Alzheimer's and other dementias are the sixth leading cause of death in the United States. They strike one in three people aged 85 or older.

Most survive for four to eight years after they’re diagnosed, much of that time in a nursing home.

As baby boomers age, the cost of caring for people with Alzheimer's and other dementias is expected to double by 2040. It’s already $157 to $215 billion a year.

Needless to say, researchers are scrambling to find measures to prevent, or even delay, dementia.

Continued on page 3.
**Trouble Ahead? How to Keep Your Brain Sharp**

So far, no one has found a magic bullet to stop Alzheimer’s disease, which gums up the brain with protein clumps and tangles. But it’s not just clumps and tangles.

Damage to the brain’s blood vessels—often due to high blood pressure, smoking, or diabetes—can also play a role, not just in dementia but in milder memory loss as well.

Here’s how to keep a clear head for as long as possible.

**Brain Basics**

Plaques and tangles. Those are the classic hallmarks of Alzheimer’s disease.

The plaques are clumps of a protein fragment called beta-amyloid. The tangles are clusters of misshapen “tau” proteins that show up later in the disease.

But plaques and tangles alone don’t explain what happens to many aging brains.

“Thirty percent of people over the age of 70 have elevated beta-amyloid and are cognitively normal,” says David Knopman, professor of neurology at the Mayo Clinic in Minnesota.

Scientists aren’t sure why. “The most prevalent idea is that amyloid deposits are only the initiating step in a chain of events that includes neurofibrillary tangles that damage neurons and synapses,” says Bruce Reed, associate director of the University of California Davis Alzheimer’s Disease Research Center. Synapses connect one neuron (nerve cell) to another (see illustration).

“It’s the damage to and loss of synapses that causes the cognitive symptoms,” adds Reed.

So amyloid alone may not cause problems if the disease is in its early stages.

“It’s maybe ten years or more between the time when amyloid deposition begins and even mild symptoms begin, and maybe 15 to 20 years before dementia develops,” says Reed.

But Alzheimer’s isn’t the only cause of dementia.

“When we look at the cause of dementia in older people, we too often assume that it’s just Alzheimer’s,” notes Reed. “But it’s uncommon to find people with dementia who just have a single pathology. Very often, it’s mixed pathology.”

The most common other problem: damaged blood vessels in the brain.1,2

“The arteries become stiffened, narrowed, and sort of tortuous,” says Reed. “It’s much harder for the blood flow to occur normally.”

That can lead to a stroke that’s obvious, or to one that’s never noticed. “Around 20 percent of older people have had a so-called silent stroke and don’t know it,” says Reed. “Cerebrovascular disease is extremely common.”

It also contributes to mild cognitive impairment, or MCI, adds Reed. (People with MCI often go on to develop dementia.)

“In fact, some of the symptoms we think of as normal brain aging may be due to injury to the brain’s blood vessels,” he notes.

Researchers know the major threats. “The big risks for vascular brain injury are smoking, high blood pressure, and diabetes,” says Reed.

The causes of Alzheimer’s pathology are more murky. But new evidence suggests that insulin may play a role.

Here’s how to keep your brain in good working order.

1. **Watch your blood pressure**

“There’s a wealth of evidence that high blood pressure is a risk factor for late-life cognitive impairment,” says Knopman.

For example, people who have high blood pressure in their 50s or 60s have a higher risk of dementia or cognitive decline when they’re older.3,4

The latest evidence comes from abnormalities seen on brain scans:

**Small strokes.** When the blood supply gets cut off, a small area of brain tissue can die from lack of oxygen. That’s a small stroke (researchers call it an “infarct”).

“It turns out that if people have a big stroke, they almost always have had the small strokes too,” says Knopman.

“But many people who have not had big strokes nonetheless have clear evidence of having had smaller strokes.” Some are visible on MRI scans, but others are only visible with a microscope during an autopsy.

And smaller strokes matter. For example, among

Illustrations: © freshidea/fotolia.com (top), adapted from National Institute on Aging (bottom).
men in the Honolulu-Asia Aging Study who did not have dementia, those with the most micro-infarcts on autopsy had the lowest scores on cognitive tests before they died.5

“Many researchers feel that the micro-infarcts that happen silently are what drives cognitive impairment due to vascular disease,” explains Knopman. “And that vascular disease is driven especially by hypertension and diabetes.”

■ White matter hyperintensities.
If an MRI of your brain shows areas with extremely bright white matter, you have a higher risk of cognitive decline.6

The brightness may mean that brain tissue is damaged. “Presumably, the connections between nerve cells are compromised, so the regions of the brain can’t communicate well,” explains Knopman.

“If you do scans of people over the age of 65, you find that all of them have a little bit of white matter hyperintensity. But only a few, who almost always have high blood pressure, have a higher burden.”

The good news: you can lower your blood pressure with diet, exercise, weight loss, and, if necessary, medication (see “The Bottom Line,” p. 7).

2. Cap blood sugar & insulin
Diabetes also takes a toll on the brain.7,8 “Type 2 diabetes is a very strong risk factor for dementia,” says Jae Hee Kang, assistant professor of medicine at Harvard Medical School and the Brigham and Women’s Hospital in Boston. “Some people call Alzheimer’s disease type 3 diabetes.”

(In type 1 diabetes, blood sugar soars because the body makes no insulin, the hormone that acts like a key to allow sugar into cells. In the more common type 2 diabetes, blood sugar soars because insulin no longer works properly—that is, people are insulin resistant.)

“There’s no question that diabetes damages small blood vessels,” says Knopman.

It may also shrink parts of the brain. A recent study found more brain atrophy in 350 people with diabetes than in 363 people without the disease.9

It’s not just those with diabetes who are at risk. People who have what doctors call “metabolic syndrome” also have a higher risk of cognitive decline.10 That’s roughly one out of three U.S. adults.

Their blood sugar levels are higher than normal, but not high enough to be diabetes. That gives them an increased risk of dementia.11

And they may have high blood insulin levels because obesity—especially an oversized waist—has made them insulin resistant. (When insulin doesn’t work well, the pancreas responds by pumping out more.)

That may also spell trouble for the brain.12 Men with high blood insulin levels declined more on cognitive tests over three years than those with lower levels.13

Why would high levels of insulin in the blood matter?

“High insulin in the body means lower insulin in the brain,” says Angela Hanson, a physician and senior fellow at the University of Washington School of Medicine.

That’s because, over time, high levels of insulin in the blood may shrink the number of receptors for insulin in the blood-brain barrier, allowing less to enter the brain, says Hanson. And insulin may help keep the brain healthy (see “Insulin, by a Nose”).

“Insulin helps clear toxic beta-amyloid out of the brain,” Hanson explains. “So if you put someone on a diet that increases brain insulin, you might have less of the toxic amyloid around.”

The key to lowering sugar and insulin in the blood—and presumably raising insulin in the brain—is to lose excess weight and exercise more.

But one pilot study suggests that it’s not just how much, but what you eat that matters.

Hanson and her colleagues assigned 20 older adults without mild cognitive impairment and 27 older adults with MCI to eat one of two diets.14 The LOW diet was low in saturated fat, and its carbs had a low glycemic index—that is, they didn’t cause a bump in blood sugar. The HIGH diet was high in saturated fat, and its carbs had a high glycemic index.

The HIGH diet was unusually high in saturated fat and sugar, but it wasn’t off the charts. “If you look at a fast-food combo meal, it’s got a sugary soda and a high-fat burger,” notes Hanson.

After four weeks, people who got the HIGH diet had higher levels of unbound beta-amyloid fragments in their cerebrospinal fluid (which bathes the brain and spinal cord), while people who ate the LOW diet had lower levels.

“The theory is that the beta-amyloid that’s not bound to fats or other lipids is free, and it’s free to wreak havoc, if you will,” says Hanson. “We believe it’s a more toxic form of beta-amyloid because it’s less likely to be cleared. But that’s hard to test in humans.”

The results seemed to fit with a finding from a similar, earlier study: the LOW diet raised insulin levels in cerebrospinal fluid (and presumably the brain), while the HIGH diet lowered insulin levels.15

“A Western diet or obesity or other things that cause high blood insulin may decrease brain insulin,” says Hanson. “If you make someone less insulin resistant with weight loss or a diet, they may have more brain insulin.”

Until more studies are done, it’s too early to know if a diet lower in saturated fat and sugars can protect the brain. But the research is encouraging.

“The most striking finding from these studies was that you could change the brain chemistry of people who have mild cognitive impairment,” says Hanson.
**Insulin, by a Nose**

In May 2012, the National Institutes of Health announced a $7.9 million study to test whether insulin, delivered via a nasal spray, could help 240 people with mild cognitive impairment (MCI) or mild to moderate Alzheimer’s.

Suzanne Craft, the trial’s chief investigator, has spearheaded research on insulin and the brain, first at the University of Washington and now as professor of internal medicine-geriatrics at the Wake Forest University School of Medicine in North Carolina.

It all started when Craft and her colleagues studied people with prediabetes. “These folks had very high insulin levels in their blood,” says Laura Baker, an associate professor of internal medicine-geriatrics at Wake Forest. “But there were very low levels in their brain.”

That observation led the researchers to try raising insulin in the brain with a nasal spray. “If you administer insulin through the nose, it has direct access to the brain,” explains Baker. “The strategy was to see if that might have a therapeutic effect on memory and thinking.”

So far, in pilot trials lasting up to four months, intranasal insulin has boosted scores on cognitive tests in people with MCI or early Alzheimer’s. The new national trial is going to last 18 months. There’s good reason to think that insulin affects memory.

“Insulin has receptors in the brain, and they’re localized in areas that are vulnerable and are quite important for the formation of brand new memories,” says Baker. “When these insulin receptors are diminished, you see memory impairments.”

What’s more, insulin may help the brain in other ways.

“The new study will look at how insulin affects beta-amyloid, how it affects inflammation, and how it affects cortisol,” says Baker.

“Cortisol is involved in the stress response in the brain, and it’s very sensitive to changes in insulin,” she explains. “If you’re stressed, your blood insulin levels skyrocket.”

Much of the research on Alzheimer’s targets beta-amyloid, says Baker.

“Using intranasal insulin is a radically different approach,” she adds.

“We see all of these patients day after day. It keeps us honest about what needs to happen. These people need something desperately, and they want to try anything. So we’re hopeful.”


“When I’m in my clinic, I can tell patients with MCI that if they eat a healthier diet and exercise, things might get better. That’s the message that keeps me going.”

**3. Get moving**

In 1999, Arthur Kramer, then at the University of Illinois, reported that healthy sedentary people aged 60 to 75 did better on tests requiring executive function if they were assigned to six months of daily walking than if they were assigned to six months of stretching. (Executive function is the ability to plan or make decisions, correct errors, or react to new situations.)

“That was a historic moment because he showed that a behavioral intervention could actually change cognition for an aging individual,” says Laura Baker, associate professor of internal medicine-geriatrics at the Wake Forest University School of Medicine in North Carolina.

“That catapulted many other trials, and it got people to ask whether exercise might be beneficial not only for body function but also for brain health.”

And it led researchers to question whether exercise could help people who were just starting to suffer memory loss.

“I thought, ‘Well, if this is working for healthy older adults, can aerobic exercise have cognitive benefits for someone with a mild cognitive impairment?’” recalls Baker.

In a 2010 study, she assigned 33 people aged 55 to 85 who had mild cognitive impairment to either high-intensity aerobic exercise or stretching. After six months, the women assigned to exercise did better on multiple tests of executive function, while the men improved on only one.

And in a trial of 28 men and women with prediabetes—which is a risk factor for cognitive decline and dementia—aerobic exercise improved executive function, though not memory tests.

“Now we’re doing a study on people with mild cognitive impairment and prediabetes, so these people have a double hit risk for dementia,” notes Baker. “And, so far, we’re seeing the same benefit.”

Her results fit with those from similar studies and with other evidence.

“Most studies find a lower risk of dementia over time for people who exercise or are lifelong exercisers versus those who don’t,” says Baker. “Collectively, this work has set the stage for a new trial that will start in July.”

The study will test 300 sedentary older people with MCI. “It will be a 12-month supervised high-intensity aerobic exercise intervention at ten different sites, and an extra six months where people continue to exercise unsupervised,” explains Baker.

“That’s because we’re trying to see if we can translate the program for community consumption at agencies like the YMCA.”

How might exercise protect the brain? One target is microscopic blood vessels.

“If you’re sedentary, blood doesn’t get to the far reaches of those small vessels,” says Baker. “These are the areas that support the kind of executive function that’s vulnerable to aging. In animals, exercise causes these small vessels to grow and expand their reach.”

Exercise may also expand brain volume and protect the endothelial cells that line blood vessels. But why stop at one explanation?

“What’s so beautiful about exercise is that it affects insulin, blood flow, mood, stress level, physiologic stress, and more,” says Baker. “Here we have this intervention that affects...”
many different systems that all work together to support brain health.”

4. Use it or lose it

Cognitive reserve. That’s what researchers call a lifetime’s worth of using your noggin.

Many studies find a lower risk of dementia in people with more education, more literacy, professional or managerial occupations, and more involvement in mentally stimulating activities (like reading, playing games, or attending classes).

In a recent study, researchers at the Baltimore Longitudinal Study of Aging tracked 239 people (average age: 57) for eight years. All had normal cognition, and most had a close relative with Alzheimer’s.

The scientists used an adult reading test, along with the participants’ vocabulary and years of education, as a measure of cognitive reserve.

Those who had a higher cognitive reserve had a lower risk of Alzheimer’s symptoms, regardless of their beta-amyloid levels. However, cognitive reserve was less protective in people with high levels of tau, a sign of more advanced disease. So brain power isn’t a cure-all.

But it helps. “People who have better intellectual activity are somehow protected against the dementia of Alzheimer’s,” says the Mayo Clinic’s David Knopman. “They may not be protected from the brain disease itself, but they’re protected from the onset of symptoms.”

Too Early to Say

Sleep. It’s clear that mice need their sleep. When scientists allow mice that have been bred to have Alzheimer’s to sleep only four hours a night, they get worse.

“Sleep restriction leads to a faster accumulation of the toxic protein beta-amyloid,” says Andrew Lim, assistant professor of neurology at the University of Toronto.

And researchers at the University of Rochester in New York recently reported that when mice sleep, the space between their brain cells expands from 14 percent of the brain’s volume to 23 percent, which may make it easier for toxic waste products and beta-amyloid to get flushed out of the brain.

“So when animals are deprived of sleep or their sleep is disrupted, less gets cleared,” says Lim.

Whether sleep does similar housekeeping in the human brain is harder to investigate, but researchers are finding clues.

For example, Lim measured nighttime awakenings in nearly 700 older adults without dementia, including some who had a version of the APOE gene that raises Alzheimer’s risk.

“Among people with the high-risk version of the APOE gene, those who had less interrupted sleep had fewer tau tangles and a lower risk of Alzheimer’s,” says Lim.

“This suggests the possibility that, especially in the roughly 20 percent of the population with the high-risk version of the APOE gene, having uninterrupted sleep may protect against the future risk of Alzheimer’s.”

But it’s still not clear if inefficient or interrupted sleep causes dementia or if dementia disrupts sleep. “We would need randomized trials to be sure,” says Lim.

Caffeine. Caffeine may protect your brain. “In our study of people who already had an increased risk of cognitive decline because of cardiovascular risk factors, consuming about 500 milligrams of caffeine a day was strongly associated with memory preservation,” says Harvard’s Jae Hee Kang.

“It seems to require high levels of caffeine—four or five cups of coffee a day.” (That’s if it’s Maxwell House or Folgers. At Starbucks, you get 415 mg of caffeine in one venti and 520 mg in two tall coffees.)

The study found no lower risk among people who drank decaf or cola or tea, possibly because they got less caffeine.

Until a trial tests caffeine against a placebo, though, it’s not clear that it protects the brain. Even so, researchers have some reason to expect that caffeine may help.

“In mice that are bred to get Alzheimer’s, caffeine can reduce or reverse the amyloid burden,” says Kang.

Another possibility: “Caffeine seems to be protective for depression, which also increases the risk of dementia.”

Berries. Blueberries can help aging rats find their way through a maze. Could they also help human brains?

“In our study of 16,000 women aged 70 or older, those who consumed at least one serving of blueberries or two servings of strawberries a week had a slower rate of memory decline over four years than those who consumed hardly any,” says Kang.

“But the effect was modest,” she adds. And no other large studies have looked.

Vitamin D. Studies find that people with lower blood levels of vitamin D have a higher risk of dementia. “But lower blood levels could
be a consequence of the disease, because people with cognitive decline may stay at home,” says Kang. That means they’re not making vitamin D from sunlight.

“We found that women in their 60s with higher vitamin D levels had better cognitive function ten years later,” adds Kang. “But few studies have done that, so the evidence is still preliminary.”

The VITAL trial, which is randomly assigning people to take vitamin D (2,000 IU a day) and/or fish oil for five years should offer answers.

“We’ll be evaluating brain health in the 3,000 oldest participants,” says Kang.

■ Mediterranean diet. “Our study didn’t find a lower risk of cognitive decline in people who eat a Mediterranean diet, but others have,” says Kang.30,31

But even if all studies agreed that a diet that’s low in saturated fat and rich in fruits, vegetables, whole grains, fish, nuts, and olive oil were protective, it would be hard to know if it’s the diet—or something else about the people who eat it—that matters.

“I’m a bit hesitant to say that the Mediterranean diet is good for cognitive health,” says Kang. “But there’s something to be said for an overall heart-healthy diet because cardiovascular health is a risk factor.”

Forget About It

Don’t rely on these supplements to keep your memory intact.

■ B vitamins. In 20 trials that randomly assigned people to take high doses of three B vitamins (folic acid, B-6, and B-12) or a placebo, not much happened.

In the Women’s Antioxidant and Folic Acid Cardiovascular Study on 5,442 people at high risk of heart attack or stroke, for example, the B vitamins had no effect on memory. They did seem to help women who got low levels from their food, though the study wasn’t designed to answer that question.

“It’s critically important for brain health to ensure that one is not deficient in folate, B-12, and B-6,” says Harvard’s Jae Hee Kang. “However, for most people, who have adequate intakes, B vitamin supplements are unlikely to help.”

■ Antioxidant vitamins. Taking high doses of vitamin E (600 IU every other day), beta-carotene (83,333 IU every other day), and vitamin C (500 mg a day) for nine years had no impact on memory or cognition in 2,824 women at high risk of cardiovascular disease.2

“In one of our trials, men who took beta-carotene for about 18 years did have a benefit,” notes Kang. But in other trials, high doses raised the risk of lung cancer in smokers or former smokers. So it’s not worth the risk even if you’ve never smoked.

■ Other supplements. In nearly 6,000 men participating in the Physicians’ Health Study, those who took an ordinary multivitamin for seniors (Centrum Silver) for 12 years did no better on cognitive tests than those who took a placebo.4

And studies have largely come up empty on phosphatidyl serine, vinpocetine, huperzine-A, and ginkgo, which are often added to “memory” supplements (see Nutrition Action, Sept. 2012, p. 9).

The Bottom Line

TO PRESERVE YOUR MEMORY:

■ Lose (or don’t gain) excess weight
■ Exercise 30 to 60 minutes a day
■ Eat a healthy diet (see “What to Eat”)
■ Control blood pressure with diet, exercise, and, if necessary, medication
■ Stay mentally and socially active

IT MIGHT ALSO HELP TO:

■ Get enough sleep
■ Eat more seafood and berries
■ Get enough vitamin D
■ Consume more caffeine

DON’T EXPECT MUCH PROTECTION FROM:

■ B vitamins
■ Vitamins C and E and beta-carotene
■ Multivitamins

■■

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