

A quest to stave off the inevitable

The idea that certain lifestyle choices could help to prevent Alzheimer's disease is gaining broader acceptance.

BY EMILY SOHN

Alzheimer's disease has long been considered an inevitable consequence of ageing that is exacerbated by a genetic predisposition. Increasingly, however, it is thought to be influenced by modifiable lifestyle behaviours that might enable a person's risk of developing the condition to be controlled. But even as evidence to support this idea has accumulated over the past decade, the research community has been slow to adopt the idea.

This reluctance was obvious as recently as 2010, when the US National Institutes of Health (NIH) brought together a panel of 15 researchers to consider the state of research on preventing Alzheimer's disease, at a conference in Bethesda, Maryland. Tantalizing findings had begun to emerge that suggested that behavioural choices such as engaging in physical exercise, intellectual stimulation and healthy eating could reduce the risk of brain degeneration. In a 2006 study (ref. 1) that followed more than 2,200 people in New York for four years, researchers found that people who adhered to a Mediterranean diet — full of whole grains, fruit and vegetables, fish and olive oil — had an up to 40% lower risk of dementia than people who ate more dairy products and meat.

For three days, the NIH panel listened to presentations on the state of the science, but its members were unconvinced. They concluded that the evidence was not strong enough to show causality between lifestyle choices and Alzheimer's disease². There was little consistency in the methods and diagnostic definitions of the condition used by different studies, and the panel pointed to conflicting results from studies that were limited by size or length, among other flaws. Plenty of promising research was under way, the panel recognized, but there was a crucial need for more long-term, large-scale population studies and rigorous, randomized controlled trials to determine which lifestyle behaviours, if any, could help to stem the tide of Alzheimer's disease.

In the eight years since then, observational studies and new trials have led to a sea change in thinking about Alzheimer's disease. Just

three years after the NIH published its sceptical stance, 109 scientists from 36 countries issued a letter³ to the G8 Dementia Summit in London that proposed that there was enough evidence to justify encouraging middle-aged people to ward off dementia by avoiding obesity and stopping smoking, among other advice, with the potential to prevent up to one-fifth of new cases by 2025. In a 2017 study⁴ that compiled the latest evidence on nine factors linked to dementia, including education in childhood and high blood pressure in mid-life, researchers estimated that 35% of the dementia burden could be attributed to potentially controllable factors — making such factors more influential than the gene variant most commonly linked to sporadic Alzheimer's disease.

Some of the most powerful evidence to support the possibility of prevention comes from prevalence data. In the past two decades, rates of dementia have fallen by up to 20% in high-income countries such as the United States, United Kingdom and Canada^{4,5}. The trend cannot be ascribed to better treatment because there are no effective therapies for halting Alzheimer's disease, which is estimated to account for around two-thirds of dementia cases. And the decline has come even as the prevalence of dementia worldwide has increased. This effect is probably the result of changes in the lifestyles of people in high-income countries. "If we had a drug that did that, people would be saying it's a miracle drug," says Gill Livingston, a psychiatrist at University College London.

BRAIN FOOD

The long-held view that cognitive decline is a natural consequence of ageing and genetics is borne of sensible reasoning. In people over the age of 65, the risk of developing Alzheimer's disease doubles every five years. And people who carry the apolipoprotein E gene variant *APOE ε4* have up to a five-times-higher risk of developing the condition than do those who lack the variant.

But even as the NIH panel urged caution, some researchers were beginning to compile a clearer case for being able to prevent Alzheimer's disease, says Leon Flicker, director of the Western Australia Centre for Health and Ageing at the University of Western



Australia in Perth. In the years since 2010, he says, a growing number of high-quality studies have built an even stronger argument.

Diet, in particular, is now thought to be an important modifiable factor. In a 2013 study⁶, researchers from Spain randomly assigned more than 500 people, aged between 55 and 80 and at high risk of developing cardiovascular diseases, to either a low-fat diet plan or a Mediterranean diet. Follow-up assessments performed after participants had followed the diets for around six and a half years showed that those who ate a Mediterranean diet scored highest on cognitive tests.

More recently, researchers have begun to determine how diet might affect the brain. Earlier this year, two studies^{7,8} showed that the brains of healthy, middle-aged people who faithfully followed a Mediterranean diet showed less atrophy on magnetic resonance imaging scans, and accumulated less of the protein amyloid- β that is a hallmark of Alzheimer's disease than did people who did not stick to the regimen. "It is the first time we are showing changes in the brain related to diet in people who are young," says Lisa Mosconi, co-author of the studies and a neuroscientist at New York University School of Medicine and the Alzheimer's Prevention Clinic at Weill Cornell Medicine in New York. "If you follow a Western diet, your brain ages faster. A Mediterranean diet is protective."

The mechanism that underlies this protection is starting to become clear. Diet seems to influence inflammation and oxidative



A Mediterranean diet rich in olive oil might help to stave off Alzheimer's disease.

researchers that looked at data from more than 55,000 people found that the risk dropped with each completed year of formal education. Advances in education, together with improvements in health care and living conditions, could explain why rates of dementia have fallen in high-income countries in the past two decades — by spurring the development of new neurons and neural connections, the brain might be able to compensate for losses in cognitive capacity that would otherwise affect daily living. Education might also help people to learn how to be more flexible and resourceful with their existing cognitive skills. “More education is a protective factor for dementia,” Flicker says. “Virtually every study finds effects ... it future-proofs your brain.”

The possibility of building a cognitive reserve that protects against future decline might explain evidence to show that, even with limited schooling, a robust social network and intellectual stimulation through puzzles and other means might help the brain to stay healthy, and that social isolation can be damaging. In their 2017 study⁴, Livingston and her colleagues were surprised to find that hearing loss had a stronger impact on cognitive health than did education. Livingston suspects that being able to hear helps to keep the brain active. In an observational study¹¹ published this year, people who wore hearing aids did not show the same elevated risk of dementia as did people with untreated hearing problems. Being married seems to make a difference, too. In a review¹² of 15 studies, also published this year, Livingston and her colleagues reported that, compared with people who were married, those who had always been single had a 42% greater risk of developing dementia.

As evidence from larger and longer-term studies accumulates, other risk factors for Alzheimer's disease, including depression and a lack of sleep, are emerging. Indeed, a 2017 meta-analysis¹³ of 27 studies found that sleep problems raise the risk of cognitive impairment by 65%, and that dysfunctional sleep could explain as

many as 15% of cases of Alzheimer's disease. Another considerable risk factor is traumatic brain injury (TBI). In a study¹⁴ published this year that included data on almost 2.8 million people in Denmark, gathered over 36 years, researchers reported that such injuries were associated with a higher risk of dementia, and that risk increased with the number of TBIs received and when TBIs occurred at a younger age.

PERSONAL ADVICE

For the most part, these findings do not run contrary to general advice on well-being. “The things we're talking about,” Flicker says, “are good for most health issues anyway.” But

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stress in the brain, high levels of which promote formation of the plaques and tangles that damage brain cells in people with Alzheimer's disease. And because signs of the disease can now be detected in brain scans decades before symptoms develop (see page S10), there might be a long window of opportunity in which to intervene, says Mosconi. “We have a very long gap to address what happens inside the brain — and potentially reverse it,” she says.

Studies that have attempted to hone in on whether specific foods and nutrients affect brain health have yielded mixed results. Robert Krikorian, director of the Cognitive Aging Program at the University of Cincinnati Academic Health Center in Ohio, points to research, including some of his own, that shows the benefits of consuming blueberries and grape juice. But the data remain limited, and other studies have produced conflicting findings on the value of numerous dietary components, including fish, omega-3 fatty acids, antioxidants and vitamins A, B and C. At the moment, support is strongest for eating a comprehensive diet as opposed to consuming any single food, Flicker says. “There's certainly some evidence for the Mediterranean diet,” he says, but the outcome of research on specific vitamins and nutrients has been disappointing.

Work to understand the effects of diet could help to explain well-established links between Alzheimer's disease and metabolic and vascular conditions such as high blood pressure, high cholesterol, obesity and type 2 diabetes. These conditions, according to a

growing body of evidence, can be mediated by food choices.

Exercise is also showing promise as a strategy for improving the health of the brain. In a 2011 meta-analysis⁹ of 15 studies that followed more than 33,000 people without dementia for up to 12 years, physical activity provided a buffer against cognitive decline — the more exercise undertaken, the better. And work in animal models has shown that exercise can elicit improvements in memory and a decrease in the accumulation of amyloid- β plaques, among other benefits. Some work suggests that only intense exercise boosts brain health, whereas other findings have revealed the benefits of resistance or basic aerobic training on specific brain processes. As researchers work out the details, they suspect that exercise might help indirectly by improving conditions such as obesity and high blood pressure, as well as more directly by helping to improve blood flow to the brain and boost the production of a protective protein called brain-derived neurotrophic factor.

SOCIAL HEALTH

Some of the most dramatic reductions in the risk of developing Alzheimer's disease have been linked to higher levels of education — with each year of schooling beyond primary school increasing the benefit. Although the 2010 NIH report noted that the effects of education can be hard to tease apart from other factors such as cognitive engagement, a 2017 analysis¹⁰ by a group of European



Richard Isaacson consults with a patient.

turning the growing evidence on risk factors for Alzheimer's disease into specific advice has been complicated, in part, because the research is full of nuances. Some work suggests, for example, that lifestyle behaviours might have different effects at various ages. Being overweight in mid-life, Flicker says, seems to increase the risk of developing Alzheimer's disease. But after the age of 60, being overweight apparently becomes protective. Cholesterol level, which is an important risk factor in middle age, also matters less later in life.

Instead of focusing on a single preventive strategy such as diet or exercise, it might make sense to combine several approaches, says Tiia Ngandu, a geriatric epidemiologist at the Finnish National Institute for Health and Welfare in Helsinki. She and her colleagues have been analysing data from the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), which was the first large randomized trial to assess a multifaceted approach to dementia prevention. From 2009 to 2011, the researchers assigned more than 1,200 adults in Finland who were aged between 60 and 77, and who had an elevated risk of dementia, to either a group that received coaching on diet, exercise, cognitive training and cardiovascular risk management, or to a control group that received only general advice on health.

Surprisingly, people in both groups showed cognitive improvements — probably because the control group had also received information enabling them to make some, if fewer, positive changes. But after two years, the researchers reported¹⁵ in 2015, the group that received coaching demonstrated a 25% greater improvement in memory, mental-processing speed and executive function, which is the brain's ability to plan and to control behaviour. Even people with the *APOE* ε4 gene variant were able to benefit from the intervention¹⁶. The team continues to monitor trial participants for dementia, but already, Ngandu says, the findings offer an encouraging message. "When people see that a family member has Alzheimer's disease, it can be quite scary," she

says. "It seems that even if you do have a genetic predisposition, there are still things you can do."

The precise course of action will probably depend on the combination of factors that affect the person being assessed, says Richard Isaacson, director of the Alzheimer's Prevention Clinic at Weill Cornell Medicine and New York-Presbyterian Hospital. Around 2009, amid growing attention from the media on the potential to modify risk, he started to hear from relatives of people with Alzheimer's disease, who wanted to know what they could do to protect themselves from the condition. In 2013, he launched the United States' first Alzheimer's disease-prevention clinic, now one of a handful of such centres across the nation.

Isaacson and his colleagues are collecting data from more than 600 people aged between 27 and 96, some of whom already have dementia. When people come to the clinic seeking ways to lower their risk of developing Alzheimer's disease, an array of information is collected from them, including data on blood-based biological markers, genetics, lifestyle habits and cognitive test scores. Secondary-school grade averages, belly-fat measurements and how much a person dreams are also taken into account. Each participant is then offered a personalized prevention strategy, which might include interventions such as intermittent fasting, interval workouts or strength training.

In 2016, Isaacson's team observed that after just six months on a personalized preventive plan, participants showed improvements in executive function and mental-processing speed¹⁷. The researchers will soon reveal results gathered from a group of more than 150 people at the New York clinic, and the early signs are encouraging. On the basis of this work, Isaacson suspects that 60% of lifestyle recommendations will be the same for everyone; eating a Mediterranean diet, for instance, seems to be a universally positive strategy. The rest should vary from person to person and could include interventions such as aggressive treatment for cardiovascular conditions, medication for sleep apnoea or participation in specific types of physical activity. "We can't have a one-size-fits-all approach. Different people can take a different road to Alzheimer's," he says. But much hypothesis testing remains to be done. "Alzheimer's prevention is still a developing, nascent field," he says. As the research evolves, so too will the clinic's approach.

The NIH has become more optimistic about preventing Alzheimer's disease and other forms of dementia since 2010. In a 2017 report¹⁸, commissioned by the NIH National Institute on Aging (NIA), a team at the US National Academies of Sciences, Engineering, and Medicine acknowledged that there had been considerable advances in the

field. Cognitive training, the management of high blood pressure, and increasing people's participation in physical activity are areas that the NIH is actively studying and in which it is supporting trials, or for which it plans to do so, says Richard Hodes, director of the NIA.

The report concluded, however, that the evidence was still not strong enough to support a fully-fledged public-health campaign to encourage people to make changes for the benefit of brain health. "The quality of evidence falls short," says Hodes. He cannot say with confidence that any such interventions will decrease the likelihood of a person developing dementia. But he does acknowledge that not everyone feels this way. "Many people who are sincere and who are knowledgeable can evaluate the level of evidence and come to different conclusions."

Being sceptical of the potential to prevent some cases of Alzheimer's disease is increasingly the minority opinion, Flicker says. And more definitive advice could become available in the next few years, thanks to data from two upcoming trials that have been modelled on FINGER. In the United States, the US-POINTER trial will begin recruiting participants later this year to assess the effects on brain health of diet, exercise, social and intellectual stimulation, and other health-management strategies for a period of two years in 2,500 older people who are at risk of dementia. Researchers who worked on FINGER are also helping to plan a similar intervention trial called MIND-CHINA, which will study a rural Chinese population, taking into account the distinctive lifestyle and culture of participants. Looking ahead, there is reason for hope. "You should be ambitious about dementia prevention," Livingston says. "It really looks like we can make a difference." ■

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