Cultivating Resilience

Early research suggests that Alzheimer's risk can be mitigated through diet, exercise and social stimulation. But definitive studies remain elusive **By Sara Harrison**

WHEN JULI COMES HOME after work, her husband doesn't regale her with stories about his photography business the way he once did. Instead he proudly shows her a pill container emptied of the 20 supplements and medications he takes every day. Rather than griping about traffic, he tells her about his walk. When they go out to a favorite Mexican restaurant, he might opt for a side salad instead of tortilla chips with his quesadilla. "He's actually consuming green food, which is new," says Juli, who asked to be identified by only her first name to protect her husband's privacy.

Over the past year Juli's husband has agreed to change his daily habits in hopes of halting the steady progression of Alzheimer's disease, which he was diagnosed with in December 2023 at age 62. Juli and her husband are both self-employed, and their insurance plans didn't cover the positron-emission tomography scans for disease tracking that a neurologist prescribed, which would have cost thousands of dollars. So they decided to spend that money on a doctor who promises that diet and lifestyle changes can treat Alzheimer's. He recommended a keto diet, along with light cardio exercise and strength training. He also prescribed a bevy of supplements, such as creatine, which Juli's husband takes alongside the

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memantine and donepezil prescribed by his neurologist. Juli doesn't expect the diet and daily walks to cure her husband, but she hopes the healthy lifestyle will help manage and even improve his condition. It feels like common sense. "You stop eating fried food, you move your butt, and you feel better," she says.

Increasingly, evidence suggests that addressing health problems such as vision and hearing loss, stress, poor diet, diabetes, obesity, high cholesterol and high blood pressure can help slow or even prevent Alzheimer's symptoms. It's a tantalizingly simple solution to a complicated condition that has proved difficult to treat. For families like Juli's that have been left with a grim diagnosis and few options, lifestyle changes bring a much needed sense of hope and agency. But researchers worry about overpromising on the efficacy of these changes, especially for people already experiencing dementia symptoms. Evidence around the importance of different diets, exercises and activities—when to start them and which to prioritize—is mixed, and only in a few high-quality studies have researchers examined large, diverse groups of people. It's a promising but nascent field of research, one that scientists worry gives patients dangerous and heartbreaking hope for a cure that doesn't exist.

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"There are a lot of claims," says Miia Kivipelto, a dementia researcher at the Karolinska Institute in Sweden. She worries about expensive but unproven regimens that promise to reverse cognitive decline, restore and protect the brain, or significantly improve cognition for people with early-stage Alzheimer's or other dementias. "Of course, people want to have hope," she says. But she cautions against making promises that can't be upheld. "It's risk reduction," she says. "That's maybe what we can promise."

Kivipelto led the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), a trial that enrolled more than 1,200 residents of Finland between the ages of 60 and 77. Results were published in 2017. They showed that after two years, participants who were given nutritional advice, exercise regimens and brain-training games had improved their executive function, processing speeds and complex memory by about 83, 150 and 40 percent, respectively, compared with those who didn't take those measures. Kivipelto has continued to follow that initial FINGER cohort and found that several years after the initial trial, their health in general continues to be better than that of their counterparts. The participants had a lower risk of stroke, had fewer medical emergency room visits and needed less inpatient care. Now Kivipelto is running World Wide FINGERS, a global network of studies investigating the same interventions in different countries and populations.

Similarly encouraging data have come from the Systematic Multi-Domain Alzheimer Risk Reduction Trial (SMARRT), a two-year randomized, controlled study. Researchers tested the effect of treating modifiable risk factors such as uncontrolled hypertension, social isolation and physical inactivity with more than 170 septuagenarians and octogenarians at high risk for dementia. Participants chose a few interventions to prioritize out of eight options, such as improved physical fitness or social connection. After two years, no matter which intervention people opted for, those who received individualized treatments had reduced risk factors for dementia and a 74 percent greater increase in cognition compared with their counterparts in the control group.

It's not clear whether these interventions prevent disease onset or simply delay it. At a certain point, prevention and treatment become almost the same thing: if people can postpone the onset of symptoms until they're 85 or 90 years old, Kivipelto says, "they might die of something else." A report from a commission on dementia from the Lancet Group—which comprises experts who make recommendations on health policy and practice—suggests that addressing a range of these lifestyle-based risk factors could help reduce the global incidence of Alzheimer's and dementia by 45 percent population-wide. For people with a genetic predisposition to dementia, introducing diet, exercise, and other modifications before symptoms appear might be particularly important for fending off illness.

The idea that diet and exercise could curb a disease that currently affects more than 55 million people globally is an exciting prospect. But scientists say the field is simply too young for anyone to make bold assertions that lifestyle interventions could act as treatments or cures. "We don't have mature information," says Howard Feldman, a neurologist at the University of California, San Diego.

One big caveat is that studies such as SMARRT and FINGER were conducted with people who had mild cognitive decline, not full-blown dementia. "There are people who are really exaggerating some of these claims," says Kristine Yaffe, a neurologist at the University of California, San Francisco, and the lead author on the SMARRT study. "There's very little evidence that these [interventions] work when people have the disease."

Also, the list of possible risk factors gets longer as more data emerge. When Kivipelto started FINGER, she didn't look at elements such as poor sleep and stress. But more evidence suggests that these factors could increase risk for Alzheimer's. Meanwhile interventions that had shown initial promise, such as the MIND diet—a diet geared toward brain health that combines elements of Mediterranean and hypertension-focused diets—weren't backed by further research.

Answering questions about lifestyle changes—what works, what doesn't and why—is particularly challenging because these interventions are not as easy to quantify as medications are. When researchers test pharmaceuticals, they're often investigating how a molecule interacts with a specific receptor. "We're gonna look at making sure that we've got tar-

get engagement, that we've got the right amount of medicine for the target and that we're getting the right effects," Feldman says. Nonmedical interventions don't work in that way. Take exercise: There's no particular receptor to examine. Instead exercise might lead to better blood flow in the brain. It might affect cerebral metabolism. It could affect insulin levels or increase oxygen flow. All these factors have been linked to the development of Alzheimer's in some way.

Then there's the matter of dosage: What is the right amount of exercise? How much should people exert themselves and for how long? And how can researchers assess compliance? When researchers test pills, they can easily dispense medication and count how many pills are left at the end of a trial. It's much harder to know whether someone in a lifestyle study has done the assigned exercises or whether all participants worked out at the same intensity.

Another big unknown is when these interventions should begin. Some research suggests that to reduce risk factors, middle age might be the most impactful time. Kivipelto says that it's never too late to start but that the most effective interventions may vary with age. Stress and sleep might be bigger risk factors in middle age, whereas social isolation might become more important as people grow older. "You should have a kind of check wherever you are in your life," she says.

Perhaps the biggest limitation, however, is that scientists can't measure all the biological and environmental systems at play, nor can they follow enough people for a long enough period to understand which systems are most important. One theory suggests that health interventions—such as diet, exercise and social stimulation—work because they boost cognitive reserve, or the ability of a person's brain to resist dementia. People with more cognitive reserve might not show symptoms even if they have the same pathology as someone else who is symptomatic. Researchers think being active, eating right and socializing might help build up that cognitive-reserve buffer. But they can't measure it. There is no known biomarker for cognitive reserve and no way to measure its effects over time. "It's an evolving concept," Kivipelto says.

Even while scientists work on more high-quality studies of lifestyle changes for Alzheimer's—with large, diverse patient populations, control groups, and careful measurements for the intensity of the intervention—numerous commercial companies claim to offer scientifically backed cures. These products, including the approach Juli and her husband are trying, are often based on research in predatory journals, which charge authors high fees to publish papers that look scientific but have none of the oversight of peer-reviewed publications. Others lack rigorous trials and rely only on case reports that don't describe study methods and can't be replicated. Still others haven't been tested in large groups or in humans at all. For example, small studies have suggested ketosis could help improve cognition, but no large-scale clinical trials have tested the hypothesis. Similarly, creatine supplements have shown promise in mice but have not been tested extensively in humans. No large, high-quality clinical trials have shown that supplements can improve human cognition or brain health, but companies selling these products now represent an industry valued at more than $6 billion globally.

Some people spend their life savings to follow a protocol that requires them to remediate mold in their homes, even though the evidence linking mold and dementia is debated. Other families report that sticking to a restrictive diet ultimately feels cruel when a parent or spouse has few pleasures left. Neurologist Joanna Hellmuth, then at the University of California, San Francisco, wrote an article in 2020 in the *Lancet Neurology* about pseudoscience and dementia, warning that fraudulent solutions can be financially and emotionally harmful for families. "Hope is important in the face of incurable diseases and intuitive interventions can be compelling," she wrote. "However, unsupported interventions are not medically, ethically, or financially benign, particularly when other parties might stand to gain."

Even under the best of circumstances, changes to diet and exercise cannot ward off Alzheimer's for everyone. Yaffe has seen patients who play bridge, go running and practice über-healthy lifestyles only to be astonished to learn they also have Alzheimer's. "There's something called bad luck, and there's something called genetics," she says. Scientists measure the impact of lifestyle modifications in population-wide estimates that don't translate to individual risk. Diet, exercise, hearing aids, and other interventions might reduce the global incidence of dementia by 45 percent, but that doesn't mean they will reduce your specific risk by the same amount. Yaffe estimates that roughly half of a person's Alzheimer's risk is based on genetics, and half probably depends on their activity level, diet and luck. But the biggest risk factor is age.

Even as Juli is gently prodding her husband to eat more broccoli, she's also preparing for his inevitable decline. The couple is in the process of moving from their two-story home in a Dallas suburb to a single-story house they are having built in a nearby gated community. Her husband will trade in his car for a golf cart, and Juli will work almost entirely from home to make sure he stays safe. She knows they are incredibly lucky to be able to afford to build their new home from the ground up. She's already designed it with a shower and doors wide enough to accommodate a wheelchair.

Juli acknowledges that it's impossible to know whether the changes to their health routines are working. There's no control group, no way to assess how her husband's disease might have progressed if they'd stuck to only medications. Right now they can afford the supplements ($150 per month), extra visits to doctors ($900 per hour twice a year), blood draws ($500 every six months), and memberships to their doctor's practice and to a platform that promotes the protocol they are following ($3,000 per year).

For Juli, the costs are justified by the change she sees in her husband. Their daily regimen gives him a sense of agency, which has alleviated some of the anxiety and depression that plagued him after his diagnosis. "It's given him work to do—and hope," she says. "If that's all we take away from it, it's worth it."