fish roe or krill, which can have as much as one-third to three-quarters of the DHA present in phospholipids," Patrick says.²⁷

"That's where we're most likely to see the greatest benefits, particularly in vulnerable APOE4 carriers."

Alzheimer's Prevention Basics

One of the most comprehensive assessments of Alzheimer's risk is Dr. Dale Bredeesen's ReCODE protocol, which evaluates 150 factors known to contribute to the disease. This protocol also identifies your disease subtype or combination of subtypes so that an effective treatment protocol can be devised.

In his book, "The End of Alzheimer's: The First Program to Prevent and Reverse Cognitive Decline,"²⁸ which describes the complete protocol, you will also find a list of suggested screening tests and the recommended ranges for each test, along with some of Bredesen's treatment suggestions.

If you're concerned about Alzheimer's, I highly recommend picking up a copy of Bredesen's book. You can also find some of the program details in his 2014 case paper, which you can download for free online.²⁹ Following are some of the lifestyle strategies Bredesen describes that I believe to be among the most important:

Eat real food, ideally organic — Avoid processed foods of all kinds, as they contain a number of ingredients harmful to your brain, including refined sugar, processed fructose, grains (particularly gluten), vegetable oils, genetically engineered ingredients and pesticides like glyphosate.

Ideally, keep your added sugar to a minimum and your total fructose below 25 grams per day, or as low as 15 grams per day if you already have insulin/leptin resistance or any related disorders.

Opting for organic produce will help you avoid synthetic pesticides and herbicides. Most will also benefit from a gluten-free diet, as gluten makes your gut more permeable, which allows proteins to get into your bloodstream where they sensitize your immune system and promote inflammation and autoimmunity, both of which play a role in the development of Alzheimer's.

Replace refined carbs with healthy fats — Diet is paramount, and the beauty of following my optimized nutrition plan is that it helps prevent and treat virtually all chronic degenerative diseases, including Alzheimer's. It's important to realize that your brain actually only needs 15% of its energy from carbs, which can easily be produced in your liver; ketones are far more important for optimal brain function.

A cyclical ketogenic diet has the double advantage of both improving your insulin sensitivity and lowering your Alzheimer's risk.

As noted by Perlmutter, lifestyle strategies such as a ketogenic diet can even offset the risk associated with genetic predisposition. (Estimates suggest genetics account for less than 5 percent of Alzheimer's cases. An estimated 75 million Americans have the single allele for APOE4. It's unknown how many Americans have the TOMM40 gene or others that may affect your risk.)

When your body burns fat as its primary fuel, ketones are created, which not only burn very efficiently and are a superior fuel for your brain, but also generate fewer reactive oxygen species and less free radical damage.

Pay close attention to the kinds of fats you eat — avoid all trans fats or hydrogenated fats that have been modified in such a way to extend their longevity on the grocery store shelf. This includes margarine, vegetable oils and various butter-like spreads.

Healthy fats to add to your diet include avocados, butter, organic pastured egg yolks, coconuts and coconut oil, grass fed meats and raw nuts such as pecans and macadamia. MCT oil is also a great source of ketone bodies.

Keep your fasting insulin levels below 3 — Lowering your insulin will also help lower leptin levels which is another factor for Alzheimer's. If your insulin is high, you're likely consuming too much sugar and need to cut back.

Optimize your omega-3 level — Also make sure you're getting enough animal-based omega-3 fats. Ideally, get an omega-3 index test done once a year to make sure you're in a healthy range. Your omega-3 index should be above 8 percent and your omega 6-to-3 ratio between 0.5 and 3.0.

Optimize your gut flora — To do this, avoid processed foods, antibiotics and antibacterial products, fluoridated and chlorinated water, and be sure to eat traditionally fermented and cultured foods, along with a high-quality probiotic if needed.

Intermittently fast — Compress your eating window to six to eight hours. Intermittent fasting is a powerful tool to jump-start your body into remembering how to burn fat and repair the insulin/leptin resistance that is a primary contributing factor for Alzheimer's. Once you have worked your way up to where you've been doing 20-hour daily intermittent fasting for a month, are metabolically flexible and can burn fat as your primary fuel, you can progress to the far more powerful KetoFast protocol, detailed in my book.

Move regularly and consistently throughout the day — It's been suggested that exercise can trigger a change in the way the amyloid precursor protein is metabolized,³⁰ thus, slowing down the onset and progression of Alzheimer's. Exercise also increases levels of the protein PGC-1 alpha. Research has shown that people with Alzheimer's have less PGC-1 alpha in their brains and cells that contain more of the protein produce less of the toxic amyloid protein associated with Alzheimer's.

Optimize your magnesium levels — Preliminary research strongly suggests a decrease in Alzheimer symptoms with increased levels of magnesium in the brain. Keep in mind that the only magnesium supplement that appears to be

able to cross the blood-brain barrier is magnesium threonate.

Optimize your vitamin D, ideally through sensible sun exposure — Sufficient vitamin D is imperative for proper functioning of your immune system to combat inflammation associated with Alzheimer's. It's important to recognize that sun exposure is important for reasons unrelated to vitamin D.

Your brain responds to the near-infrared light in sunlight in a process called photobiomodulation. Research shows near-infrared stimulation of the brain boosts cognition and reduces symptoms of Alzheimer's, including more advanced stages of the disease.

Delivering near-infrared light to the compromised mitochondria synthesizes gene transcription factors that trigger cellular repair, and your brain is one of the most mitochondrial-dense organs in your body.

Curcumin supplementation — Research^{31,32} published last year suggests curcumin supplementation may lower your risk of Alzheimer's by improving memory and focus. The double-blind, placebo-controlled study, published in the American Journal of Geriatric Psychiatry, included 40 adults between the ages of 50 and 90 who reported mild memory lapses.

None had a diagnosis of dementia at the time of their enrollment. Participants randomly received either 90 milligrams of curcumin twice a day for 18 months, or a placebo.

A standardized cognitive assessment was administered at the start of the study and at six-month intervals thereafter, and the level of curcumin in their blood was measured at the beginning and end of the study.

Thirty of the participants also underwent positron emission tomography (PET) scans to assess their level of amyloid and tau deposits before and after treatment, both of which are strongly associated with Alzheimer's risk.

Those who received curcumin saw significant improvements in memory and concentration, while the control group experienced no improvement. PET scans confirmed the treatment group had significantly less amyloid and tau buildup in areas of the brain that control memory, compared to controls. Overall, the curcumin group improved their memory by 28 percent over the year-and-a-half-long treatment period.

Curcumin has also been shown to increase levels of brain-derived neurotrophic factor (BDNF),³³ and reduced levels of BDNF have been linked to Alzheimer's disease. Yet another way curcumin may benefit your brain and lower your risk of

dementia is by affecting pathways that help reverse insulin resistance, hyperlipidemia and other symptoms associated with metabolic syndrome and obesity.³⁴

Avoid and eliminate mercury from your body — Dental amalgam fillings are one of the major sources of heavy metal toxicity; however, you should be healthy before having them removed. Once you have adjusted to following the diet described in my optimized nutrition plan, you can follow the mercury detox protocol and then find a biological dentist to have your amalgams removed.

Avoid and eliminate aluminum from your body — Common sources of aluminum include antiperspirants, nonstick cookware and vaccine adjuvants.

Avoid flu vaccinations — Most flu vaccines contain both mercury and aluminum.

Avoid statins and anticholinergic drugs — Drugs that block acetylcholine, a nervous system neurotransmitter, have been shown to increase your risk of dementia. These drugs include certain nighttime pain relievers, antihistamines, sleep aids, certain antidepressants, medications to control incontinence and certain narcotic pain relievers.

Statin drugs are particularly problematic because they suppress the synthesis of cholesterol, deplete your brain of coenzyme Q10, vitamin K2 and neurotransmitter precursors, and prevent adequate delivery of essential fatty acids and fat-soluble antioxidants to your brain by inhibiting the production of the indispensable carrier biomolecule LDL.

Limit your exposure to wireless radiofrequencies like cellphones, Wi-Fi and routers — Radiation from cellphones and other wireless technologies trigger excessive production of peroxynitrites,³⁵ a highly damaging reactive nitrogen species.

Increased peroxynitrite production from cellphone exposure will damage your mitochondria, stem cells, DNA, cell membranes and proteins.^{36,37} Your brain is the most mitochondrial-dense organ in your body. Increased peroxynitrite generation has also been associated with increased levels of systemic inflammation by triggering cytokine storms and autonomic hormonal dysfunction.

Optimize your sleep — Sleep is necessary for maintaining metabolic homeostasis in your brain. Without sufficient sleep, neuron degeneration sets in, and catching up on sleep during weekends will not prevent this damage.³⁸⁻³⁹⁻⁴⁰ It is very clear this is one of the most important and overlooked areas and many fail to integrate this into their lifestyle.

Sleep deprivation causes disruption of certain synaptic connections that can impair your brain's ability for learning, memory formation and other cognitive functions. Poor sleep also accelerates the onset of Alzheimer's disease.⁴¹ Most adults need seven to nine hours of uninterrupted sleep each night. Deep sleep is the most important, as this is when your brain's glymphatic system performs its cleanout functions, eliminating toxic waste from your brain, including amyloid beta.

Challenge your mind daily — Mental stimulation, especially learning something new, such as learning to play an instrument or a new language, is associated with a decreased risk of dementia and Alzheimer's. Researchers suspect that mental challenge helps to build up your brain, making it less susceptible to the lesions associated with Alzheimer's disease.

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