

## Hope to prevent Alzheimer's? Grab the olive oil and hop on a treadmill

By Eric Adler, Nov. 26, 2016



Ann Poehler's strides quicken on the treadmill. Her feet pound. Her heart races from 150 to 160 beats per minute and more.

A plastic tube jutting from the Prairie Village woman's mouth feeds carbon dioxide levels to a computer here inside the University of Kansas [Alzheimer's Disease Center](#).

The computer records every

respiration while an exercise physiologist coaches her to push harder.

"Can you hang in there like for 15 more seconds?" he urges, making an initial chart of her vitals for an exercise study geared to combat what, for people over 50, is the second-most-feared disease in the United States, just behind cancer. "Good job. Great work. ... Hang on."

At 65, Poehler is cognitively healthy and wants to stay that way. She watched Alzheimer's rob her grandmother of her memory and life. Now her mother is in a memory care unit.

Like millions of aging Americans, Poehler hopes to escape the cataclysm of the brain-wasting disease that now afflicts some 5.4 million people in the U.S., a number that only promises to grow as baby boomers age, if a cure or preventive is not found.

A national study, published online Monday in the journal [JAMA Internal Medicine](#), offered positive signs on what has long been a bleak landscape. It showed that the rate of dementia in people 65 and older had decreased from 11.6 percent in 2000 to 8.8 percent in 2012 for reasons that, not fully understood, researchers are exploring.

The fact remains that one out of every three people over age 85 in the U.S. — and at least one out of 11 over age 65 — now has clinical Alzheimer's.

"If there's anything I can do to figure out this disease, to cut back on it, or to cure it, that would be great," Poehler said before stepping onto the treadmill. "I'm worried about it. It's in my family. So I would love for this study, or the studies that are going on right now, to affect my life. That would be the best."

Researchers at the KU Alzheimer's Disease Center think so, too.

Over the past five years, the center at 4350 Shawnee Mission Parkway in Fairway has established itself as one of the top research centers in the nation dedicated to attacking Alzheimer's disease.

In 2011, the National Institute on Aging, part of the National Institutes of Health, awarded the KU center \$6 million over five years for research. Last month, the center won an additional \$8.5 million for research through 2021. The National Institutes of Health has designated it one of 31 [national centers of excellence on Alzheimer's](#).

Each center has its own Alzheimer's research mission. At KU, the focus is on prevention — stalling or stopping the disease by looking precisely into how exercise, experimental medications and diet (including a low-carb Mediterranean diet heavy on fish, nuts and olive oil) may boost the body's metabolism to combat or protect against the disease.

No one has found a single cause or cure for Alzheimer's. Only two classes of drugs even exist to stall some symptoms, with the most recent drug approved by the Food and Drug Administration 13 years ago. But strides are being made on every front.

Research at KU has so expanded since 2011 — with nearly 1,000 volunteers taking part in some 75 Alzheimer's studies — that the center is now actively [looking to enroll 700 additional volunteers](#) (age 60 and over, healthy people with no signs of Alzheimer's, as well as those with some impairment) to be part of studies on exercise, diet and medication over the next three to five years.

Fourteen studies are now underway, with more coming.

In October, the Washington-based Global Alzheimer's Platform Foundation — tasked with increasing the nation's pool of study volunteers, thus hastening therapies to market — announced the formation of "K.C. Memory Strings Alliance" among local physicians' groups, large area employers and others to help point volunteers toward studies.

“It (Alzheimer’s) is an enormous problem. But it is a hopeful time,” said physician and researcher Jeffrey Burns, who co-directs the center and its studies with director, physician and researcher Russell Swerdlow. “I’ve never seen more hope in the field in the 15 years I’ve been doing this.”

Some of what is being studied may even now help those fearing Alzheimer’s.

### **More exercise**

For 40 years, Rick Royer worked as a math teacher at Shawnee Mission East High School before retiring in 2012. He coached basketball, too.

“Jeff Burns was a student of mine,” Royer, 65, said of the Alzheimer’s physician, whom Royer also coached as a player. Now it’s one of Burns’ studies putting Royer through his paces.

Like Poehler, Royer is part of a study called APEX, Alzheimer’s Prevention Through Exercise. Also like Poehler, he is cognitively normal, with no memory problems or any other impairments. But his family has a history of Alzheimer’s.

“I have my grandfather and my mother,” Royer said.

His grandfather died of the disease in his 90s. Royer’s mother, Jill Peck Royer, now 94, began having memory problems when she was about 87. Royer first noticed it when he took his mother, a member of the Pi Beta Phi sorority at KU, to a university in Michigan for the celebration of a chapter she helped start there some 50 years before.

“It was apparent she was slipping,” Royer said. “At that point of time, it was just forgetfulness, but it was pronounced for her....She was an impressive gal. She had a very impressive intellect, an incredible vocabulary.”

Some six months ago, there were danger signs, Royer said, including the day she put a pot of water on the stove, forgot it was there and allowed it to boil dry. She now lives in a memory care unit in her hometown of Abilene, Kan.

Although neither Royer nor Poehler is cognitively impaired, each received a free PET scan — positive emission tomography — to search for clues to Alzheimer’s as part of their initial work-up for the exercise study.

In the past, Alzheimer’s could be diagnosed only at death through an autopsy. But within the last three years, PET brain scans have become available at major Alzheimer’s centers. The scans are extremely expensive, costing about \$5,000. Neither Medicare nor insurance pays for them, although a national study, known as the [iDEAS study](#), was recently launched at centers including KU to assess whether Medicare should pick up the cost.

For Royer and Poehler, the brain scans clearly showed low-level deposits of beta-amyloid protein plaques, one of the two main hallmarks of the disease.

The condition is named for German psychiatrist Alois Alzheimer, who made his mark on history in 1906 when he reported finding protein plaques in the autopsied brain of a 50-year-old woman who had dementia. He also found tangles of what are now known as tau (rhymes with “now”) protein.

Plaque deposits, which build up in the spaces between cells, and tangles, which clog the inside of cells, are thought to be the main culprits behind the brain cell death that leads to Alzheimer’s calamitous effects.

A vital note, however, is that just because people have plaques and tangles doesn’t mean they absolutely will develop clinical Alzheimer’s.

Right now, about one out of every three people over age 65 is thought to have elevated amyloid levels. Higher levels put individuals at higher risk. But it is not at all clear if they will be hit by the disease’s memory loss or dementia.

At KU, Burns pulled up several scans with glowing yellow areas that showed the brains to be swathed in the clogging protein. Yet the patients were cognitively normal.

Why do some people with plaques and tangles get Alzheimer’s and others do not? It could have much to do with the amount or concentration of plaques and tangles, how much they expand, the rate at which they expand or the parts of the brain they affect.

Researchers now think that for people who eventually develop Alzheimer’s, deposits of amyloid plaque may begin to build up as early as 10 to 20 years before the first signs of memory loss.

“That is 10 to 15 years where we could be doing something to either delay the onset or prevent it from occurring,” Burns said.

That something could be exercise.

The point of the APEX study is to assess whether regular and moderately intense aerobic exercise can slow the development of plaques and tangles and perhaps stall the disease.

Four times each week, Royer drives to the YMCA in Olathe. He puts on a heart monitor and steps onto the treadmill. There, he exercises, as the study demands, for 38 minutes each time — about 150 minutes each week — while making sure his heart rate reaches a certain level. He will do this for a year, raising the goal for his breathing and heart rate as he goes.

“I don’t think I’m doing it for me,” Royer said after he ended his workout. “I think it’s the disease that’s probably going to be the biggest deal in our country, maybe in the world.”

Burns has good reason to think the study will be effective.

Since 2008, [more than 20 studies](#) have found that even mild physical activity can maintain and even improve cognitive function while decreasing the risk for impairment. Studies have shown that the more fit people are, the greater their aerobic capacity, the less brain shrinkage they have.

APEX will chart the differences in the accumulation of brain amyloid in those who exercise regularly and those who do not.

“We think exercise might actually modify the disease process,” Burns said. “We think it may do more than (current) medication.”

Not enrolling yet — and for which close to 639 healthy volunteers between ages 65 and 80 will be sought nationwide — is another major exercise study that KU will be part of called [IGNITE](#), short for “Investigating Gains in Neurocognition in an Intervention Trial of Exercise.”

Burns predicted that, at its conclusion, the \$21.8 million National Institutes of Health-funded study could rank as the most definitive to date on the true effects of exercise on the brains of healthy, older adults. Knowing precisely how exercise affects a healthy brain will help determine ways to keep brains healthy.

KU researchers will work with Alzheimer’s researchers at Northeastern University, the University of Pittsburgh and the University of Illinois to use brain images, plaque scans, blood work and a battery of physical and psychosocial tests to measure individuals in three groups: volunteers who exercise with moderate intensity for 150 minutes per week; volunteers who exercise moderately for 225 minutes per week; and a control group of volunteers who stretch and tone for 150 minutes per week.

“Our advice we boil down to this,” Burns said. “What’s good for the heart is good for the brain. And we’re working hard to prove it.”

### **Mediterranean diet**

That a healthy diet leads to a healthy heart is uncontested. Whether there is a precise type of diet that protects against Alzheimer’s dementia, however, is far less clear. Different studies offer differing evidence.

Most studies, and most Alzheimer’s experts, agree that smoking is a risk factor for dementia. So is diabetes.

[A 2015 analysis in the American Journal of Psychiatry](#) concluded that people with diabetes who have the kind of mild cognitive impairment seen in the early stages of Alzheimer’s tend to be more likely to progress to full Alzheimer’s dementia than those without diabetes. Monday’s study in JAMA Internal

Medicine calculated that diabetes increased the risk of dementia, for which Alzheimer's is the greatest cause, by 39 percent.

After that, data can be confusing.

For example, a variety of studies holds that people with midlife obesity are at greater risk for dementia. Yet a [recent analysis that was published in 2015 in the journal The Lancet](#) Diabetes & Endocrinology, looking at data on some 2 million people over two decades, found exactly the opposite: Overweight and perhaps even obese people at midlife were at lower risk of dementia. Those who were underweight were at greater risk. The study published Monday again backs this up, showing that being overweight or obese was tied to a 30 percent *reduction* in the odds of getting dementia.

Some studies show that high blood pressure is a risk factor; others have found that later-life hypertension may protect against cognitive decline.

Same with high cholesterol. Some studies show it's bad, others not so much.

But so far, what's broadly called the Mediterranean diet stands out.

The term describes a way of eating practiced by people in the countries surrounding the Mediterranean Sea — plenty of fish, olive oil, whole grains, lean protein and lots of fresh fruits, nuts, berries and vegetables. It limits sugars, refined carbohydrates and unhealthy fats, like from fried foods.

Mediterranean people who eat that way tend to have lower rates of a number of diseases, including cancers, Parkinson's and heart disease.

In 2013, a meta-analysis in the journal Epidemiology [reviewed a dozen studies](#) on the diet regarding dementia. It concluded that nine of 12 showed that people who adhered to the diet had "better cognitive function, lower rates of cognitive decline and reduced risk of Alzheimer disease."

At the KU center, researchers recently finished a small, 20-person trial study to see how well people might stick to the diet and benefit. The results, not yet in, will help determine whether KU will launch a larger study.

### **Testing drugs**

Walt James met his wife, Deborah, when they were in high school in Ohio. They became sweethearts. At the end of this month, the Manhattan, Kan., couple — Walt's now 66, Deb is 63 — will celebrate their 46th wedding anniversary.

Deb has Alzheimer's.

It started to show in mild ways four years ago. Now it has progressed to the point that she easily becomes forgetful. Conversations wander. She loses track.

“I remember one statement she made to me,” Walt James said of the diagnosis. “It sounded bad, but it was really poignant: ‘Why couldn’t it be cancer?’ There are no survivors with Alzheimer’s. With cancer, at least, there’s some hope.”

The hope now, Walt James said, is that maybe they can help others.

Deb James recently took part in an ongoing study at KU to judge the effect of a drug called oxaloacetate, which has already been shown in studies of mice to generate cell growth in the memory parts of their brains.

The study, run by physician and researcher Russell Swerdlow, is called TOAD, short for Trial of Oxaloacetate in Alzheimer’s Disease.

While some theories hold that amyloid plaque, tau proteins, brain inflammation or some combination are the root cause of Alzheimer’s, Swerdlow is in the camp of researchers who think that the clogging proteins are more a horrible symptom, not a cause. The real culprit, he and others maintain, lies in metabolic changes that occur inside brain cells as they age.

That brings Swerdlow to mitochondria, often called the powerhouses inside cells. It is mitochondria’s role, like small power generators, to create the energy that cells use to function. But as people age, the mitochondria inside their cells, like aging generators, become less efficient. The number of mitochondria inside cells also dwindles, Swerdlow said.

Brain cells wither and weaken.

Swerdlow’s idea: “Rev up the mitochondria,” he said. “Get the mitochondria to hang in there longer.”

Oxaloacetate holds out promise that it might do that. Unlike a synthetic drug, the compound is a natural part of every cell’s normal energy cycle. It’s common enough to be sold and marketed on internet sites as a broad health-improving supplement.

Swerdlow does not recommend people go out and randomly begin taking it. Part of the current study, in fact, is designed to see whether, and how well, the drug is tolerated.

“We don’t know how much we need to give people,” Swerdlow said. “The goal of the TOAD study is not to prove whether it works or doesn’t work. The goal of the TOAD study is to find a dose at which we say, ‘Oh, it is changing something in the brain.’”

“What we’re trying to do is look and see if we’re turning the light back on in terms of metabolism.”

Despite the highest hopes, that can be hard to do, as a recent study showed.

For the last 20 months, Ree Greenwood of Atchison, Kan., has headed to the KU center once each month to receive an infusion of another experimental medication — [solanemuzab](#), commonly known as “sola.”

Produced by the pharmaceutical giant Eli Lilly, sola is an antibody drug that had been designed to possibly home in on and destroy amyloid plaques in the brain. It is significant because no drugs on the market currently attack plaques or tangles directly.

Like many study volunteers, Greenwood, 71, has an intimate interest in Alzheimer’s.

“My father had Alzheimer’s,” the retired teacher said. “I think it is a horrible, horrible way to die.”

Greenwood does not have Alzheimer’s or any signs of memory loss or dementia. But like a third of people her age, her brain scans do show some amyloid plaques. That led her to join an ongoing study, the national [A4, or Anti-Amyloid Treatment in Asymptomatic Alzheimer’s study](#).

The hope: If the drug can attack plaque early, it might also prevent or slow the development of the disease, along with cognitive loss and dementia.

On Wednesday, however, Eli Lilly delivered disappointing news when it announced that a long-term Phase III clinical that it had been conducting with solanemuzab in people with mild Alzheimer’s showed that it does not slow cognitive impairment in those patients. Lilly’s stock price plunged on the announcement.

Greenwood said that preventing the disease for herself is not the prime reason she was part of the study.

“I just wanted to do anything I could to contribute to the knowledge,” she said.