

Your Heart, Your Belly and Alzheimer's

People with so-called “metabolic syndrome” may be at a higher risk of developing Alzheimer's disease and dementia. Here's what you should know.

BY AMY PATUREL, M.S., M.P.H.

Imagine for a moment what life would be like if you couldn't remember what you did last year, or even last week. How would it feel to spend your days reliant on another person to perform daily activities like eating, cleaning, and going to the bathroom? Just ask one of the 5.3 million Americans who suffer from Alzheimer's disease (AD). And if expert projections are accurate, that number will triple by the year 2050.

AD is a degenerative condition that attacks the brain, causing impaired memory, cognition, and behavior. Although the progression of the disease varies, all patients will ultimately require 24-hour supervision.

But what if people who are at high risk of AD could prevent the disease years before it starts?

“There are many things you can do to reduce your risk of developing AD,” says Murali Doraiswamy, M.D., professor of psychiatry, chief of the Biological Psychiatry Division at Duke University Medical Center in TK, and co-author of *The Alzheimer's Action Plan* (St. Martin's Press, 2008). “But you shouldn't wait until you're in your 60s and 70s to make lifestyle changes. You need to take action in mid-life.”

A new body of research suggests that people who develop metabolic syndrome, a cluster of conditions including obesity,

high blood pressure, high blood cholesterol, and diabetes, are at a higher risk of developing AD (See box, “Do You Have Metabolic Syndrome?” page 20). Metabolic syndrome has become increasingly common and now affects an estimated 47 million adults in the United States.

According to the American Heart Association, the underlying causes of metabolic syndrome are overweight/obesity, physical inactivity, and genetic factors. And while you can't change your genes, you can address the two other factors.

Metabolic syndrome increases the risk of type 2 diabetes, coronary heart disease, and other diseases related to plaque buildups in artery walls (such as stroke and peripheral vascular disease). In turn, many of those conditions have been linked with AD and dementia.

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MORE THAN THE SUM OF ITS PARTS?

Why do some experts think that mid-life metabolic syndrome is an important risk factor for later-life dementia? According to David Knopman, M.D., professor of neurology at the Mayo Clinic in Rochester, MN, and associate editor of the journal *Neurology*, there are two possibilities. One is that diabetes and hypertension are directly responsible for the underlying pathology of Alzheimer's disease, which



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involves toxic levels of proteins that build up in the brain. The proteins form “plaques” and “tangles” that destroys cerebral tissue.

The second theory is that diabetes and hypertension cause cerebrovascular disease (in which blood vessels supplying the brain are damaged), and this contributes to dementia by leading to strokes and mini-strokes.

However, the jury is still out. “Metabolic syndrome is a combination of things that may or may not be equal to the sum of its parts,” says Dr. Knopman. “It includes diabetes and hypertension, and those two things by themselves are important. But it also includes cholesterol, and cholesterol levels may have nothing to do with dementia or brain aging.” Ongoing research is trying to answer these questions.

In the meantime, neurologists such as Dr. Doraiswamy suggest that treating metabolic syndrome could prevent dementia. “No single study has shown that by successfully treating metabolic syndrome you can cut your risk of vascular dementia.” (Vascular dementia is an umbrella term used for cognitive impairments caused by problems in blood vessels that feed the brain.) “But common sense dictates that controlling your risk of metabolic syndrome will cut your risk of vascular dementia, because it reduces your risk of stroke,” he says.

Do Have Metabolic Syndrome?

Some scientists argue that metabolic syndrome isn't a true “condition” but simply a combination of different risk factors. Regardless, the evidence suggests that any of the following problems can increase your risk for developing AD and other diseases.

- ▶ **ABDOMINAL OBESITY:** A waistline measuring greater than 35 inches for women and 40 inches for men. If you're at high risk for diabetes, the measurement is 31 to 35 inches for women and 37 to 39 inches for men. (NOTE: this is not your pant size, but what the tape measure says when you measure your waist).
- ▶ **HIGH TRIGLYCERIDES:** Levels of 150 mg/dL or higher, or taking medication for high triglycerides.
- ▶ **LOW HDL:** Levels below 40 mg/dL for men and below 50 mg/dL for women, or taking medication for low HDL.
- ▶ **HIGH BLOOD PRESSURE:** At or about 130/85, or taking medication for high blood pressure.
- ▶ **HIGH BLOOD SUGAR:** Fasting blood sugar (blood glucose) of 100 mg/dL or higher, or receiving treatment for high blood sugar.

CEREBROVASCULAR DISEASE

The link between cerebrovascular disease and dementia is controversial. “At one point, cerebrovascular disease was believed to be the dominant cause of dementia,” Dr. Knopman noted in an editorial he wrote for *Neurology* in 2008. “Then, as recently as a decade ago, it was thought to be exceedingly rare. By 2005, the pendulum had swung back to a larger role for cerebrovascular disease in cognitive disorders.”

The latest consensus: If cerebrovascular disease is present, it takes fewer AD pathological features—those plaques and tangles—to produce the same degree of dementia.

In fact, studies show that people in midlife who have chronic uncontrolled high blood pressure (called hypertension) are more likely than their nonhypertensive counterparts to develop AD. Hypertension causes vessels in the brain to become stiff, decreasing blood flow to the brain.

What's more, hypertension increases the risk of stroke, and studies show a dramatic increase in the risk for dementia in the first few years after a stroke. In one study, up to 30 percent of stroke survivors developed dementia in the first six months after their stroke. Another study suggested that the risk of dementia is nine times higher in people who had a recent stroke compared to people of the same age and sex without a new stroke.

“Hypertension increases the risk of stroke,” says Sudha Seshadri, M.D., associate professor of neurology at Boston University School of Medicine and senior investigator of the Framingham Heart Study. “And having a stroke doubles your risk of getting clinical dementia. Once you take stroke out of the picture, though, the relationship between blood pressure and cognition is not that clear.”

Treating hypertension and preventing stroke may help stave off dementia and AD. In one study of nearly 1,300 Japanese-American men published in the journal *Stroke* in 2006, the risk of AD was 65 percent lower in those who had been treated for hypertension than in those whose blood pressure was untreated.

DIABETES

More than 23 million people in the United States have diabetes, and the rates are rising. And in one study, people with type 2 diabetes were 65 percent more likely to develop AD than those without the disease.

Scientists aren't sure how diabetes and AD are related, but they suspect that insulin is involved. Insulin directly affects learning and memory, so disturbances



of insulin signaling pathways in the brain may be connected to brain aging and AD. What's more, insulin regulates the metabolism of beta-amyloid and tau. These proteins are the building blocks of amyloid plaques and neurofibrillary tangles—the hallmarks of AD.

“In a crude way some people think AD might be a form of diabetes in the brain, where the brain isn't able to use glucose properly,” says Dr. Doraiswamy.

Inadequate insulin production and insulin resistance both interfere with the brain's ability to use glucose properly. But experts claim they each have different consequences for the brain. People who have inadequate insulin production are more likely to have clinical AD, while those who have insulin resistance often have both AD and vascular dementia.

So the impact of diabetes on late-life dementia may be twofold. First, diabetes may directly influence the underlying disease process in Alzheimer's, through the interactions of insulin and beta-amyloid. Second, diabetes might increase the risk of late-life dementia through what is known as diabetic microvascular disease, which disease affects the finer blood vessels in the body, including the capillaries.

“Diabetes increases microvascular disease, which causes changes in the brain,” says Dr. Seshadri. “So the link between diabetes and AD is not just by stroke, or high glucose or insulin resistance; it might also be these small covert changes in the brain. We suspect there are something like 12 different mechanisms” for how diabetes impacts the onset and progression of AD.

Researchers suspect that preventing or correcting insulin abnormalities may help people with age-related memory impairment and AD. Unfortunately, studies using diabetes

drugs to improve AD symptoms have yielded mixed results.

On the plus side, The Diabetes Prevention Program, a large study of people at high risk for diabetes, found that lifestyle intervention reduced developing diabetes by 58 percent during a 3-year period. The reduction was even greater, 71 percent, among adults aged 60 years or older. So if there is a link between diabetes and AD, then a lifestyle approach to preventing diabetes might help protect against AD as well.

WHAT IS DEMENTIA?

Dementia is a broad diagnosis given to people whose memory is so impaired it affects daily functioning. And while not all dementia is due to Alzheimer's Disease, everyone who has Alzheimer's Disease also has dementia.

BELLY FAT

Most people who have insulin resistance are also struggling with obesity. Abdominal or central obesity (increased waist circumference) is the form of obesity most strongly associated with metabolic syndrome. “Body mass index probably increases the risk for poor cognitive function, but central body fat seems to be the stronger risk factor,” says Dr. Seshadri.

At the University of California in San Francisco, a group of researchers, including assistant professor of medicine Alka Kanaya, M.D., found very strong links between metabolic

syndrome and cognitive function.

“There was a significant association between how fat people were and their scores on cognitive tests,” Dr. Kanaya says. And while her studies found sex-related differences (men who had high body fat were more likely to suffer from cognitive declines than women who had high body fat), studies on patients with AD have found that abdominal fat has an impact on cognitive function, regardless of sex.

In a 2007 study published in the *Archives of Neurology*, researchers found that patients with AD had significantly larger mean waist circumferences compared to cognitively normal controls. Other studies suggest that abdominal fat causes problems long before AD begins. A 2008 study published in the journal *Neurology* found that people who have larger stomachs in their 40s are more likely to have dementia when they reach their 70s. The study tracked 6,583 people between the ages of 40 and 45 and found that 36 years later, those with the highest amount of abdominal fat were nearly three times more likely to develop dementia than those with the lowest amount of belly fat. And with 50 percent of Americans

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who have an excess abdominal fat, that's a problem.

It's possible that the association between abdominal fat and dementia is being driven not by waist circumference but by a mix of conditions or behaviors of which abdominal obesity is just one part. In fact, people who are both obese and have a large belly are 3.6 times more likely to develop dementia than those of a normal weight and body size. Regardless of the specific mechanism, one thing is certain: a large belly in mid-life increases the risk of diabetes, stroke, cardiovascular disease, and dementia.

WHAT'S THE CALL TO ACTION?

One of the most exciting possibilities to come out of this research is that controlling risk factors like obesity, blood sugar, and blood pressure might help prevent or slow the progression of AD.

When it comes to aging, Dr. Seshadri claims what people fear most is AD. They're not worried about dropping dead from a heart attack, but they don't want to wither away from a disease that robs them of their dignity and independence. "Insofar as that can be a motivating factor for people, I think that's a good thing," she says.

The bottom line: Don't wait. Controlling most of the risk factors that make up metabolic syndrome has been shown to reduce the risk of heart disease and stroke, so implementing the necessary lifestyle changes certainly isn't harmful. And it could preserve your memory years down the line. "When metabolic syndrome appears during mid-life, it has 20 or 30 years before the typical age of onset of dementing illness to do its damage," says Dr. Knopman.

The key to reducing your risk of AD is paying attention to your numbers when you're relatively young. According to Dr. Doraiswamy, starting at age 40, people need to know their body weight, body mass index (a measurement of height and weight), blood pressure levels, and blood cholesterol levels. "If those numbers aren't in the normal range, you're at a higher risk of stroke and you're almost certainly at a higher risk for memory loss," he claims.

There are many things you can do to reduce your vascular risk factors. Our genes are set up so they can be turned on and off by how you live your life. Eat well, exercise, avoid smoking (and smokers), and keep your stress levels in check.

"There's an interaction between diet and genes that determines how much and how soon plaques build up in the brain," says Dr. Doraiswamy. "For example, if rats eat a high-fat, high-cholesterol diet,

their brains get riddled with these amyloid plaques." Not so if they're on a low-cholesterol diet.

In fact, studies show that following a Mediterranean Diet—fruits, vegetables, whole grains, fish, and a daily glass of red wine or red grape juice—lowers blood pressure, reduces inflammation, and protects against neurological disease. The idea is to reduce the amount of saturated fat (which is very common in the American diet) and replace it with healthy fats like olive oil and omega 3s (from fish).

"The message is still: What's good for the heart is good for the brain," says Dr. Doraiswamy. "Anything you can do to reduce your risk of heart attack and stroke will help keep your memory intact 20 years down the road." NN

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Walking: The No-Fuss Way to Exercise

Regular exercise keeps you healthy and has been shown to improve your ability to think, problem solve, and cope with stress. And no exercise is as simple, convenient, and affordable as walking. Before you get started, make sure your doctor looks you over, knows about your exercise plan, and gives you his nod of approval. Then all you need is a good pair of walking shoes and you're ready to go. Here, some tips on how to get started and get the most out of your walk.

- ▶ **START SLOWLY:** Gradually increase your pace to a brisk walk, fast enough that you find it tough to carry on a conversation. At first, you may only be able to handle a 10-minute walk a few times a week. Keep at it, and you'll tack on more steps in no time.
- ▶ **PRACTICE GOOD FORM:** Walk tall, relax your shoulders, and bend your elbows at 90-degree angles. Swing your arms as you walk, landing on your heels and rolling through your foot to push off firmly with your toes.
- ▶ **ADD AN INCLINE:** Adding an incline or stairs to your walk also increases the number of calories burned. Try walking the stairs at a local park or stadium, or climb up sand dunes or a natural hill in your neighborhood. If you're walking on a treadmill, select the interval training option with an incline.
- ▶ **SNEAK IN YOUR WORKOUT:** If you don't have an hour to kill in the morning, try incorporating several walks into your day. Park your car as far away from the store as possible. When you have a lull at work, take a few fast laps around the parking lot. Better yet, walk to work!