How to Reduce Your Risk of Alzheimer’s Without Taking Drugs

While most cases of dementia may be unavoidable, a great many may be prevented or delayed via simple changes in diet and other habits. In principle, the earlier in life a person starts making these changes, the better the preventive effect would be.

By Jim Schnabel for The Dana Foundation, www.dana.org

Scientists now know a lot about Alzheimer’s disease, and preventive therapies probably aren’t far off. But even when they become available, such therapies will almost certainly be very expensive. The only products currently being tested in large-scale Alzheimer’s prevention trials are antibodies against the Alzheimer’s-associated amyloid beta (Aβ) protein. Antibodies are large and delicate proteins that must be produced in cells and delivered to patients by needle in a clinic or doctor’s office. Therapies based on solutions of antibodies are increasingly common in medicine, and include the blockbusters Humira for arthritis and Herceptin for cancer, but they typically cost thousands of dollars for a single infusion. Giving such a product on a continuing basis to all the over-60s in America, to help keep them from getting Alzheimer’s, would cost trillions of dollars each year.

Someday, elderly people may be able to take much cheaper Alzheimer’s preventives, in the form of statin-like one-a-day pills, or even a several-jab vaccination against Aβ. But that day still seems far off.

Fortunately, most of us can start lowering our Alzheimer’s risk right now, without expensive patented drugs. A study published last July in Lancet Neurology examined prior Alzheimer’s risk-factor research around the world, and estimated that about one-third of the Alzheimer’s cases in Western countries are attributable to just seven lifestyle-related “modifiable risk factors.” That suggests that, while most cases may be unavoidable, a great many may be preventable via simple changes in diet and other habits—changes that tend to benefit health generally. In principle, the earlier

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Avoid chronic stress
Stop smoking
Avoid obesity, diabetes, hypertension, and vascular disease
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Drink moderately if at all
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in life a person starts making these changes to minimize Alzheimer’s risk factors, the better the preventive effect will be.

Stay physically active
The authors of the Lancet Neurology study determined that the greatest modifiable risk factor for Alzheimer’s in the US, UK and Europe is physical inactivity. One of every five Alzheimer’s cases appears to be linked to this bad habit. It’s not hard to see why: the couch-potato lifestyle promotes known risk factors such as obesity, diabetes, inflammation, depression, high blood pressure, and atherosclerosis, and is also associated with another risk factor, low educational status (see below for more on those).

The opposite of physical inactivity, exercise, has been linked to lower Alzheimer’s dementia risk and slower cognitive decline in the elderly, as well as to less brain amyloid buildup (in elderly people and in Alzheimer’s-model mice) and reduced levels of other Alzheimer’s biomarkers. Exercise also appears to have a broad rejuvenating effect on the brain (again, in mice too) by boosting the efficiency of brain waste-removal.
increasing effect, after physical inactivity. A study in people with a moderately higher risk of Alzheimer’s for genetic reasons, exercise—probably through its neurogenesis-boosting effect, at least in part—helps prevent the age-related shrinkage of the hippocampus, a memory-related region that is vulnerable to both aging and Alzheimer’s. Exercise moreover appears to slow the age-related shrinkage of the broader medial temporal lobe, which contains the hippocampus and includes other important memory areas, and the prefrontal lobe, which handles executive functions and is also hit hard in Alzheimer’s.

“I believe that we will never isolate a single mechanism by which exercise works on the brain,” says Kirk Erickson, who researches exercise and aging at the University of Pittsburgh. “This is, in fact the reason why exercise works so well—because it influences so many different physiological pathways.”

Avoid depression, maintain purpose

According to the Lancet Neurology study, depression currently ranks second in apparent risk-increasing effect, after physical inactivity. A study last year in the British Journal of Psychiatry quantified that effect as a 65% increase in apparent risk among the subjects covered by their analysis. Such a jump in risk would be remarkable if confirmed, for the baseline risk of Alzheimer’s among the elderly is already high.

How depression would promote Alzheimer’s isn’t yet clear. One possibility is that chronic psychological stress (see below), which is well known to cause depression, ends up weakening the brain in a way that leaves it more vulnerable to Alzheimer’s. The effect may work through the hippocampus. Depression is associated with a decrease in hippocampal neurogenesis, a shrinkage of the hippocampus, and a decline in hippocampus-related cognitive performance. It thus may render the hippocampus more vulnerable to a degenerative condition such as Alzheimer’s that also targets the hippocampus and closely connected regions. Depression in many cases features reduced signaling in serotonin neurotransmitter systems in the brain, which in turn has been linked to higher production of the Aβ protein. Other biological mechanisms that could plausibly explain how depression leads to dementia include “inflammatory changes, and deficits of nerve growth factors,” UCSF researchers Amy L. Byers and Christine Yaffe noted in a recent review.

Since hippocampal shrinkage occurs in Alzheimer’s even in the absence of depression, some scientists wonder if late-life depression is a symptom rather than a cause of the Alzheimer’s process—or even a reaction to the initial mental decline it brings. A clinical trial showing that alleviating depression reduces Alzheimer’s risk might settle the debate. But it may be hard to set up a conclusive test, because standard antidepressants may help ward off Alzheimer’s in more direct ways than by treating depression. A recent small trial found evidence that an SSRI antidepressant drug can lower Aβ production by boosting serotonin signaling.

In any case, studies linking depression to a higher incidence of Alzheimer’s have been complemented by research linking positive moods to a lower incidence of Alzheimer’s. In one recent study, researchers at Rush University Medical Center found that people with a strong sense of purpose in life—a “tendency to derive meaning from life’s experiences”—at the outset of the study were much less likely to show symptoms of Alzheimer’s or mild cognitive impairment (MCI), and in general were slower to decline cognitively, in the ensuing seven years. Autopsies later revealed that those who had had a sense of higher purpose in their lives did not have a lower burden of Aβ plaques and other Alzheimer’s-type pathology, but still had fared better cognitively.

It isn’t yet clear how a sense of purpose in life—“eudaimonic well-being”—would ward off dementia. However, a study last year by other researchers offered a hint, by linking that form of well being to a reduced expression of stress- and inflammation-related genes. UCLA researcher Steven W. Cole, senior author of that study, suggests that having a sense of higher purpose—feeling that one is part of a cause greater than one’s self—makes one more resistant to the stresses of ordinary life and their adverse health consequences. “People with high levels of eudaimonic well-being may be less stressed by things that threaten them personally because the things they care most about lie in the world outside them, he says.

Consistently with this, other studies have found a greater chance of late-life Alzheimer’s among women with mid-life neurotic personality ratings, and among men and women with serious psychiatric diagnoses related to stress, including anxiety disorders.

Avoid chronic stress

Chronic stress is known to impair human health in various ways, including mental health, so it’s not surprising that epidemiological studies have associated it with a higher risk of Alzheimer’s. Perhaps the best known study in recent years, conducted at Gothenburg University in Sweden, followed 800 women who had
reported common psychosocial stress (e.g., from divorce) at a psychiatric examination in 1968. Over nearly four decades of follow-up, women who had reported more psychosocial stressors in 1968 were later diagnosed with Alzheimer’s at a significantly higher rate on average. Similarly, an American study last year linked more self-reported stress in elderly people to greater age-related cognitive decline. Although reducing harmful chronic stress is desirable anyway because it should generally improve health, more studies are needed to determine the precise relationship between chronic stress and Alzheimer’s.

One possible mechanism is the stress-related alteration of the hippocampus, seen also in depression, which includes declines in neurogenesis and might render it less resistant to the Alzheimer’s process. Another is the stress-induced weakening of the prefrontal cortex, a brain region that is perhaps just as important for cognition, and is also affected prominently in Alzheimer’s. Chronic stress also has been linked to inflammation, insulin resistance, and potentially disease-promoting changes in the Alzheimer’s-related tau protein.

There are many ways to reduce stress; non-drug methods include physical exercise, more sleep, engagement in hobbies and other interesting activities, and meditative techniques including yoga and “mindfulness.”

Stop smoking

Tobacco smoking is another proposed risk factor, and certainly a plausible one. On its way to shortening life expectancy, smoking promotes hypertension, vascular disease, and diabetes. All three of those maladies (see below) are considered Alzheimer’s risk factors. Smoking also appears to accelerate the aging of at least some tissues, including the brain (in rats), and has been shown to increase Aβ accumulation, neuroinflammation, and other Alzheimer’s-promoting factors in a standard mouse model of the disease. The recent Lancet Neurology study came up with the figure of 59% increased Alzheimer’s dementia risk among elderly smokers, based on epidemiological research.

Oddly enough, smoking was once thought to reduce Alzheimer’s risk. Some early and small studies suggested as much, and their results seemed consistent with smoking’s apparently powerful preventive effect against Parkinson’s disease (through mechanisms that might include the beneficial stimulation of nicotinic receptors on neurons, and the smoke-induced upregulation of neuronal antioxidant systems). However, a large-scale prospective study by eminent British epidemiologists in 2000 found no significant effect of smoking on Alzheimer’s incidence. Other studies have come to similar conclusions, though more recent ones have linked smoking to a significantly elevated Alzheimer’s dementia risk. Whichever is true—no increased risk or some increased risk—you’re probably better off in a general way by not smoking.

Avoid obesity, diabetes, hypertension, and vascular disease

The Lancet Neurology study concluded that 7.3%, 4.5%, and 8.0% of current Alzheimer’s dementia cases in the US are attributable to midlife obesity, type 2 diabetes, and midlife hypertension, respectively, although of course all three of those conditions are interrelated—and all are associated with vascular disease.

The mechanisms through which these conditions contribute to Alzheimer’s haven’t been determined completely. However, hypertension raises the risk of strokes and mini-strokes, which in turn seem to predispose people to Alzheimer’s, possibly by weakening or killing areas of brain tissue, and by promoting cerebrovascular deposits of Aβ. Other linking mechanisms, including disruptions of key brain networks by hypertension, have been proposed. Moreover the e4 genetic variant of the apolipoprotein-E fat-molecule transporter—a variant that is fairly common in the human population—has been linked to higher risks of both atherosclerosis and Alzheimer’s.

Several recent population studies, described at a recent Alzheimer’s conference, have found evidence that Alzheimer’s is becoming less common among the elderly in developed countries. The proposed reasons include the now-widespread use, in those countries, of relatively safe and effective blood pressure-lowering and cholesterol-lowering drugs.

Eat better

It stands to reason that if diabetes, vascular disease, and hypertension promote or predispose to Alzheimer’s, then the dietary factors that lead to them—saturated fats, red meats, processed sugar, sodium—should be avoided.

There is some evidence too that specific dietary factors including fish may reduce the risks both of Alzheimer’s and general age-related cognitive decline. Several recent studies have linked a Mediterranean diet (olive oil, nuts, fish, red wine) and the similar DASH diet (which emphasizes lower sodium levels) to slower cognitive decline among older people. A large-scale Spanish clinical trial recently found that a Mediterranean diet reduced heart attacks, strokes, and cardiovascular-related deaths in a high-risk population.
by about one-third—and that should translate into brain benefits too, given the links between cardio- and cerebrovascular problems and Alzheimer’s.

There is also increasing evidence that dietary molecules called advanced glycation end-products (AGEs), and their precursors, can promote inflammation, diabetes and Alzheimer’s. In a recent study, researchers from the Icahn School of Medicine at Mount Sinai found that removing a major AGE precursor called methylglyoxal from the chow of aging mice reduced their usual memory and learning deficits in humans too. And indeed a 2009 study of calorie-restriction in monkeys would show up in a popular one in Western countries, is known as the “5:2” (for its regimen of intermittent fasting (two days of severe calorie restriction per week, and five days’ normal or increased consumption). Even though 5:2 dieters may end up with a normal calorie intake on the whole, their two-day-per-week fast may evoke the same protective processes in their bodies that are stimulated by calorie restriction. Initial studies have suggested that 5:2-type intermittent fasting reduces weight and insulin resistance in overweight women more effectively than simple calorie restriction, and improves cognition in mice.

Such effects could translate into a better resistance to Alzheimer’s, since, as National Institute on Aging researcher Mark P. Mattson notes: “Insulin resistance at midlife increases the risk of developing Alzheimer’s later in life.”

Mattson and his colleagues now are setting up a study in overweight older women that should shed more light on intermittent fasting’s ability to prevent Alzheimer’s. The clinical trial will, he says, “critically evaluate the effects of intermittent fasting on cognitive functions, neuronal network activity and brain neurochemistry in subjects at risk for cognitive impairment because of their age and metabolic status.”

Animal studies so far suggest, Mattson adds, that intermittent fasting boosts production of the neuron-protecting hormone BDNF (brain-derived neurotrophic factor), along with “chaperone” molecules that help get rid of Aβ and tau aggregates. “In addition,” he says, “the ketones produced during fasting are known to be neuroprotective, and may also activate signaling pathways involved in synaptic plasticity”—the neuronal mechanism underlying learning and memory. (See Mattson’s TEDx talk: Why Fasting Bolsters Brain Power.)

Some researchers have found evidence that restricting animal-derived protein—particularly during the 50-65 age range—may be another good way to slow cognitive aging, reduce Alzheimer’s risk, and perhaps improve health generally.

Drink moderately if at all

At least 140 published studies have looked for some link between alcohol use and Alzheimer’s risk. Some have indicated a significantly higher risk of Alzheimer’s dementia with drinking. A recent Chinese study suggested a doubled risk of Alzheimer’s with daily drinking, and a more than tripled risk for related vascular dementia. A study published in the British Medical Journal in 2004 found that more alcohol intake brought more Alzheimer’s risk for carriers of the apo-E4 gene variant, a major inherited risk factor for Alzheimer’s. A study presented at the Alzheimer’s Association conference in 2012 found that women who started drinking in later life doubled their risk of cognitive impairment.

However, these studies are far from conclusive, since drinking habits may be connected to other health-related behaviors that worsen Alzheimer’s risk, and since alcohol abuse can cause its own form of dementia. Most studies seem to have found little or no evidence for an adverse effect of ordinary drinking on Alzheimer’s risk. To the contrary, some studies, including one reported prominently in the New England Journal of Medicine in 2005, found indications that moderate drinking has a beneficial effect at preserving cognition. The author of a recent review for the US National Institutes of Health
concluded that: “Although an increased risk of [Alzheimer’s] with alcohol use is plausible based on biological evidence, the epidemiologic evidence does not support an association. In the few studies that report a significant association, alcohol consumption is more often found to reduce the risk of [Alzheimer’s] than to increase it.” Similarly, the authors of a 2011 meta-analysis of published studies wrote: “Overall, light to moderate drinking does not appear to impair cognition in younger subjects and actually seems to reduce the risk of dementia and cognitive decline in older subjects.”

**Reduce your inflammation**

One of the more consistent neural signs of Alzheimer’s is the presence of microglia—the brain’s resident immune cells—in an inflammatory, “activated” state in affected brain areas. That neural inflammation may be aimed in part at a beneficial clearing out of Aβ and tau aggregates, as well as dead and dying brain cells. But inflammation anywhere in the body, especially chronic inflammation, can cause collateral damage to healthy tissue. In the case of microglial cells, the activated, inflamed state appears to increase their tendency to cause collateral damage to brain cells, and at the same time to reduce their capacity to clear away accumulating Aβ. Neuroinflammation even appears to stimulate greater production of Aβ. Thus, for more than two decades now, researchers have been looking at the possibility that inflammation is an accelerant of the Alzheimer’s process, and maybe even a trigger.

There has been some striking epidemiological evidence for this idea. In 1992, for example, scientists reported that Japanese lepers treated long-term with the drug dapsone—an antibacterial that is also a powerful, brain-penetrating anti-inflammatory drug—had a markedly lower prevalence of Alzheimer’s. Some studies of arthritis patients treated chronically with nonsteroidal anti-inflammatory drugs (NSAIDs) found that they too seemed less prone to Alzheimer’s. Meanwhile genetic studies linked variants of some immune-related genes to higher Alzheimer’s risk. Scientists have been exploring specific immune pathways in the brain and have shown that blocking some of them quiets microglial inflammation and reduces Aβ buildup and cognitive deficits in transgenic mice that model Alzheimer’s.

A small clinical trial of the NSAID indomethacin, reported in 1993, suggested that it might stop or even reverse the course of Alzheimer’s dementia in people. But since then, larger clinical trials have essentially ruled out the possibility of preventing Alzheimer’s with common NSAIDs. Those trials also have shown that, given NSAIDs’ side effects, their chronic use may end up doing more harm than good in elderly patients.

Non-NSAID compounds that target microglial activation pathways in the brain are still being investigated. Other possible methods for reducing chronic inflammation include weight/fat loss, a Mediterranean diet, physical exercise and (see below) maintaining an adequate store of vitamin D.

**Keep up your levels of vitamin D**

Epidemiological studies have long suggested a link between low vitamin D levels and a greater susceptibility to Alzheimer’s. Two recent longitudinal studies—tracking people over time—have also provided support for such an association. One found that subjects with low (<25 nmol/L) vitamin D at the start of the study later developed signs of Alzheimer’s at more than twice the rate of those who started with adequate levels (greater than or equal to 50 nmol/L). A more definitive, large-scale clinical trial of vitamin D’s effects in preventing diseases—including Alzheimer’s—is ongoing.

How could vitamin D help the brain ward off Alzheimer’s? Perhaps by preventing the chronic inflammation that may exacerbate the disease, and also by exerting a broadly “trophic,” health-boosting effect on neurons, thus enabling them to better survive stresses. Some studies have found that vitamin D also boosts the clearance of Aβ and may even dial down its production by neurons. In any case, Børge G. Nordestgaard, senior author of the first of the longitudinal studies cited above, notes that “low vitamin D has been associated with many different diseases and also increased mortality, so low vitamin D could be just some sort of marker of poor health generally.”

Vitamin D supplements are available over the counter, but probably for most people the best way to boost vitamin D levels is to spend more time outdoors in the sunshine.

**Avoid head injury**

Significant head injuries are associated with a higher risk of dementia later in life, including Alzheimer’s dementia. A recent study of nearly 200,000 US veterans’ medical records found, for example, that traumatic brain injury (TBI) “in older veterans was associated with a 60% increase in the risk of developing dementia” in the nine years following injury. Another large study in 1999 found no jump in the overall Alzheimer’s incidence among TBI cases but did find that people with TBI tended to get Alzheimer’s about a decade earlier than expected.
A 2010 study in transgenic “Alzheimer’s mice” found that a more natural, less lonely mouse social environment boosted neurogenesis, reduced disease-linked forms of tau and Aβ, and enhanced the animals’ ability to learn.

As for some other risk factors, not every study that has looked for a link between intellect and Alzheimer’s has found it. Certainly there are potential confounding factors: Years before it is formally diagnosed, Alzheimer’s may cause enough impairment to reduce one’s willingness to engage in mentally demanding tasks. Also, people with less education and less social engagement tend to be less healthy generally, in part because they are less likely to have healthy dietary and other habits.

A well controlled clinical trial, showing that intellectual or social engagement over a relatively long period in late middle age causes a significant reduction in Alzheimer’s risk, would settle the issue. But even in the absence, for now, of such trial results, it is almost certain that engaging in more intellectual and social activities won’t hurt you. Indeed, laboratory and human studies have long found that a “socially enriched” environment brings multiple health benefits.

Get enough sleep—but not too much

Inadequate sleep may bring a higher risk of Alzheimer’s and of faster cognitive decline generally. A study in 2011 found, for example, that elderly women who had sleep-disturbing apnea were roughly twice as likely to go on to develop MCI or dementia as those who slept normally.

This is an area that deserves more study, but there are several hypothetical mechanisms of causation, which in principle could be working together. Sleeplessness generally lowers cognitive performance, and particularly hurts memory consolidation, and thus could be weakening the very structures—the hippocampus and its nearest neighbors—that are hit earliest and hardest in Alzheimer’s. There is some evidence that chronic sleeplessness also promotes obesity and diabetes—which on their own seem to be risk factors for Alzheimer’s. Aβ levels in cerebrospinal fluid appear to rise by day and fall by night, hinting that sleep-related processes enhance Aβ clearance—and that impaired sleep could promote Aβ buildup.

One caveat here is that, even if sleep problems promote Alzheimer’s, the reverse may also be true. Sleep disturbances are common in people who have progressed all the way to Alzheimer’s dementia, and have long been considered symptoms of the disease. Similarly, a study in 2012 found that in Alzheimer’s-
model transgenic mice, the accumulation of Aβ into plaques eventually disrupts the animals’ normal sleep-wake cycle. That disruption may occur through the dysregulation of the system that produces orexin, a wakefulness-promoting hormone.

Another caveat, which is probably relevant to any discussion of the health benefits of sleep, is that more sleep doesn’t necessarily mean more benefit. Indeed, the inclination to sleep for more than 8 hours per night may be an indicator of underlying health problems. Research so far suggests that people who live longest get an intermediate level of sleep, around 7 hours per night, with lifespan falling off at shorter and longer sleep durations. A recent study found that elderly people who reported getting 9 hours or more of sleep per night had about 60% more chance of dying of dementia in the study period than those reporting 6-8 hours sleep.

**Summing up**

Though not everyone will be able to avoid Alzheimer’s, research suggests that a large subset of aging people could do so, in effect, by adopting key elements of a healthier lifestyle. These lifestyle changes—which should benefit health generally—include getting plenty of exercise; eating less, shifting to a Mediterranean style diet and getting plenty of vitamin D; avoiding stress and depression and, ideally, finding some higher purpose in life; avoiding hypertension, diabetes, cardiovascular disease and chronic inflammation; drinking moderately if at all and never smoking; staying intellectually and socially active; avoiding head injury; and getting enough sleep.

*Jim Schnabel is a science journalist and author based in Florida
Illustrations by Aimee Norkett*

**Other resources on lifestyle and Alzheimer’s risk:**
- Alzheimer’s Association
- National Institute on Aging
- Dana Alliance for Brain Initiatives: Staying Sharp